ÓRGANO DE DIFUSIÓN CIENTÍFICA DE LA ACADEMIA MEXICANA DE CIRUGÍA

FUNDADA EN 1933

ISSN: 2444-0507

CIRUGÍA Y CIRUJANOS

Content

Original articles

681 Can the screw number in volar locking plate fixation for distal radius fractures predict the Patient-Rated Wrist Evaluation outcome?
Miodrag Vranješ, Milan Majkić, Nikola Vukosav, and Branko Baljak

686 Comparative analysis of operative treatment of fractures of the proximal humerus using two different surgical techniques
Srđan Ninković, Nataša Janjić, Nikola Vukosav, Milan Milinkov, Oliver Dulić, and Predrag Rašović

693 Interobserver variation in the Parkland scale. Are we seeing the same thing?
José L. Maldonado-Calderón, Lydia E. Nava-Rivera, Antonio Urbina-Zeglen, Marco V. Herrera-Santos, Pilar Carranza-Rosales, Javier Morán-Martínez, and Nadia D. Betancourt-Martínez

699 Clinical efficacy of radiofrequency ablation guided by high-density mapping on persistent atrial fibrillation
Ting Huang, Han Xie, and Ning Ma

708 Model for analysis of actors in divergence or convergence of strategic health objectives
Martha K. Torres-Salgado

718 Animal experimental study of 3D-printed titanium implants based on magnesium-zinc ion surface modification to promote oral soft-tissue closure
Shuo Huang, Fang Guo, Ning Liu, Kaijin Hu, and Changkui Liu

725 Extranodal Rosai-Dorfman disease in the breast: a literature review from 1969 to 2023
Jorge S. Haro-Cruz, Laura M. Rodríguez-Barrios, Ana C. Díaz-Degollado2, Guillermo Álvarez-Sánchez, Marisol Guitián-González, Claudio D. Rojas-Gutiérrez, Erick Zuñiga-Garza, Israel Salgado-Adame, Ruddy F. Canaan-Figueroa, Allan F. Delcid-Morazán, Sara I. Rodríguez-Barrios, and Daniel Chacón-Galvis

735 Comparing costs and timing of ankle sprain care in two first-tier care systems
Arlette R. Ordóñez-Flores, José J. Rivera-Sánchez, M. Valeria Jiménez-Baez, David Rojano-Mejía, Macedonia G. Moreno-Tovar, and Alma I. Guerrero-Martínez

741 Visual and refractive outcomes after SMILE vs FS-LASIK: a paired-eye study
Arturo Ramirez-Miranda, Angie De-la Mota, Guillermo García-De la Rosa, Juan C. Serna-Ojeda, Jorge E. Valdez-García, Daniela Fábregas-Sánchez-Woodworth, Alejandro Navas1, Aida Jiménez-Corona, and Enrique O. Graue-Hernandez

751 Characteristics and mortality in patients with cancer and COVID-19
Alejandro Hernández-Solís, Andrea Quintana-Martínez, Arturo Reding-Bernal, Alejandro Hernández-de la Torriente, and Pablo Álvarez-Maldonado

PERMANYER MÉXICO
www.permanyer.com

Volume 92, No. 6, November-December 2024

Journal Citation Reports™ from Clarivate, 2022, Medline/PubMed, EBSCO Essentials™

10110AMEX246

ORIGINAL ARTICLE

Can the screw number in volar locking plate fixation for distal radius fractures predict the Patient-Rated Wrist Evaluation outcome?

¿Puede el número de tornillos en la fijación con placa de bloqueo volar para fracturas de radio distal predecir el resultado de la Evaluación de la Muñeca Calificada por el Paciente?

Miodrag Vranješ[1,2], Milan Majkić[1,2], Nikola Vukosav[1,2], and Branko Baljak[2]*

[1]Faculty of Medicine, University of Novi Sad; [2]Clinic for orthopedic surgery and traumatology, Clinical Center of Vojvodina. Novi Sad, Serbia

Abstract

Objective: *The optimum number of screws in a volar locking plate (VLP) for distal radial fractures (DRF) fixation has not been established. We conducted a retrospective observational study aimed to evaluate the relationship between the number of used screws and the post-operative results provided by the patient-rated wrist evaluation (PRWE) questionnaire.* **Method:** *A total number of 62 surgically treated participants for DRF were included in the study between July 2019 and September 2022. Information was gathered regarding the number and arrangement of screws by examining X-ray images and using health records. We were looking at five variables: the total number of screws, the number of proximal fragment screws, the number of distal fragment screws, the number of locking screws, and finally number of cortical screws.* **Results:** *Our data suggests that the number of screws in VLP for DRF fixation is a weak predictor of post-operative results and is therefore unlikely to influence the PRWE score.* **Conclusions:** *The ability to predict outcome by knowing the number of screws turned out to be an unreliable prognostic sign.*

Keywords: *Distal radius fracture. Patient-rated wrist evaluation. Screw number. Volar locking plate.*

Resumen

Objetivo: *El número óptimo de tornillos en la placa volar de bloqueo para la fijación de fracturas distales del radio no ha sido establecido. Realizamos un estudio observacional retrospectivo con el objetivo de evaluar la relación entre el número de tornillos utilizados y los resultados posoperatorios proporcionados por el cuestionario de Evaluación de la Muñeca Calificada por el Paciente (PRWE, Patient-Rated Wrist Evaluation).* **Método:** *Se incluyeron en el estudio 62 participantes tratados quirúrgicamente por fractura distal del radio entre julio de 2019 y septiembre de 2022. Se recopiló información sobre el número y la disposición de los tornillos mediante la revisión de imágenes de rayos X y el uso de registros médicos. Se analizaron cinco variables: número total de tornillos, número de tornillos en el fragmento proximal, número de tornillos en el fragmento distal, número de tornillos de bloqueo y número de tornillos corticales.* **Resultados:** *Nuestros datos sugieren que el número de tornillos en la placa volar de bloqueo para la fijación de fracturas distales del radio es un predictor débil de los resultados postoperatorios, y por lo tanto es poco probable que influya en la puntuación de la PRWE.* **Conclusiones:** *La capacidad de predecir el resultado mediante el conocimiento del número de tornillos resultó ser un signo pronóstico poco fiable.*

Palabras clave: *Fractura del radio distal. Evaluación de la Muñeca Calificada por el Paciente. Número de tornillos. Placa volar con bloqueo.*

***Correspondence:**
Miodrag Vranješ
E-mail: miodrag.vranjes@mf.uns.ac.rs

Date of reception: 27-11-2023
Date of acceptance: 06-03-2024
DOI: 10.24875/CIRUE.M24000791

Cir Cir (Eng). 2024;92(6):681-685
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Open reduction and internal fixation of distal radial fractures (DRF) with a volar locking plate (VLP) has become a standard surgical method[1]. This procedure enables early post-operative wrist movement and has shown good functional outcomes[2]. Unstable and multifragmentary DRF require anatomical reconstruction and stable fixation to allow for optimal functional outcome[3]. These multifragmentary fractures require a greater number of screws when using VLP to accomplish a stable fixation. Although additional screws can be used to ensure firm fixation, the use of extra screws can be associated with an increased risk of complications such as joint and tendon irritation[4]. Therefore, it is well known that unstable and multifragmentary fractures have a significantly worse post-operative result[5].

Many studies concerning the distal radius VLP have been published. Typically, they compare different VLP designs or positions of screws[6-8]. We identified also numerous studies investigating the success of the VLP surgical procedure using the patient-rated wrist evaluation (PRWE) questionnaire[9-13], but no studies concerning the number of used screws. Therefore, there is an objective need to evaluate this relationship between the number of used screws and the post-operative results provided by the PRWE questionnaire. We are guided by the opinion that more screws are needed in unstable and multifragmentary fractures and will therefore show worse PRWE results.

Methods

Study design

We included participants who were surgically treated during the period between July 2019 and September 2022 (i.e., 38-month period) in the University Hospital in Novi Sad, Serbia.

The applied inclusion criteria were: (i) ≥ 18 years of age; (ii) surgical treatment of DRF using a VLP; and (iii) follow-up at least 6 months after the procedure. Patients were excluded if they had a (i) pre-existing neurologic hand injury; (ii) compartment syndrome; (iii) dementia; (iv) psychiatric disorders, and/or (v) multiple upper limb injuries (except distal ulna fractures).

Surgical procedure

The surgical procedure was performed by three different surgeons using a VLP (Aptus, Medartis, Switzerland) through a *flexor carpi radialis* approach and under image intensification (BV Endura, Philips, The Netherlands). During the procedure, a tourniquet was used. Postoperatively, the wrist was bandaged for 2 weeks, and active finger flexion and extension exercises were encouraged. Two-week post-operative dressings and sutures were removed. No strengthening work, heavy pushing, pulling, or lifting was allowed for 8 weeks post-operative. Physiotherapy was commenced, with an aim to achieve full range of movement at the wrist and hand.

Parameters of interest

Extracted data from the patient health record include sex, age, and date of the injury. All four researchers were gathering information regarding the number and arrangement of screws by examining X-ray images and using health records. Five variables of interest were as follows: (i) the total number of screws; (ii) number of proximal fragment screws; (iii) number of distal fragment screws; (iv) number of locking screws and finally; and (v) number of cortical screws. As the number of samples, using the structural modeling observation should be at least 10-15 times the number of variables, the sample size should be 50-75 people. Finally, the sample size of our follow-up survey was determined to be 62 patients (n = 62).

In addition, wrist function was assessed using the validated PRWE questionnaire[14]. The PRWE questionnaire is a 15-item patient-reported measure of pain and function, specific to the wrist. It scores between 0 and 100, with higher scores indicating poorer outcomes. All four researchers independently conducted the interview. Given the broad catchment area of our institution, patients were contacted by telephone. For this sake, the informed consent was waived.

Data analysis

The first stage of data analysis implied examination of the average number for each screw type or position (variables of interest) used during the VLP procedure and comparison with the PRWE scores. For the screw type or position where a statistically significant difference in the PRWE score was found, new groups were

formed to examine a possible link between number of specific screws used and the PRWE scores. More precisely, screw-specific groups were stratified according to the amount of screws used (i.e., [i] less than average; [ii] average, and [iii] above the average) and finally compared for variations in the PRWE scores. Finally, the link between the total number of screws used and the PRWE score was accessed in the same fashion.

The statistical analysis was performed using R-project software (Bell Laboratories, United States, version 4.2.2.). We used the Kruskal–Wallis test for the comparison of all variables (number of screws) and the Dunn *post hoc* test where we got significance. A $p < 0.05$ was considered statistically significant.

Results

Demographic characteristics of enrolled patients

One hundred nine patients (n = 109) were included in the study over a 38-month period. After the initial number was identified, 47 patients were excluded due to death, or dementia or were lost to follow-up due to a change of residence. This left a total number of 62 patients for evaluation (62/109; 56.88%), including 24 males and 38 females. The mean age of all enrolled patients was 50.58 years (95% CI 46.79-54.36). More specifically, women were on average 9 years older than men (54 years; 95% CI 49.40-58.96 vs. 45 years; 95% CI 38.97-50.77). The average duration of follow-up in all enrolled patients (calculated from the day of injury) was 22 months (95% CI 19.14-24.59).

As far as continuing employment, the majority of patients (55/62; 88.7%) continued their previous occupation, while others were either not able to continue their previous occupation (3/62; 4.8%) or they got retired but were capable of recreational activity (4/62; 6.4%).

Frequency of specific screw-type usage during VLP and link with the PRWE score

The average number of screws used during the VLP procedure was 6.67 (95% CI 6.38-6.97). Among them, locking and distal fragment screws were used the most (on average 3.83 and 3.75/VLP procedure, respectively), while proximal and cortical screws were used in slightly less number (2.93 and 2.83/VLP procedure, respectively).

Table 1. Kruskal Wallis tests show a significant difference between the number of distal screws

Variable	χ^2	df	p
Number of distal fragment screws	7.474	2	0.024(*)
Number of proximal fragment screws	1.590	2	0.451(ns)
Number of cortical screws	3.799	2	0.150(ns)
Number of locking screws	4.576	2	0.101(ns)

*statistically significant (i.e., $p < 0.05$); ns: not significant.

Table 2. Dunn test for number of distal fragment screws shows significant difference in the PRWE score

Number of screws used comparison	Difference	p
Less than average (< 4) versus average (4)	2.667	0.003(*)
Less than average (< 4) versus more than average (> 4)	1.481	0.069(ns)
Average (4) versus more than average (> 4)	–0.621	0.267(ns)

*statistically significant (i.e., $p < 0.05$); ns: not significant.

The mean total score for the PRWE was 18.42, (95% CI 13.67-23.17). Only four patients (4/62; 6.4%) had a PRWE score over 50, while majority (30/62; 48.3%) had PRWE scores < 15. As the PRWE score is not normally distributed (Kolmogorov-Smirnov, D = 0.691, $p < 0.001$) non-parametric tests were used for further comparisons (i.e., Kruskal-Wallis tests with the PRWE score being the dependent variable). We found a significant difference in the PRWE score between patients with the distal number of screws compared to other used screws (Table 1). Dunn *post hoc* test was conducted for both variables to see between which groups the difference exists. In addition, we found a significant difference in the PRWE score between the patients who had an average number of screws inserted (i.e., four screws) compared to the group where less than average number of screws was used (Table 2). The group with less than 4four screws has statistically significantly higher scores than the group with four screws.

Finally, when we examined patients according to the total number of screws received we found a significant difference in the PRWE score between patients who had average screws (7) compared to those less than average (< 7) and more than average (> 7 screws) (Table 3). In both cases, the group with seven screws has a statistically significantly lower PRWE score compared to the two other groups.

Table 3. Dunn test for total number of screws shows significant difference in the PRWE score

Number of screws used comparison	Difference	p
Less than average (< 7) and Average (7)	3.225	< 0.001(**)
Less than average (< 7) and more than average (> 7)	1.025	0.152(ns)
Average (7) and more than average (> 7)	−1.671	0.047(**)

**statistically highly significant (i.e., p < 0.001); ns: not significant.

Linear regression was used to predict the PRWE score. The model was created with all the before-stated variables as predictors. The following results were obtained: $R^2 = 0.168$, $F(7, 544) = 1.554$, $p = 0.169$. The overall model is not significant so no further interpretation is needed. Variables used in this study (i.e., screw type and screw number used) cannot successfully predict the PRWE score.

Discussion

Our data suggests that the number of screws in the VLP surgical procedure for the treatment of DRF is a weak predictor of post-operative results and is therefore unlikely to influence the PRWE score. While we were able to demonstrate significance between two distal fragment screw groups as well as significance among the three groups in the total number of screws, the meaning of that significance is lost in the entire context of the work.

The total number of screws used during the procedure ranged 4-12 screws. Using fewer screws is generally considered sufficient, with no need to fill all the plate holes, there is no consensus about how many screws and which screws should be chosen[8].

VLP fixation of DRF is mostly performed using between four and nine distal locking screws[7], thus there is no general position or optimal screw number that should be used. Our number of 3.75 screws was below this range. Synek et al. stated that configurations with just three distal screws can outperform (higher stiffness or lower peri-implant strains) those with five screws depending on the screw selection[8]. On the contrary, Mehling et al. stated that three screws in the distal part created an unstable condition and there should be at least four screws, two of these screws should be in a different direction[6]. Additional screws can be used to ensure firm fixation, using extra screws we can anticipate higher costs and increased risk of tendon irritation complications[4].

Similarly, three bicortical screws are commonly used for the proximal fragment, but the question of how many screws are necessary has also not been answered sufficiently[7,15]. Our number of 2.93 screws is slightly below this range. Schindelar et al.[15] used a number of 3.2 proximal fragment screws in both of their groups and they had no statistical differences in fixation failure. One reason for using a lower number of screws, in our study, could be the fact that we tend to put an external fixator in extremely multifragmentary distal radius fractures, other than reconstruct with a VLP and a high number of screws. Second, the "paid per screw" compensation for the surgeon is not custom in our health-care system.

The PRWE questionnaire is commonly used and extensively validated in literature[16]. Moreover, evidence supports the use of the PRWE questionnaire after a 6-month period of the distal radius fixation[17] as it is the case in our study (22 months).

Our mean PRWE score of 18.42 is lower than the score of Duprat et al. whose results were 22.97 and 20.56 in their splinting and non-splinting groups, consecutively. Although, they conducted the PRWE questionnaire early at 3 and 6 months postoperatively[10]. In a randomized controlled trial with a 3-year follow-up by Südow et al., the mean PRWE result of 7 is significantly better[18]. Similarly, Dennison et al. documented a PRWE score of 5.4 and 5.1 in their two groups of early and late rehabilitation protocol[19]. Worth mentioning is the existence of bias in their case, where they excluded patients with diabetes, metabolic diseases, and if they had a concomitant ulnar side fracture. Therefore, the lower PRWE score in our study can be explained by our mild exclusion criteria and the fact of short experience in using VLP for distal radius fractures by < 4 years.

As the VLP procedure enables early mobilization and good fracture healing outcomes[2], likewise is the return to work. Patel et al. documented that 28 patients (93.3% out of 30) returned to their pre-injury employment[20]. Watson et al. conducted a study with 133 participants and noted a 90% return to work at the 26th week[21]. In accordance with our higher PRWE score, our return to work incidence was lower (88.7%).

There are several limitations of this study. Foremost is our ability to contact only 56.8% of the patients, which results mostly from the large geographic area served by our institution. One important limitation was that the study was retrospective, which may limit data quality. Worth mentioning is also the short monitoring period of 6 months in some cases, although our mean follow-up was 21.87 months.

Although our sample size was adequate to allow comparison between groups on the independent variables in regards to the PRWE score, the medians of the groups are distributed closely together, so it is likely that we would not find any significance with a larger sample. Finally, our study did not take into account the location of the distal fracture screw relative to the proximal or distal row nor the type of screw, i.e., cortical or locking.

Conclusion

As medicine and lifestyle improve, we can expect a greater number of VLP procedures for DRF. Patient demand for surgical treatment that will provide adequate wrist function will increase. The ability to predict outcome by knowing the number of screws turned out to be an unreliable prognostic sign. Counseling patients and selecting appropriate post-operative rehabilitation plans should be rather focused on the anatomical restoration of fragments.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Li Y, Zhou Y, Zhang X, Tian D, Zhang B. Incidence of complications and secondary procedure following distal radius fractures treated by volar locking plate (VLP). J Orthop Surg Res. 2019;14:295.
2. Leixnering M, Rosenauer R, Pezzei C, Jurkowitsch J, Beer T, Keuchel T, et al. Indications, surgical approach, reduction, and stabilization techniques of distal radius fractures. Arch Orthop Trauma Surg. 2020;140:611-21.
3. Ring D, Prommersberger K, Jupiter JB. Combined dorsal and volar plate fixation of complex fractures of the distal part of the radius. J Bone Joint Surg Am. 2004;86:1646-52.
4. Neuhaus V, Badri O, Ferree S, Bot AG, Ring DC, Mudgal CS. Radiographic alignment of unstable distal radius fractures fixed with 1 or 2 rows of screws in volar locking plates. J Hand Surg Am. 2013;38:297-301.
5. Trumble TE, Schmitt SR, Vedder NB. Factors affecting functional outcome of displaced intra-articular distal radius fractures. J Hand Surg Am. 1994;19:325-40.
6. Mehling I, Müller LP, Delinsky K, Mehler D, Burkhart KJ, Rommens PM. Number and locations of screw fixation for volar fixed-angle plating of distal radius fractures: biomechanical study. J Hand Surg Am. 2010;35:885-91.
7. Jung HS, Jung HS, Baek SH, Lee JS. How many screws are needed for reliable stability of extra-articular nonosteoporotic distal radius fractures fixed with volar locking plates? Clin Orthop Surg. 2020;12:22-8.
8. Synek A, Baumbach SF, Pahr DH. Towards optimization of volar plate fixations of distal radius fractures: using finite element analyses to reduce the number of screws. Clin Biomech (Bristol, Avon). 2021;82:105272.
9. Javed S, Shahid R, Thimmiah R, El-deen M. Volar locking plate osteosynthesis for distal radial fractures. J Orthop Surg (Hong Kong). 2015;23:323-6.
10. Duprat A, Diaz JJ, Vernet P, Gouzou S, Facca S, Igeta Y, et al. Volar locking plate fixation of distal radius fractures: splint versus immediate mobilization. J Wrist Surg. 2018;7:237-42.
11. Saving J, Severin Wahlgren S, Olsson K, Enocson A, Ponzer S, Sköldenberg O, et al. Nonoperative treatment compared with volar locking plate fixation for dorsally displaced distal radial fractures in the elderly: a randomized controlled trial. J Bone Joint Surg Am. 2019;101:961-9.
12. Eikrem M, Brannsten H, Bjørkøy D, Lian T, Madsen JE, Figved W. Volar locking plate versus dorsal locking nail-plate fixation for dorsally displaced unstable extra-articular distal radial fractures: functional and radiographic results from a randomized controlled trial. JB JS Open Access. 2021;6:e21.00068.
13. Maccagnano G, Noia G, Vicenti G, Baglioni M, Masciale MR, Cassano GD, et al. Volar locking plate versus external fixation in distal radius fractures: a meta-analysis. Orthop Rev (Pavia). 2021;13:9147.
14. Kleinlugtenbelt YV, Krol RG, Bhandari M, Goslings JC, Poolman RW, Scholtes VA. Are the patient-rated wrist evaluation (PRWE) and the disabilities of the arm, shoulder and hand (DASH) questionnaire used in distal radial fractures truly valid and reliable? Bone Joint Res. 2018;7:36-45.
15. Schindelar L, Petrucelli P, Wang W, McEntee R, Kistler J, Laroche K, et al. Early loss of fixation after surgical treatment of distal radius fractures: does the number of screws matter? J Orthop. 2020;22:539-42.
16. Mehta SP, MacDermid JC, Richardson J, MacIntyre NJ, Grewal R. A systematic review of the measurement properties of the patient-rated wrist evaluation. J Orthop Sports Phys Ther. 2015;45:289-98.
17. Fang C, Fang E, Yee DK, Kwan K, Leung G, Leung F. A comparison of six outcome measures across the recovery period after distal radius fixation-which to use and when? J Orthop Surg (Hong Kong). 2021;29:2309499020971866.
18. Südow H, Severin S, Wilcke M, Saving J, Sköldenberg O, Navarro CM. Non-operative treatment or volar locking plate fixation for dorsally displaced distal radius fractures in patients over 70 years - A three year follow-up of a randomized controlled trial. BMC Musculoskelet Disord. 2022;23:447.
19. Dennison DG, Blanchard CL, Elhassan B, Moran SL, Shin AY. Early versus late motion following volar plating of distal radius fractures. Hand (N Y). 2020;15:125-30.
20. Patel S, Deshmukh A, Yadav P, Phalak M, Gurnani S, Yadav S, et al. Assessment of functional and radiological outcomes of comminuted intra-articular distal radius fracture treated with locking compression plate. Cureus. 2022;14:e21398.
21. Watson N, Haines T, Tran P, Keating JL. A comparison of the effect of one, three, or six weeks of immobilization on function and pain after open reduction and internal fixation of distal radial fractures in adults: a randomized controlled trial. J Bone Joint Surg Am. 2018;100:1118-25.

ORIGINAL ARTICLE

Comparative analysis of operative treatment of fractures of the proximal humerus using two different surgical techniques

Análisis comparativo del tratamiento operatorio de fracturas del húmero proximal utilizando dos técnicas quirúrgicas diferentes

Srđan Ninković[1,2], Nataša Janjić[1,2], Nikola Vukosav[1,2], Milan Milinkov[1,2], Oliver Dulić[1,2], and Predrag Rašović[1,2]*

[1]Clinic for Orthopedic Surgery and Traumatology, University Clinical Center of Vojvodina; [2]Department of Surgery, Faculty of Medicine, University of Novi Sad. Novi Sad, Serbia

Abstract

Objective: *The purpose of this study was to examine the surgical treatment of two-part and three-part proximal humerus fractures utilizing two approaches.* **Method:** *Study involved a total of 40 individuals. Twenty patients were treated with plates and screws and 20 with intramedullary locking nail osteosynthesis. We created 10 pairs of patients that were matched in age, gender, and fracture type, with the sole difference being the osteosynthetic material used. The mean follow-up was 4 years (1-9 years). We evaluated the results of treatment using Constant's scoring scale.* **Results:** *The mean value of Constant's scoring scale was 78.05 for patients treated with plates and screws and 67.55 for those treated with intramedullary stabilization. There was no statistically significant difference between the groups nor were there statistically significant differences in post-operative range of motion (ROM).* **Conclusions:** *The results of Constant's scoring scale were higher for patients whose fractures were stabilized with a plate and screws. The same group of patients had a higher degree of mobility and better ROM. Even while there was a general tendency toward better outcomes when using plates and screws for fixation, there was no indication as to which surgical technique offers the best results.*

Keywords: *Shoulder. Humeral head. Shoulder fractures. Intramedullary nailing. Internal fracture fixation.*

Resumen

Objetivo: *Examinar el tratamiento quirúrgico de fracturas de dos partes y tres partes del húmero proximal utilizando dos enfoques.* **Método:** *El estudio involucró un total de 40 pacientes, de los que 20 fueron tratados con placas y tornillos, y los otros 20 con osteosíntesis de clavo bloqueado intramedular. Se hicieron 10 pares de pacientes emparejados por edad, sexo y tipo de fractura, siendo la única diferencia el material de osteosíntesis utilizado. El seguimiento promedio fue de 4 años (rango: 1-9 años). Se evaluaron los resultados del tratamiento utilizando la escala de Constant.* **Resultados:** *El valor promedio de la escala de Constant fue de 78.05 para los pacientes tratados con placas y tornillos, y de 67.55 para aquellos tratados con estabilización intramedular. No hubo diferencia estadísticamente significativa entre los grupos, y tampoco hubo diferencias estadísticamente significativas en el rango de movimiento posoperatorio.* **Conclusiones:** *Las puntuaciones de la escala de Constant fueron más altas en los pacientes cuyas fracturas se estabilizaron con placa y tornillos. Estos pacientes tuvieron un mayor grado de movilidad y un mejor rango de movimiento. Aunque se observó una tendencia general hacia mejores resultados al usar placas y tornillos para la fijación, no hubo indicación de qué técnica quirúrgica ofrece los mejores resultados.*

Palabras clave: *Hombro. Cabeza humeral. Fracturas de hombro. Clavo bloqueado intramedular. Fijación interna de fracturas.*

***Correspondence:**
Srđan Ninković
E-mail: srdjan.orto@gmail.com

Date of reception: 20-08-2023
Date of acceptance: 29-11-2023
DOI: 10.24875/CIRUE.M23000792

Cir Cir (Eng). 2024;92(6):686-692
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Fractures of the proximal humerus are the second most common upper limb fractures in adults and make up 5% of all fractures[1]. The prevalence of these fractures is highest among the elderly, but the younger, more active population is becoming increasingly susceptible.

Shoulder fractures are fraught with controversy, not only in terms of the indications for surgery (that is, which fractures should or should not be operated on), but also in terms of the surgical procedures and implant choices that should be used for the fixation. Many different methods of treating proximal humerus fractures have been published in the medical literature, but there is still no consensus on the best way to treat these injuries[2-6]. The purpose of surgery is to achieve anatomic fracture reduction and stable primary fixation to accelerate the healing process and start post-operative rehabilitation as soon as possible, with the least amount of time spent in immobilization as possible[7,8].

The most frequently applied methods of osteosynthesis of proximal humeral fractures include minimally invasive techniques using K-wires, sutures and/or screws, plate fixation, intramedullary locking nails, or arthroplasty procedures (partial or reverse prosthesis). The choice of surgical approach is determined by fracture type, patient age, bone quality, comorbidities, and functional requirements[2,7,9-12].

The purpose of this study is to analyze the operative treatment of two- and three-part fractures of the proximal humerus, categorized by Neer[13], at the Clinic for Orthopedic Surgery and Traumatology, University Clinical Center of Vojvodina in Novi Sad, utilizing plates and screws and intramedullary nailing.

Method

The study was approved by the Ethics Committee of the University Clinical Center of Vojvodina. This retrospective analysis included 40 patients of both genders with displaced two-part and three-part fractures of the proximal humerus who were surgically treated between June 2010 and October 2019. Classification of fractures was based on a true AP and Y radiograph projection, validated by the same surgeon utilizing Neer classification[13]. The indication for surgical treatment was made according to the Neer criteria[13] –45° of humeral head angulation and 1 cm dislocation of fragments (head, greater, and lesser tubercles and the body of the humerus). Large tubercle dislocations > 5 mm were deemed to be unstable fracture patterns[6,14], and were an indication for surgical treatment. The study excluded patients with fractures that involved humeral diaphysis and articular surface of humeral head ("head splitting fractures"), patients with open or ipsilateral fracture of the same arm, polytraumatized patients, patients with neurovascular lesions of the operated arm, and those who had refused to participate in the survey.

Data for analysis were obtained from medical history, as well as during outpatient examinations at the Clinic for Orthopedic Surgery and Traumatology.

Osteosynthesis of the fracture was achieved using plate and screws or intramedullary locking nail (Fig. 1). Surgery was performed on the radiolucent table with the patient in the "beach chair" position. Deltopectoral approach was utilized for plating of the fractures, whereas the nailing was performed and managed through a minimally invasive anterolateral technique (deltoid splitting approach). During surgery, the position of fragments was verified with C-arm. Regardless of the type of osteosynthesis, post-operative Desault immobilization was indicated for a period of 4-6 weeks, with the upper arm in 45° of abduction, elbow in 90° of flexion, and neutral rotation of the forearm. The duration of immobilization depends on the fracture pattern, the patient's age, the quality of reduction, and the fixation strength. For the first 48 h, parenteral antibiotic prophylaxis, which included first-generation cephalosporins, was administered. Post-operative X-rays were made 10 days, after the surgery, after 3 and 6 weeks, 3 and 6 months postoperatively. The mean follow-up time was 4 years (1-9 years). All patients were operated on by the same surgeon.

We evaluated the results of treatment using Constant's scoring scale as well as Disabilities of the Arm, Shoulder, and Hand (DASH score)[15,16]. A goniometer was used to quantify range of motion (ROM), while muscular strength was determined by the amount of kg weight in kilograms, the patient could hold in 90° shoulder abduction[16]. Values of ROM and muscle[17] strength were compared between the operated and healthy shoulder. Constant's score is the difference between the values obtained after the examination of the healthy and operated shoulder and can be graded as excellent (< 11), good (12-20), fair (21-30), or poor (> 31). The DASH score is a numerical measure that assesses the disability and functional limitations of

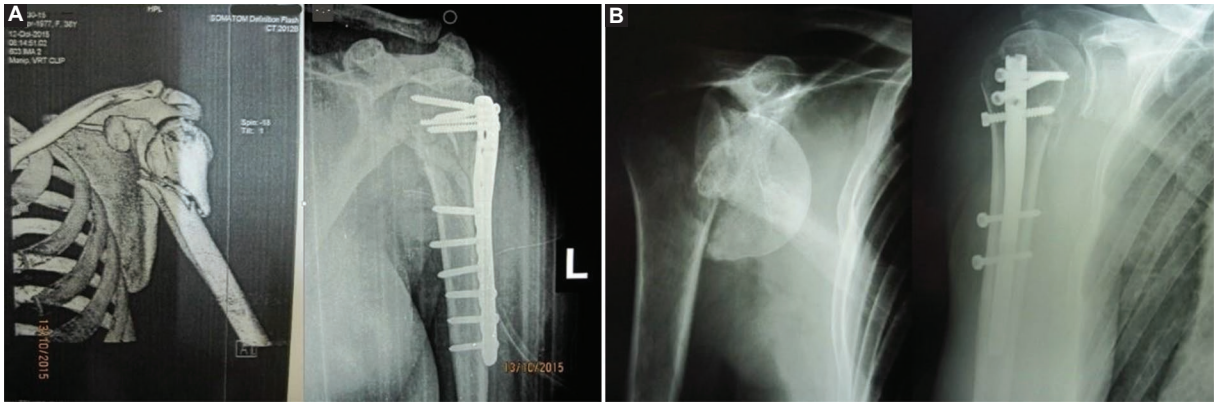

Figure 1. A: *plate and screws osteosynthesis.* **B:** *intramedullary locking nail osteosynthesis.*

the upper extremity, including the arm, shoulder, and hand, typically represented on a scale from 0 to 100, with higher scores indicating greater disability and lower function. The obtained results were statistically analyzed using the Student t-test and χ^2 test with a significance level of 0.05.

Results

Out of the 40 patients enrolled in this study, 16 were males (40%) and 24 were females (60%). Twenty patients were treated with a plate and screws and 20 with an intramedullary locking nail. We created 10 pairs of patients that were matched in age, gender, and fracture type, with the sole difference being the osteosynthetic material used (10 pairs with two-part dislocated fractures and 10 pairs with a dislocated three-part fracture, where it affected a lesser or greater humeral tubercle). The minimum follow-up time was 1 year.

The average age was 58 ± 13 years. The oldest participant was 77 years old and the youngest 28 years old. The average age of patients treated with plate and screw osteosynthesis was 58.2 ± 11.8 years, while the average age of patients treated with intramedullary locking nail was 59.4 ± 12.9 years. Considering the average body mass index (BMI), our sample fell into the overweight category (BMI = 26 ± 5). Of the patients included in study, 22 sustained injuries to their right arm, whereas 18 sustained injuries to their left arm. The dominant hand was injured in 60% of patients. The majority of patients did not engage in any sort of athletic participation activity –24. The large proportion of patients with a humerus fracture was recreational athletes[13], whereas only two were

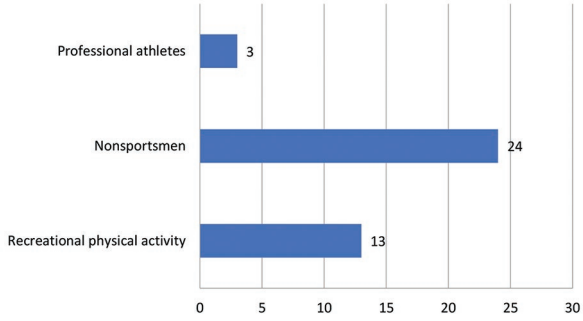

Figure 2. *The level of sport activity.*

professional athletes (Fig. 2). The leading causes of injury in our sample were falls (29 patients, 72.5%), motor vehicle accidents (eight patients, 20%), and recreational activities (three patients, 7.5%). The diagnosis of fractures of the proximal humerus was made on the day that the accident occurred, and the fractures were treated within 7 days of the injury.

The mean value of Constant's scoring scale was 78.05 in patients who were treated with plates and screws and 67.55 in patients treated with intramedullary nails. Statistical analysis did not find a significant difference between these two groups, although the Constant's score showed higher values in the patient group treated with plates and screws (Table 1).

The values of the DASH score are presented in table 2, and no statistically significant difference is observed between the two groups. The results are largely consistent with the Constant score, with slightly better outcomes observed in the group treated with plates and screws.

Table 1. Results of constant's scoring scale

Constant's scoring scale outcome	Plate osteosynthesis (%)	IM nail osteosynthesis (%)	Total (%)
Excellent	7 (35)	5 (25)	12 (30)
Good	5 (25)	3 (15)	8 (20)
Fair	3 (15)	3 (15)	6 (15)
Poor	5 (25)	9 (45)	14 (35)
Mean value	78,05	67,55	100
Total	20	20	40

Table 2. Results of DASH scoring scale

DASH scoring scale outcome	Plate osteosynthesis (%)	IM nail osteosynthesis (%)	Total (%)
Minimal to no disability	13 (65)	9 (45)	22 (55)
Mild disability	3 (15)	3 (15)	6 (15)
Moderate disability	3 (15)	5 (25)	8 (20)
Severe disability	1 (5)	3 (15)	4 (10)
Extreme disability	0	0	0
Total	20	20	40

DASH: disabilities of the arm, shoulder, and hand.

Table 3. Range of motion in observed groups

Motion type	Cumulative range of motion - Plate Group	Cumulative range of motion - Nail Group
Flexion (°)	135.45 ± 42.5	119.7 ± 45.6
Abduction (°)	123.4 ± 45.5	113.75 ± 45.6
External rotation (°)	52.25 ± 14.5	41.7 ± 18.3
Internal rotation (°)	65 ± 17.6	61 ± 19.2

There was no statistically significant difference in the ROM between groups, although it tended to be larger in the group of patients treated with plate and screw osteosynthesis (Table 3).

We observed complications in four patients. Superficial wound infection was observed in two patients in the screw and plate fixation group. Chronic pain due to migration of osteosynthetic material was found in two patients treated with intramedullary nail.

During the follow-up, neither delayed union nor nonunion was noted in any of the patients.

Discussion

Upper arm fractures are of major significance in contemporary orthopedic trauma because they are one of the most prevalent causes of morbidity and disability in the elderly and can have severe repercussions in young, working populations[18]. The primary aim of surgical therapy for fractures of the proximal humerus is to achieve anatomic fracture reduction and stable fixation that allows early functional rehabilitation. Modern implants for extramedullary and intramedullary fracture stabilization provide optimum stability, while less invasive surgical techniques promote rapid bone healing and excellent revascularization[7,19].

Out of 40 patients included in our study, 20 of them were treated with plate and screw osteosynthesis of the proximal humerus. They achieved Constant's score value of 78.05. Südkamp et al.[20] studied the outcomes of 1087 patients who received surgical treatment for proximal humerus fractures with plate and screw fixation and observed an average Constant's score of 70.6, which is lower compared to our results.

This disparity in outcome results may be due to the absence of grouping based on fracture type in the aforementioned paper, which included more complex fracture patterns, as well as a significantly larger sample size. This difference in sample size may account for our overestimation of Constant's score in comparison. A recent study[21] which retrospectively analyzed 28 patients who were treated with second generation nails reported an average Constant's score of 83.1 at 1-year follow-up. Advances in operative technique over the years resulted in better overall results in patients treated with an intramedullary nail. Guo et al.[21] also showed that there was no statistical significance when comparing the nail to the plate and screw fixation.

Gradl et al.[22] compared the treatment results of 152 patients who underwent surgery with plates and screws and intramedullary nails. The average value of Constant's scoring scale for plate fixation was 77%, and for nail fixation, it was 81%. Despite the better score value for patients treated with nail fixation, this difference did not reach statistical significance. Trepat et al.[23], in their study involving 29 patients, also found no statistically significant difference in results between the two treatment techniques. In a 2016

randomized controlled trial evaluating 72 patients, Gracitelli et al.[24] reported that there was no significant mean difference in the Constant-Murley score at the 12-month follow-up (70.3 points for the nail group vs. 71.5 points for the plate group; p = 0.750). Our results indicate no statistically significant difference in outcome between patients treated with plate and screw fixation (78.05) and intramedullary nailing (67.55), confirming the findings of the previously mentioned studies. In contrast to our results, Boileau et al.[18] demonstrated a better post-operative outcome in patients treated with plate and screw fixation. They justified their results by emphasizing the importance of accurate reduction and strong fixation of the greater tubercle, leading to smaller/negligible loss of abduction and external rotation, and consequently, better functional results.

In accordance with the findings of prior investigations[25], older patients in our study had worse Constant score outcomes. Several studies comparing locking plates to third-generation intramedullary nails concluded that there is a high risk of secondary displacement and fracture non-union in elderly patients with poor bone quality[26,27]. This can be a consequence of reduced regenerative capacity of the tissues in these patients, reduced motivation, and the presence of comorbidities.

In our study, we included the DASH score as an additional tool for evaluating treatment outcomes in patients with proximal humerus fractures, alongside the commonly used Constant score. We compared the results of the DASH scores between two distinct groups of participants and found that there was no statistically significant difference between them. This finding is in line with previous research on the subject[24,28]. Furthermore, it is worth noting that the results obtained from the DASH score assessment were consistent with those obtained from the Constant score assessment in both groups of participants.

Lekic et al.[29] conducted a retrospective study that included 24 shoulders, divided into equal groups of 12 treated with intramedullary nail osteosynthesis and 12 treated with a locking plate. They assessed the ROM in these patients, specifically forward elevation of the arm, and compared the two groups. The average forward elevation of the arm in patients treated with intramedullary nail fixation was 134° (range, 60-160) and with locking plate was 141° (range, 90-180), showing no statistically significant difference. A similar outcome was observed in flexion (forward elevation) with 119.7° in patients treated with intramedullary nail osteosynthesis and 135.5° in patients treated with plate and screw fixation. In a retrospective study, Schulte et al.[30] included 43 patients who underwent plate and screw osteosynthesis. The average flexion in their patients was 140°, and external rotation was 58°, which was comparable to the results we measured: an average flexion of 135.5° and external rotation of 52.2°. For the majority of everyday tasks requiring shoulder flexion and abduction up to 90°, patients in our research were able to fully and independently execute necessary daily activities.

We observed complications in four patients (10%). Superficial wound infections were found in two patients in screw and plate fixation group and were treated conservatively with regular dressing changes and administration of antibiotics. Two patients treated with an intramedullary nail reported the presence of chronic pain, a consequence of the migration of osteosynthetic material. These patients were treated symptomatically with non-steroidal anti-inflammatory drugs and cryotherapy. Upon radiographic evidence of fracture healing union, the osteosynthetic material was removed, resulting in complete pain relief.

Our study showed no statistical difference in the complication rates in either group of patients, but the complications in the nail group required reoperation. Our results are consistent with those of Gracitelli et al.[24] who showed a higher complication rate in the nail group with no statistical difference, emphasizing the fact that there were more complications in the nail group that required reoperation.

Lekic et al.[29] in their sample of 24 shoulders, 12 had undergone intramedullary nailing, with 5 of them (42%) encountering complications. Two patients in this group (16.6%) had deltoid muscle calcification, which resulted in mild pain: one patient (8.3%) experienced painful heterotopic ossification within the subacromial area and two patients (16.6%) acquired painful hardware in the proximal shoulder.

In the same study, there was also report of locking plate technique complication, in shoulders (33%): screw penetration in joint cavity in (three [25%] and one asymptomatic head osteonecrosis [8.3%]). Our results show a 10% of complication rate, which is substantially lower than found by Lekic et al. (37%). Upon reviewing the paper, we could not find any drastic deviation in the operative protocol (osteosynthesis used or operative approach) nor could we find any significant deviation in the patient sample. Despite the complication observed in this study, all fractures demonstrated complete union by 3 months.

Our results also show that union was achieved in all fractures by 4 months.

Studies that used rigid fixation generally showed an incidence of osteonecrosis of the humeral head ranging from 0% to 25%[2,7,9]. In our sample, we did not have partial nor complete osteonecrosis of the humeral head. We hypothesize that the higher incidence of osteonecrosis in procedures with rigid osteosynthesis (IMF and LP) may be the result of implant cutout, which can occur in 7-25%[29,31], more aggressive tissue dissection, but could also be attributable to the longer follow-up time in these studies. Egol et al.[31] identified glenohumeral cutout in 16% of patients following angular stable plate fixation; however, only 50% of these patients underwent revision surgery. The author explains that a high rate of screw penetration can be attributed to poor bone stock. In the case of antegrade nailing, Mittlmeier et al.[8] advised not overdrilling the medial cartilage and selecting fixation screws 2-3 mm shorter than planned.

Numerous studies have examined which implant produces the best outcome for specific types of fractures, and they have all reached the same conclusion: with three-part fractures, osteosynthesis with plate and screws yields better outcomes, but with two-part fractures (fractures of the surgical neck), intramedullary nailing yields superior results and faster recovery[2,7,13]. While analyzing our results, we could neither confirm nor deny the superiority of one particular method, but from clinical experience, we share the same opinion as the above authors. In addition to this conclusion, we emphasize that even though better results are achieved with intramedullary fixation in the treatment of two part fractures, the occurrence of complications when using IM nails in our study showed a greater need for reoperation. These complications increase the risks for patients and the cost of overall treatment.

Constraints of this study include its retrospective nature and its relatively small sample size, both of which may hinder a better understanding of the effectiveness of particular operative techniques. Nevertheless, despite these limitations, the study has provided us with valuable insight and direction for future research.

Conclusion

Our results show that patients with plate and screw fracture stabilization had a higher Constant score, as well as DASH score, than patients where locking intramedullary nail is used, without statistical significance. The same group of patients had a higher degree of mobility compared to those who underwent intramedullary nail surgery but also without statistical significance. All these factors points to plate fixation as a potential superior choice of osteosynthesis. However, due to more frequent complication with plate fixation in the form of implant cutout and osteonecrosis, there is still no consensus on which operative technique and type of implant give the best results in the surgical treatment of these fractures.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Charles MC, James DH, Margaret MM, William MR, Paul T, Michael DM. Rockwood and Green's Fractures in Adults. 8th ed. Philadelphia, PA, USA: Wolters Kluwe Health; 2015.
2. Björkenheim JM, Pajarinen J, Savolainen V. Internal fixation of proximal humeral fractures with a locking compression plate: a retrospective evaluation of 72 patients followed for a minimum of 1 year. Acta Orthop Scand. 2004;75:741-5.
3. Gerber C, Werner CM, Vienne P. Internal fixation of complex fractures of the proximal humerus. J Bone Joint Surg Br. 2004;86:848-55.
4. Gierer P, Simon C, Gradl G, Ewert A, Vasarhelyi A, Beck M, et al. Complex proximal humerus fractures-- management with a humeral head prosthesis? Orthopade. 2006;35:834-40.
5. Hessmann MH, Blum J, Hofmann A, Kuchle R, Rommens PM. Internal fixation of proximal humeral fractures: current concepts. Eur J Trauma. 2003;29:253-61.
6. Resch H, Povacz P, Frohlich R, Wambacher M. Percutaneous fixation of three- and four-part fractures of the proximal humerus. J Bone Joint Surg Br. 1997;79:295-300.
7. Lill H, Hepp P, Rose T, Konig K, Josten C. The angle stable locking-proximal-humerus-plate (LPHP) for proximal humeral fractures using a small anterior-lateral-deltoid-splitting-approach: technique and first results. Zentralbl Chir. 2004;129:43-8.
8. Mittlmeier TW, Stedtfeld HW, Ewert A, Beck M, Frosch B, Gradl G. Stabilization of proximal humeral fractures with an angular and sliding stable antegrade locking nail (Targon-PH). J Bone Joint Surg Am. 2003;85:136-46.

9. Gradl G, Dietze A, Arndt D, Beck M, Gierer P, Borsch T, et al. Angular and sliding stable antegrade nailing (Targon PH) for the treatment of proximal humeral fractures. Arch Orthop Trauma Surg. 2007;127:937-44.
10. Stedtfeld HW, Mittlmeier T. Fixation of proximal humeral fractures with an intramedullary nail: tipps and tricks. Eur J Trauma Emerg Surg. 2007;4:367-74.
11. Tamai K, Ohno W, Takemura M, Mashitori H, Hamada J, Saotome K. Treatment of proximal humeral fractures with an intramedullary nail. J Orthop Sci. 2005;10:180-6.
12. Wijgman AJ, Roolker W, Patt T, Raaymakers E, Marti R. Open reduction internal fixation of three and four part fractures of the proximal part of the humerus. J Bone Joint Surg Am. 2002;84:1919-25.
13. Neer CS 2nd. Four-segment classification of proximal humeral fractures. J Shoulder Elbow Surg. 2002;11:389-400.
14. Hintermann B, Trouillier HH, Schafer D. Rigid internal fixation of fractures of the proximal humerus in older patients. J Bone Joint Surg Br. 2000;82:1107-12.
15. Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. Clin Orthop. 1987;214:160-4.
16. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UEGG). Am J Ind Med. 1996;29:602-8. Erratum in: Am J Ind Med. 1996;30:372.
17. Klobučar H. Istraživanje Čvrstoće Fiksacije Tetive Infraspinatusa Ovce Transosealnom Metodom i Metodom Dva Reda Koštanih Sidara [dissertation]. Zagreb, Rep. Hrvatska: Sveučilište u Zagrebu, Medicinski Fakultet; 2009.
18. Boileau P, Pennington SD, Alami G. Proximal humeral fractures in younger patients: fixation techniques and arthroplasty. J Shoulder Elbow Surg. 2011;20:S47-60.
19. Kettler M, Biberthaler P, Braunstein V, Zeiler C, Kroetz M, Mutschler W. Treatment of proximal humeral fractures with the PHILOS angular stable plate: presentation of 225 cases of dislocated fractures. Unfallchirurg. 2006;109:1032-40.
20. Südkamp N, Bayer J, Hepp P, Voigt C, Oestern H, Kääb M, et al. Open reduction and internal fixation of proximal humeral fractures with use of the locking proximal humerus plate. Results of a prospective, multicenter, observational study. J Bone Joint Surg Am. 2009;91:1320-8.
21. Guo Z, Sang L, Meng Q, Tian L, Yin Y. Comparison of surgical efficacy of locking plates and interlocking intramedullary nails in the treatment of proximal humerus fractures. J Orthop Surg Res. 2022;17:481.
22. Gradl G, Dietze A, Kääb M, Hopfenmüller W, Mittlmeier T. Is locking nailing of humeral head fractures superior to locking plate fixation. Clin Orthop Relat Res. 2009;467:2986-93.
23. Trepat AD, Popescu D, Fernandez-Valencia JA, Cune J, Rios M, Prat S. Comparative study between locking plates versus proximal humeral nail for the treatment of 2-part proximal humeral fractures. Eur J Orthop Surg Traumatol. 2012;22:373-9.
24. Gracitelli ME, Malavolta EA, Assunção JH, Kojima KE, dos Reis PR, Silva JS, et al. Locking intramedullary nails compared with locking plates for two- and three-part proximal humeral surgical neck fractures: A randomized controlled trial. J Shoulder Elbow Surg. 2016;25:695-703.
25. Grawe B, Le T, Lee T, Wyrick J. Open reduction and internal fixation (ORIF) of complex 3- and 4-part fractures of the proximal humerus. Does age really matter? Geriatr Orthop Surg Rehabil. 2012;3:27-32.
26. Bu G, Sun W, Li J, Yang T, Li M, Wei W. MutiLoc nail versus philos plate in treating proximal humeral fractures: a retrospective study among the alderly. Geriatr Orthop Surg Rehabil. 2021;12:21514593211043961.
27. Davey MS, Hurley ET, Anil U, Condren S, Kearney J, O'Tuile C, et al. Management options for proximal humerus fractures - A systematic review & network meta-analysis of randomized control trials. Injury. 2022;53:244-9.
28. Sun Q, Ge W, Li G, Wu J, Lu G, Cai M, et al. Locking plates versus intramedullary nails in the managemet of displaced proximal humeral fractures: a systematic review and meta-analysis. Int Orthop. 2018;42:641-50.
29. Lekic N, Montero NM, Takemoto RC, Davidovitch RI, Egol KA. Treatment of two-part proximal humerus fractures: intramedullary nail compared to locking plate. HSS J. 2012;8:86-91.
30. Schulte LM, Matteini LE, Neviaser RJ. Proximal periarticular lolocking plates in proximal humeral fractures: functional outcomes. J Schoulder Elbow Surg. 2011;20:1234-40.
31. Egol KA, Ong CC, Walsh M, Jazrawi LM, Tejwani NC, Zuckerman JD. Early complications in proximal humerus fractures (OTA Types 11) treated with locked plates. J Orthop Trauma. 2008;22:159-64.

ORIGINAL ARTICLE

Interobserver variation in the Parkland scale. Are we seeing the same thing?

Variación interobservador en la escala de Parkland. ¿Estamos viendo lo mismo?

*José L. Maldonado-Calderón[1], Lydia E. Nava-Rivera[2], Antonio Urbina-Zeglen[1], Marco V. Herrera-Santos[1], Pilar Carranza-Rosales[3], Javier Morán-Martínez[2], and Nadia D. Betancourt-Martínez[2]**

[1]Departamento de Cirugía, Hospital General Universitario Dr. Joaquín Del Valle Sánchez, Facultad de Medicina, Universidad Autónoma de Coahuila (UAdeC), Torreón, Coahuila; [2]Departamento de Biología Celular y Ultraestructura, Facultad de Medicina, UAdeC, Torreón, Coahuila; [3]Departamento de Biología Celular y Molecular, Centro de Investigación Biomédica del Noreste, Instituto Mexicano del Seguro Social. Monterrey, Nuevo León. México

Abstract

Objective: *The aim of this study was to analyze the reliability of agreement between surgeons when using the Parkland Grading Scale for Acute Cholecystitis (PGS-AC).* **Method:** *A total of 43 images taken out of videos of laparoscopic cholecystectomies (LCs) were collected, they were used to frame an online questionnaire that was sent to 18 surgeons and resident doctors who classified the images according to the Parkland scale criteria, followed by the evaluation of concordance between observers applying the Fleiss κ test.* **Results:** *A global Fleiss' κ value of 0.213 was obtained, which corresponds to a low interobserver concordance. Factors such as being a surgical resident, having more than 10 years of experience performing this type of procedure, or performing more than 2 LCs per week, were related to greater concordance in diagnosis.* **Conclusions:** *The low concordance found when using the Parkland grading scale, translates into a high interobserver variation related to multiple variables, which is why, we are not seeing the same.*

Keywords: *Cholecystectomy. Interobserver variation. Acute. Parkland scale.*

Resumen

Objetivo: *Analizar la fiabilidad de la concordancia entre cirujanos al utilizar la PGS-AC (Parkland Grading Scale for Acute Cholecystitis).* **Método:** *Se recolectaron 43 imágenes extraídas de vídeos de colecistectomías laparoscópicas y se realizó un cuestionario en línea que se envió a 18 cirujanos y médicos residentes, quienes clasificaron las imágenes según los criterios de la PGS-AC. Se evaluó la concordancia entre observadores aplicando la prueba kappa de Fleiss.* **Resultados:** *Se obtuvo un valor kappa de Fleiss global de 0.213, lo que corresponde a una baja concordancia interobservador. Factores como ser residente de cirugía, tener más de 10 años de experiencia realizando este tipo de procedimientos o realizar más de dos colecistectomías laparoscópicas por semana se relacionaron con una mayor concordancia en el diagnóstico.* **Conclusiones:** *La baja concordancia encontrada al utilizar la PGS-AC se traduce en una alta variación interobservador relacionada con múltiples variables, por lo que no estamos viendo lo mismo.*

Palabras clave: *Colecistectomía. Variación interobservador. Aguda. Escala de Parkland.*

Correspondence:
Nadia D. Betancourt-Martínez
E-mail: nabetancourtm@uadec.edu.mx

Date of reception: 18-07-2023
Date of acceptance: 25-08-2023
DOI: 10.24875/CIRUE.M23000794

Cir Cir (Eng). 2024;92(6):693-698
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Laparoscopic cholecystectomy (LC) has been proposed as the gold standard for the treatment of symptomatic cholelithiasis[1]. More than 750,000 LCs are performed each year in the United States[2], making this one of the most common elective surgeries in the world. Among the indications for LC is acute cholecystitis (AC), for which precise diagnostic criteria and management algorithms based on its severity have been established[3,4]. There are several classifications for AC, such as that of the American Association for the Surgery of Trauma, which includes clinical, imaging, intraoperative, and pathology description[5]. However, due to its complexity and the large number of variables involved, it has not yet been adopted by the surgical community on a wider scale. Recently, a classification of intraoperative findings, called the Parkland grading scale for AC (PGS-AC), has been proposed to determine and grade the difficulty of LC[6]. This scale (validated in 2019) consists of five grades, of which, grade 1 represents a normal gallbladder (GB) and grade 5 the most severe grade[7]. However, due to the short time, it has been established, the PGS-AC is not exempt from being evaluated for possible biases in its application through concordance studies[8]. The aim of this study was to analyze the evaluations of surgeons and their reliability of agreement in rating 43 cholecystectomies using the PGS-AS.

Method

Place of study

The study was carried out in the General Surgery service of the General University Hospital of the Faculty of Medicine of the Autonomous University of Coahuila Campus Torreón; Torreón, Coahuila, Mexico.

Selection of the samples

Videos of LCs performed between 2020 and 2021 were randomly selected. From these videos, 43 images were obtained under the following criteria:

- Make a screenshot of the image that best represents the grade according to the Parkland scale (always before starting the dissection)
- Check that the instruments did not interfere with the image visualization.

Questionnaire framing

With the obtained images, a questionnaire was framed as a tool to classify each image in one of the 4° according to the PGS or to classify the image as unclassifiable. This questionnaire was applied to 13 surgeons and five residents of the region who met the following inclusion criteria: being a surgeon or resident doctor, performing laparoscopic surgery, and operating in hospitals in the region.

Ethical considerations

The protocol was approved by the Bioethics Committee of the School of Medicine of the Autonomous University of Durango Campus Laguna with reference number 130/20.

Statistical analysis

The data obtained from the questionnaires were analyzed using the statistical package IBM SPSS statistics version 26. Descriptive statistics was used such as mean, standard deviation, and percentage frequencies. To evaluate the concordance between the evaluators (n = 18), the Fleiss' κ statistic was used. The global and individual κ value was determined for each classification category (unclassifiable and grade IV), stratifying by age, gender, grade, subspecialty, years of experience, number of surgeries performed per week, and work sector. Comparisons of κ values between strata were made using the z-test for two samples.

Results

In this study, a total of 18 evaluators were included for the rating of 43 images, obtaining a total of 774 data points. The mean age of the participating evaluators was 38.50 ± 11.66 years and 58.8% of the sample were male. Most of the observers have a medical specialty (72.2%) and 27.8% complete their medical residency. Of the total number of specialists, 38.5% have a subspecialty such as advanced laparoscopy and endoscopy. The average years of experience of the evaluators was 10.17 ± 10.93 with an average number of surgeries per week of 2.22 ± 1.35. 22.2% of the evaluators sample work in public hospitals, whereas 61.1% work in public and private hospitals (Table 1).

The global values of Fleiss' κ in which all the degrees of the Parkland scale are included, as well

Table 1. Characteristics of the evaluators

Variable	n	Half	OF	Minimum	Maximum
Age (years)	18	38.50	11.66	26.00	63.00
Gender					
Feminine	8 (41.2)				
Male	10 (58.8)				
Residency	5 (27.8)				
Residence grade (year)	5	2.20	1.30	1.00	4.00
Specialty	13 (72.2)				
Subspecialty	5 (38.5)				
Years of experience	18	10.17	10.93	0.00	31.00
Number of surgeries per week	18	2.22	1.35	0.00	5.00
Work sector					
Private	3 (16.37)				
Public	4 (22.2)				
Both	11 (61.1)				

Values are presented as mean and SD (standard deviation) or frequencies (%).

Table 2. Overall values (including all grades) of Fleiss' κ, stratified by different variables

Variable	Overall value of Fleiss' κ	CI 95%	p[sa]
Global	0.213	0.212-0.213	< 0.0001
Age (years)			
≥ 38	0.251	0.250-0.252	< 0.0001
< 38	0.203	0.202-0.203	< 0.0001
Gender			
Feminine	0.209	0.209-0.210	< 0.0001
Male	0.204	0.204-0.205	< 0.0001
Degree			
Home	0.162	0.161-0.164	< 0.0001
Specialty	0.231*	0.231-0.232	< 0.0001
Subspecialty			
With Subspecialty	0.190	0.189-0.192	< 0.0001
No subspecialty	0.215	0.214-0.215	< 0.0001
Years of experience			
≤ 10 years	0.186	0.186-0.187	< 0.0001
> 10 years	0.274†	0.272-0.275	< 0.0001
Number of surgeries per week			
≤ 2	0.165	0.164-0.166	< 0.0001
> 2	0.249‡	0.248-0.250	< 0.0001
Work sector			
Private/Public	0.190	0.190-0.191	< 0.0001
Both	0.255†	0.254-0.256	< 0.0001

*p < 0.001. †p < 0.0001. ‡p < 0.00001, when comparing between categories; 95% CI: 95% confidence intervals. a: p value of the Fleiss' κ statistic.

as the "unclassifiable" category, are shown in table 2. The global value was 0.213 (CI 95 %: 0.212-0.213) (p < 0.0001), indicating a weak strength of concordance. The global Fleiss' κ was calculated, stratifying by age, gender, degree, subspecialty, years of experience, number of surgeries performed per week, and work sector. The level of agreement for all strata ranged from slight (κ ≤ 0.20) to fair (κ = 0.21-0.40). For comparisons of the κ value between strata, the reliability of agreement was higher for specialists in contrast to residents (0.231 [0.231-0.232] vs. 0.162 [0.161-0.164], respectively), as for the category of > 10 years of experience compared to the category of ≤ 10 years (0.274 [0.272-0.275] vs. 0.186 [0.186-0.187], respectively). In addition, statistically significant differences between the global κ values were found for: number of surgeries performed per week, with this variable's results being higher for the category of > 2 surgeries in contrast to ≤ 2 (0.249 [0.248-0.250] vs. 0.165 [0.164-0.166], respectively); as well as for work sector, where those evaluators who work in private and public sectors have a significantly higher value of κ, than surgeons who work in a single sector (private or public) (0.255 [0.254-0.256] vs. 0.190 [0.190-0.191], respectively) (Table 2).

For the concordance assessment by individual categories (grade IV and unclassifiable), the highest κ values were for the categories of greater severity, grades IV and V (0.248 [0.248-0.249] vs. 0.405 [0.404-0.405], respectively); indicating weak to moderate concordance for these categories (Fig. 1A). When stratifying by age, it was found that older evaluators (≥ 38 years) tend to have greater concordance in classifying grades II, IV, and V (κ = 0.262 [0.260-0.264], 0.398 [0.396-0.4] and 0.512 [0.510-0.514], respectively), and significantly lower for unclassifiable cases (κ = 0.141 [0.140-0.143]) compared to younger evaluators (κ = 0.144 [0.254-0.257], 0.167 [0.166-0.169], 0.397 [0.396-0.399], and 0.249 [0.246-0.251]) (p < 0.0001) (Fig. 1B). According to gender, female evaluators have lower concordance for grades IV and V (κ = 0.176 [0.174-0.178] and 0.292 [0.291-0.294]) and a higher concordance when classifying in grade III as well as in unclassifiable (κ = 0.223 [0.221-0.225] and 0.287 [0.285-0.269]) compared to the male evaluators (κ = 0.282 [0.280-0.283], 0.527 [0.526-0.529], 0.109 [0.108-0.111], and 0.108 [0.106-0.109]) (p < 0.0001) (Fig. 1C). On the other hand, specialists tend to have greater agreement when evaluating grades I-II and IV (κ = 0.247 [0.246-0.248],

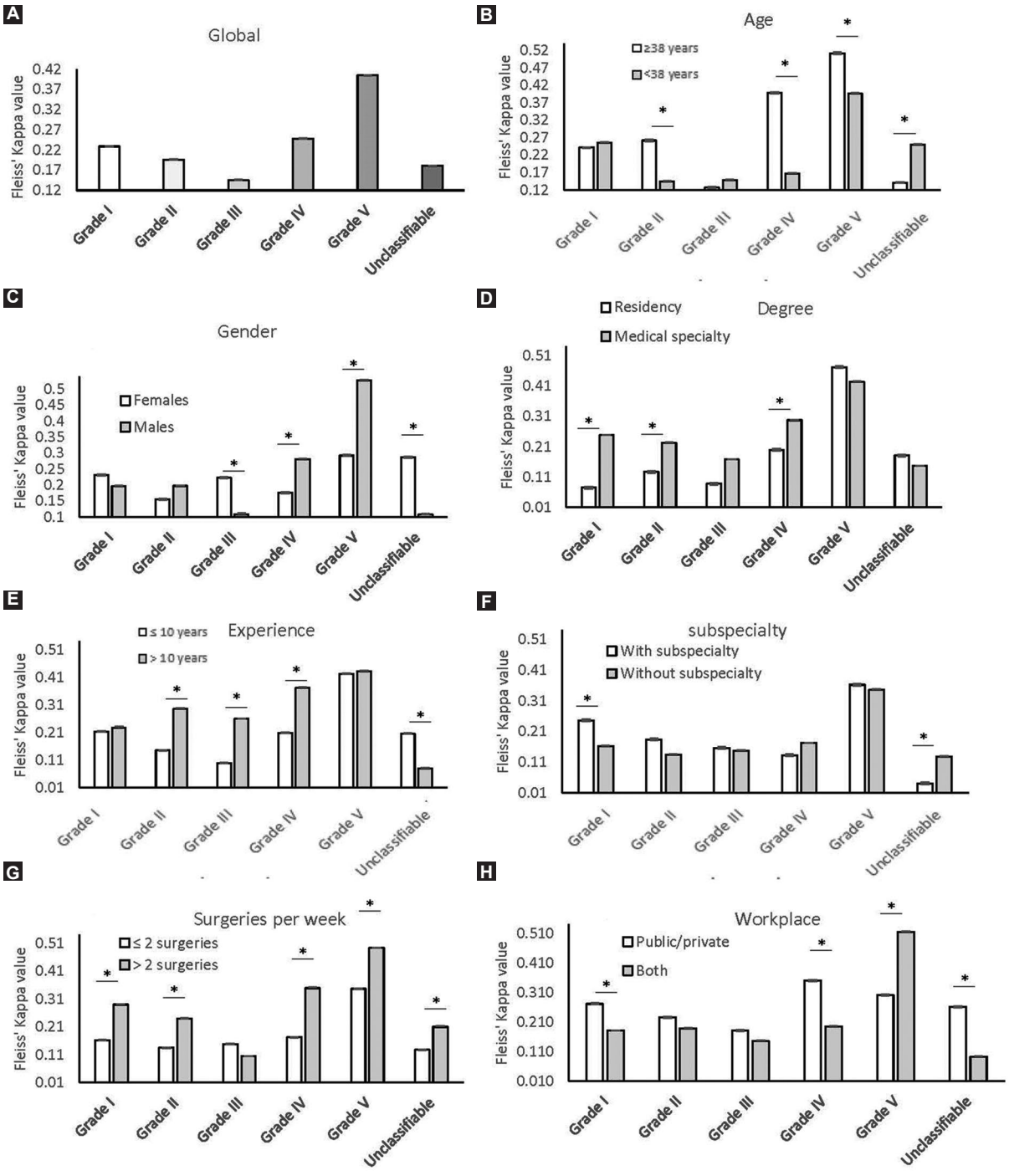

Figure 1. *Fleiss κ values by category of the Parkland scale and stratifying by different variables.* **A:** *κ values of the total sample.* **B:** *κ values by age strata.* **C:** *gender.* **D:** *degree.* **E:** *experience as a surgeon.* **F:** *subspecialty.* **G:** *surgeries performed per week.* **H:** *health sector (private/public). (*p < 0.0001).*

0.222 [0.221-0.224], and 0.297 [0.296-0.298]) compared to residents (κ = 0.075 [0.072-0.078], 0.127 [0.124-0.130], and 0.199 [0.196-0.202]) (p < 0.0001) (Fig. 1D).

Surgeons with more than 10 years of experience maintain higher concordance when evaluating grades II-IV (κ = 0.296 [0.293-0.298], 0.259 [0.256-0.261], and 0.372 [0.369-0.374]) and a lower concordance the unclassifiable category (κ = 0.080 [0.077-0.082]) in contrast to evaluators with less experience (κ = 0.146 [0.144-0.147], 0.099 [0.096-0.1], and 0.209 [0.208-0.210])

($p < 0.0001$) (Fig. 1E). For surgeons with a subspecialty, agreement is higher for grade I (0.246 [0.243-0.249]) and significantly lower for the unclassifiable category ($\kappa = 0.04$ [0.037-0.043]) compared to evaluators without a subspecialty ($\kappa = 0.221$ [0.220-0.222] and 0.190 [0.189-0.191]) ($p < 0.0001$) (Fig. 1F). Performing more than two surgeries a week is related to greater concordance classifying with all grades except for grade III ($\kappa = 0.289$ [0.287-0.291], 0.239 [0.237-0.240], 0.349 [0.347-0.351] 0.492 [0.490-0.494], and 0.210 [0.208-0.212]) compared to surgeons performing two or fewer surgeries per week ($\kappa = 0.162$ [0.160-0.163], 0.134 [0.133-0.136], 0.172 [0.170-0.173], 0.346 [0.345-0.348], and 0.127 [0.126-0.129]) ($p < 0.0001$) (Fig. 1G). The evaluators who work in a single hospital (public or private), have a greater concordance for grades I, IV, and for the category of not classifiable ($\kappa = 0.270$ [0.268-0.273], 0.350 [0.348-0.352], and 0.260 [0.258-0.263]) and significantly lower for grade V ($\kappa = 0.3$ [0.298-0.302]) compared to surgeons who work in public and private hospitals ($\kappa = 0.180$ [0.179-0.181], 0.194 [0.193-0.196], 0.092 [0.09-0.093], and 0.514 [0.512-0.515]) ($p < 0.0001$) (Fig. 1H).

Discussion

The Parkland scale for AC is based on intraoperative findings during a LC and consists of five grades which predict surgical difficulty, while helping to predict the need for conversion to open surgery. Requesting help early on during the surgery from more experienced surgeons can predict better post-operative results, improve surgeon reimbursement, or have even been reported to be useful for discriminating the severity of the disease itself[8]. The scale has an interclass correlation coefficient of 0.804 (95% CI: 0.733-0.867; $p = 0.0001$)[6], as reported by Madni et al., during the imagological evaluation of severely inflamed GBs. In contrast, in this study, a low interobserver concordance was found, according to the κ index, which resulted in 0.213 (95% CI: 0.212-0.213) ($p < 0.0001$). This last value also contrasts with that reported by Baral et al.[9], who conclude that this scale is useful for predicting possible post-operative outcomes such as white blood cell's augment, conversion to open surgery, subtotal cholecystectomy, duration of surgery, and bile leaks in patients undergoing LC in rural settings. However, in this last study, the variation between the four surgeons, all belonging to the same institution, was not evaluated, in addition to the fact that most of the images were classified by a single individual, which represents a great bias during the evaluation; even more so due to what was found in the present study, in which the factor "place of work," propitiates a significant variation for higher grade classifications. On the other hand, the potential of this scale to discriminate the severity of AC has been reported, however, as in the previous study, only two highly experienced surgeons were included, performing more than 300 surgeries per year, as reported by the authors, although concordance between both surgeons was not analyzed[10]. The reported experience agrees with what was obtained in this study, which states that the experience of observers with more than 10 years of experience maintains a greater concordance between them for the identification of intermediate categories, which are the most difficult to classify. Being consistent to Madni et al., who also reported that the surgeons who evaluated, these images belonged to the same division of burns, trauma, and intensive care of the same institution, which could have added bias to their assessment. In our work, the observers belonged to different institutions, both public and private in the region, which we consider a strength to our favor. Another aspect that strengthens the development of our work is the number of observers. Since there were 18 observers evaluating 43 images, we were able to obtain 774 data points to analyze, compared to what was done by other studies, in which 550 data points were obtained[6]. In the study conducted by Madni et al., observations were obtained from a retrospective review of intraoperative "initial views" (still images) of the GB. However, it was decided to carry it out in this format to identify the inter-observer variation among a greater number of professionals, as well as the factors involved in this subjectivity, similar to our strategy.

Modifications to the scale have been proposed to make each grade more objective and specific. In concordance with Sugrue et al., we propose a modification to the PGS based on the "type" quality of the adhesions, since sometimes loose adhesions that are easy to remove decrease in grade as they are removed without much effort at the beginning of the dissection, which completely changes the perspective of having an initial view with a high Parkland when performing a CL with a low Parkland after a shallow dissection. Thus, we propose the subclassification of each grade, starting from grade II in firm or loose adhesions[8]. In addition, an issue we consider important is the name, since this tool was proposed as the Parkland Scale for cholecystitis, however, as

surgeons we know that a significant portion of LCs is due to scheduled surgeries for symptomatic cholelithiasis, not only due to AC, and at the time of LCs, there can be changes due to recurrent biliary colic and/or previous AC (adhesions) and not precisely acute inflammatory changes. This is confirmed by histopathological analysis since most of the LCs performed are reported as chronic cholecystitis. Due to this, we propose to rename the Parkland scale for cholecystitis to the Parkland scale for LC. We do not question the usefulness of the Parkland scale as a tool for the intraoperative stage of LC; however, it should be used with more caution and be subjected to public scrutiny to the framing of similar studies that test its accuracy before using it in an indiscriminate and universal way. To the best of our knowledge, this is the first study that tests the interobserver variation of the Parkland scale, and the consideration of variables that could influence this variation; however, we consider the important to carry out a multicenter study, with a greater number of observers considering previous experience using the scale, to be able to extrapolate this data.

Conclusion

There is little concordance between observers when the PGS is applied, which translates into a high inter-observer variation related to variables such as their age, gender, professional degree, experience, and place of work. In response, we are not seeing the same.

Acknowledgments

The authors thank the Department of Surgery of the Hospital General Universitario Joaquín del Valle Sánchez in Torreón, Coahuila, Mexico, for their willingness and collaboration in the development of this study.

Funding

The authors declare that there was no financial support for this study.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Sanford DE. An update on technical aspects of cholecystectomy. Surg Clin North Am. 2019;99:245-58.
2. Moghul F, Kashyap S. Bile duct injury. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
3. Gutt C, Schläfer S, Lammert F. The treatment of gallstone disease. Dtsch Arztebl Int. 2020;117:148-58.
4. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25:41-54.
5. Tominaga GT, Staudenmayer KL, Shafi S, Schuster KM, Savage SA, Ross S, et al. The American association for the surgery of trauma grading scale for 16 emergency general surgery conditions: disease-specific criteria characterizing anatomic severity grading. J Trauma Acute Care Surg. 2016;81:593-602.
6. Madni TD, Leshikar DE, Minshall CT, Nakonezny PA, Cornelius CC, Imran JB, et al. The Parkland grading scale for cholecystitis. Am J Surg. 2018;215:625-30.
7. Madni TD, Nakonezny PA, Barrios E, Imran JB, Clark AT, Taveras L, et al. Prospective validation of the Parkland grading scale for cholecystitis. Am J Surg. 2019;217:90-7.
8. Elkbuli A, Meneses E, Kinslow K, Boneva D, McKenney M. Current grading of gall bladder cholecystitis and management guidelines: is it sufficient? Ann Med Surg (Lond). 2020;60:304-7.
9. Baral S, Chhetri RK, Thapa N. Utilization of an intraoperative grading scale in laparoscopic cholecystectomy: a Nepalese perspective. Gastroenterol Res Pract. 2020;2020:8954572.
10. Lee W, Jang JY, Cho JK, Hong SC, Jeong CY. Does surgical difficulty relate to severity of acute cholecystitis? Validation of the parkland grading scale based on intraoperative findings. Am J Surg. 2020;219:637-41.

ORIGINAL ARTICLE

Clinical efficacy of radiofrequency ablation guided by high-density mapping on persistent atrial fibrillation

Eficacia clínica de la ablación por radiofrecuencia guiada por mapeo de alta densidad en el tratamiento de la fibrilación auricular persistente

*Ting Huang[1], Han Xie[1], and Ning Ma[2]**

[1]Department of Cardiovascular, The Central Hospital of Wuhan; [2]Department of Cardiology, Shandong Provincial Hospital Heze Hospital. Wuhan, 430014, China

Abstract

Objective: *The study aimed to explore the clinical efficacy of radiofrequency ablation (RFA) guided by high-density mapping on persistent atrial fibrillation (PsAF).* **Method:** *A total of 190 patients with PsAF undergoing RFA were divided into a routine group (n = 105) and a high-density mapping group (n = 85). The indicators of therapeutic efficacy were collected and compared.* **Results:** *A statistically significant difference was found in the overall rate of post-operative recurrence between the two groups (11.58% vs. 23.81%, χ^2 = 5.055, p = 0.025). The effects of different treatment methods on SF-36 score varied (FSF-36 treatment = 43.142, p < 0.05), and SF-36 scores at 3, 6, and 12 months of both groups were in the same order: the high-density mapping group > the routine group. While surgery guided by high-density substrate mapping (odds ratio = 0.453, 95% confidence interval: [0.232-0.784], p < 0.001) was a protective factor for recurrence.* **Conclusion:** *For patients with PsAF, more accurate mapping is conducted on the atrial substrate using a PentaRay electrode, which further verifies that the success rate of individualized ablation strategy is like mainstream procedures, and it significantly improves the subsequent health status of patients and reduces their incidence of adverse reactions.*

Keywords: *High-density mapping. Voltage mapping. Persistent atrial fibrillation. Catheter ablation.*

Resumen

Objetivo: *Explorar la eficacia clínica de la ablación por radiofrecuencia guiada por mapeo de alta densidad en el tratamiento de la fibrilación auricular persistente.* **Método:** *Ciento noventa pacientes con fibrilación auricular persistente que recibieron ablación por radiofrecuencia se dividieron en dos grupos: convencional (n = 105) y mapeo de alta densidad (n = 85). Se recopilaron y compararon los indicadores de eficacia.* **Resultados:** *La diferencia en la tasa total de recurrencia posoperatoria entre los dos grupos fue estadísticamente significativa (11,58% vs. 23,81%; χ^2 = 5055; p = 0.025). Los efectos de los diferentes métodos de tratamiento en el puntaje SF-36 variaron (FSF-36 tratamiento = 43.142, p < 0.05), y los puntajes SF-36 a los 3, 6 y 12 meses de ambos grupos siguieron el mismo orden: grupo de mapeo de alta densidad > grupo convencional. Por su parte, la cirugía guiada por mapeo de matriz de alta densidad (OR: 0.453; IC95%: 0.232-0.784; p < 0.001) es un factor protector contra la recurrencia.* **Conclusión:** *Para los pacientes con fibrilación auricular persistente, el uso de electrodos Pentaray para mapear con mayor precisión en la matriz auricular verificó aún más que la tasa de éxito de la estrategia de ablación individualizada es similar a la de la cirugía convencional, mejorando significativamente el estado de salud posterior del paciente y reduciendo la incidencia de reacciones adversas.*

Palabras clave: *Cartografía de alta densidad. Mapeo de voltaje. Fibrilación auricular persistente. Ablación por catéter.*

***Correspondence:**
Ning Ma
E-mail: 48725826@qq.com

Date of reception: 11-01-2024
Date of acceptance: 09-02-2024
DOI: 10.24875/CIRUE.M24000795

Cir Cir (Eng). 2024;92(6):699-707
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Atrial fibrillation (AF) is a complex arrhythmia characterized by rapid and uncoordinated atrial activation, with high disability and mortality[1,2]. The latest research shows that the standardized incidence of AF in Chinese adults is about 1.6%, with an estimated number of patients reaching 20 million[3]. As the aging deepens and continues to increase over the next 30 years, it will become one of the biggest epidemics and public health challenges[4].

AF is a chronic progressive disease. At present, a comprehensive management strategy for AF treatment is currently being implemented[5]. Catheter ablation (CA), as the initial treatment, benefits patients more than drug therapy, and may alter the pathogenic mechanism of AF and its progression to persistent AF (PsAF)[6]. At present, it has been demonstrated that further addition of other ablation lines based on PVI, such as mitral isthmus line, cavotricuspid isthmus (CTI) line, left atrial roof, bottom and posterior wall ablation, can achieve modification of additional AF substrates[7]. Although various ablation technologies have been developed in addition to PVI, there is still uncertainty about whether AF patients can benefit from additional ablation strategies[8]. Therefore, the current surgery is still based on PVI.

The key to the success of radiofrequency ablation (RFA) lies in the ability to clarify its electrophysiological mechanisms and accordingly select appropriate ablation plans. Morillo et al.[9] have reported that AF can cause ultrastructural changes in the atrium, which can lead to atrial enlargement and an increase in extracellular matrix, resulting in asynchronous conduction. Heterogeneous intra-atrial conduction can cause voltage reduction. In addition, the presence of widespread low-voltage and complex fractionated atrial electrograms (CFAEs) in the atrium under a pathological condition has also been proven[10]. As a result, an abnormally slow conduction zone, as well as conduction blocks and reentries appear, all of which can facilitate AF maintenance. Moreover, the alteration of atrial substrates is currently considered an important factor in the recurrence and maintenance of AF following a CA procedure. According to the study of Verma et al.[11], low-voltage area (LVA) and scar can predict long-term recurrence of AF after PVI. Therefore, atrial substrate mapping is particularly important.

Routine single-ablation electrode mapping has a limited sampling range and consumes a long time. Without detailed information on cardiac surgery procedures, it is difficult to achieve accurate high-density mapping, which is also an important reason for the low success rate and high recurrence rate of RFA in such patients[12,13]. With the advancement of catheter mapping technology in AF, three-dimensional (3D) electroanatomic mapping (EAM) systems can more accurately, realistically and intuitively reflect the voltage changes and potential activity of atrial substrates, contributing to a deeper understanding of atrial electrical remodeling. They have gradually become a hot topic in the research on AF substrates. Compared with PxAF patients, PsAF patients have more stubborn and irreversible lesions, and a higher recurrence rate after routine RFA; However, there are only a few studies on the clinical efficacy of RFA based on high-density substrate mapping guided by 3D EAM in PsAF patients, and the most are case reports. On this basis, the present study focuses on patients with PsAF and explores the clinical efficacy and safety of RFA based on high-density substrate mapping guided by 3D EAM, is expected to improve clinical efficacy and reduce recurrence rate in patients with PsAF.

Method

Subjects

A total of 190 patients with PsAF undergoing RFA in our hospital from January 1, 2019, to June 30, 2021, were retrospectively collected using a convenient sampling method. According to different surgical methods, they were divided into a routine group (n = 105) and a high-density mapping group (n = 85).

Inclusion criteria

(1) Patients met the diagnostic criteria for PsAF and were confirmed by 12-lead electrocardiogram (ECG) or dynamic ECG, and PsAF lasted for more than 7 days without self-termination (5); (2) transesophageal ultrasound was performed preoperatively, without surgical contraindications such as left atrial appendage thrombus (LAAT); (3) surgical procedure was based on PVI and successful. Surgical success was defined as antiarrhythmic drug use within 3 months after surgery, without an episode of AF, atrial flutter or atrial tachycardia lasting $\geq$ 30 s, and (4) patients received RFA for AF for the 1st time, with 18 years $\leq$ age $\leq$ 80 years.

Exclusion criteria

(1) Patients had a previous history of ablation for AF; (2) patients had valvular AF and secondary AF caused by other factors, such as hyperthyroidism leading to AF and thyroid dysfunction; (3) patients had AF during the acute phase of myocardial infarction (MI); (4) patients had pre-operative contraindications due to various causes, such as allergy to iodine contrast agent and femoral artery occlusion in both lower limbs; and (5) Patients were unable to accept regular anticoagulation therapy after surgery, had incomplete clinical data, or were lost to follow-up.

This study was approved by the Ethics Committee of our hospital, and all participants signed the informed consent.

Research methods

The routine group received routine single-ablation electrode mapping but no high-density substrate mapping guided by 3D EAM, while the remaining treatments were the same as the high-density mapping group.

– Pre-operative preparation: Within 3 days before surgery, all subjects underwent transesophageal echocardiography to exclude LAAT and left atrial thrombus, as well as pulmonary vein computed tomography angiography (CTA) to determine the presence of mural thrombus, and further understand the anatomical position and structure of the left atrial appendage and bilateral pulmonary veins. Relevant antiarrhythmic drugs were discontinuated preoperatively (not < 5 half-life periods). In the case of oral anticoagulation with warfarin before admission, the INR value was adjusted and maintained at 1.8-2.5. In patients with novel oral anticoagulants (NOACs) before surgery, the drugs were stopped once in the morning on the day of surgery.

– High-density substrate mapping guided by 3D EAM: After pre-operative routine disinfection and towel laying, the patients were subjected to local infiltration anesthesia with 1% lidocaine hydrochloride injection. Assisted by X-ray digital subtraction angiography, the right internal jugular vein was first punctured and placed with a coronary sinus (CS) electrode, and then, the right femoral vein was punctured for placing a SwartzL1 sheath along the right femoral vein, followed by puncture of the atrial septum for intravenous injection of heparin (70-100 IU/kg). During surgery, 1000 IU/h heparin was added, and the patients' activated coagulation time was closely monitored and maintained at 250-350 s. Subsequently, left and right pulmonary vein CTA was performed to further understand the position of their openings. Supported by the long sheath, the PentaRay mapping electrode was inserted into the left atrium (LA). The right atrial substrate mapping method was consistent with the left atrial mapping method: Guided by the 3D EAM system CARTO3, high-density mapping of left atrial electroanatomic substrates was performed using synchronous mapping electrodes under AF rhythm, and a 3D model of the atrium was constructed to export 3D electroanatomic and voltage substrate maps.

– Radiofrequency CA: After mapping of the left and right atrial substrates in AF patients, RFA was conducted using a Smartouch pressure-monitoring catheter with a 4-mm head, with discharge parameter settings: power 50 W, temperature 43℃, cold saline flow rate 30 mL/min, and discharge time per point 15 s (10-12 s on the left atrial posterior wall). CA procedures: first, PVI was conducted; second, modified left atrial BOX linear ablation was carried out (based on PVI, left atrial roof and bottom ablation was performed, with the bottom line connecting to the ablation loop of the left pulmonary vein along the endometrial surface of the CS); third, individualized substrate modification was conducted in electrically induced lesions based on high-density substrate mapping during AF rhythm. Characteristics of endocardial potential in electrically induced lesions were as follows: (1) Location distribution: LVA of substrate mapping under AF rhythm (especially in the transition zones of different colors within the LVA); (2) Frequency observation: Relative high frequency of local potential (compared with A-wave on the CS); (3) Discrepancy measurement: High discrepancy of local potential (the potential duration in a single beat by PentaRay generally accounted for 80% or more of the average circumference of the CS, and some electrodes had visible or invisible CFAEs); (4) Potential rearrangement and marking: Adjacent mapping electrodes had a tendency to divergent or reversal potentials (electrode arrangement was adjusted to spiral expansion).

– Surgical endpoint: Sinus rhythm was restored by intraoperative individualized substrate modification in electrically induced lesions as much as possible. Electrical cardioversion was adopted for lower and more regular atrial frequency without restored sinus rhythm after ablation.

– Post-operative treatment: After surgery, routine bedside ECG was used to record ECG changes. The patients were monitored by an ECG telemonitoring system. The puncture sites were locally treated with compression bandages to stop bleeding, and the patients were asked for immobilization for 6 h. Post-operative anticoagulation therapy lasted for at least 3 months using warfarin (with a target INR maintained between 2.0-3.0) or NOACs (dabigatran, rivaroxaban, etc.). Three months later, whether anticoagulation therapy continued was based on the CHA2DS2-VASc score. AF recurrence was defined as an episode of atrial tachycardia, atrial flutter, or AF lasting months later, whether anticoagulation therapy continued was based on the CHA2DS2-VASc score. AF recurrence was defined as an episode of atrial tachycardia, atria2 months after surgery). Three months after surgery was the "blanking period" of AF, after which the patients were followed up by outpatient visits, telephone, or WeChat for post-operative recurrence.

Data collection

Clinical data

The following baseline data were collected: age, gender, history of AF, body mass index (BMI), echocardiography (left atrial diameter, right atrial diameter, and ejection fraction), CHA2DS2-VASc score, comorbidities, and pre-operative use of cardiovascular drugs. The indicators of efficacy, including immediate surgical success rate, surgical duration, recurrence 3, 6, and 12 months after surgery, readmission, secondary surgery, and SF-36 score 3, 6, and 12 months after surgery, were collected. The indicators of safety included complications such as pericardial tamponade, pericardial effusion, severe bleeding, stroke, and sychnosphygmia (atrial tachycardia).

As a concise health survey questionnaire, SF-36 comprehensively summarizes the quality of life of respondents from eight aspects: physical function, role physical, bodily pain, general health, vitality, social function, role emotional, and mental health. The higher the score, the better the condition[14].

Endpoints

At present, it is believed that the inflammation and changes in the autonomic nervous system caused by ablation injury to the LA are a reasonable explanation for temporarily triggering atrial tachyarrhythmia[15], and 3 months after ablation is a surgical blanking period[16]. If necessary, antiarrhythmic drugs and reablation can be adopted in a 3-month blanking period[17]. Primary endpoints were as follows: AF, atrial flutter and (or) sychnosphygmia (atrial tachycardia) lasting > 30 s recorded not in the surgical blanking period 3 months after surgery[18], and death from AF-related events. Secondary endpoints included thrombotic events such as stroke, peripheral arterial thrombosis and transient ischemic attack, and death from non-AF-associated diseases.

Follow-up

Telephone follow-up was conducted at 3, 6, and 12 months, respectively, to determine whether there were any episodes of arrhythmia like those before surgery and whether ECG or 24-h dynamic ECG indicated an episode of atrial flutter, AF, or atrial tachycardia. In the case of a recurrence, whether rhythm should be restored, and how it should be restored were considered. Cerebral infarction, systemic embolism, heart failure, etc. were clarified before readmission. The patients with symptoms such as palpitations and shortness of breath during the follow-up were notified to visit a nearby hospital for an ECG or 24-h dynamic ECG examination. The cause of death was explored in dead patients.

Statistical analysis

Statistical processing was carried out using SPSS 26.0. The K-S method was used to test for normality. The measurement data that satisfied normality were expressed as ($x \pm s$), and their inter-group mean comparisons were conducted by the *t*-test. The counting data were expressed as frequency (*n*) or rate (%), and analyzed with the χ^2 test for those satisfying normality and the Fisher's exact probability test for those not satisfying normality. The skewed data were compared using the *Kruskal–Walis H*-rank sum test. Logistic regression analysis was adopted for risk factors of recurrence after RFA in AF patients. The predictive value of various indicators in recurrence after RFA in AF patients was explored using a receiver operating characteristic curve. The significant level was set at $\alpha = 0.05$.

Table 1. Comparison of general data between the two groups

Item	High-density mapping group (n = 95)	Routine group (n = 105)	$t/\chi^2/Z$	p
Age (year, x ± s)	60.36 ± 9.44	62.60 ± 9.34	1.328	1.240
Gender (male/female)	71/24	65/40	3.774	0.052
History of AF (month, M [Q1, Q3])	4 (1, 12)	5 (2, 12)	–1.610	0.107
BMI (kg/m^2, x ± s)				
Echocardiography	25.63 ± 3.53	25.83 ± 3.46	0.798	0.440
Left atrial diameter (mm, x ± s)	40.47 ± 3.58	41.96 ± 4.81	0.788	0.440
Right atrial diameter (mm, x ± s)	38.22 ± 5.19	38.92 ± 5.03	0.007	0.933
Ejection fraction (%, x ± s)	60.09 ± 9.59	56.27 ± 10.75	1.118	1.020
CHA2DS2-VASc score (point, x ± s)	2.00 ± 1.76	2.38 ± 1.74	1.557	0.120
Comorbidity (*n*)				
Hypertension	43	53	0.543	0.461
Coronary heart disease	3	4	0.063	0.802
Diabetes	5	6	0.020	0.889
Chronic obstructive pulmonary disease	1	1	-	1.000[a]
Preoperative use of cardiovascular drugs (n)				
ACEI/ARB	72	80	0.004	0.947
Diuretic	29	42	1.955	0.162
β-blocker	45	46	0.255	0.614
Calcium-channel blocker	15	21	0.599	0.439
Positive inotropic agent	12	14	0.022	0.883

BMI: body mass index; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; a: Fisher's exact probability test.

Results

General data

In the high-density mapping group, there were 95 patients, including 71 males and 24 females, with an average age of 60.36 ± 9.44 years, a history of AF for 4[1,12] months, and an average BMI of 25.63 ± 3.53 kg/m^2. The routine group included 105 patients, including 65 males and 40 females, with an average age of 62.60 ± 9.34 years, a history of AF for 5[2,12] months, and an average BMI of 25.83 ± 3.46 kg/m^2. The two groups showed no statistically significant differences in age, gender, history of AF, BMI, echocardiography (left atrial diameter, right atrial diameter, ejection fraction), CHA2DS2-VASc score, comorbidities, or pre-operative use of cardiovascular drugs ($p > 0.05$), as seen in table 1.

Indicators of efficacy

As for immediate surgical success rate, surgical duration, recurrence 3, 6, and 12 months after surgery, readmission and secondary surgery, the results revealed a statistically significant difference in the overall rate of postoperative recurrence between the two groups (11.58% vs. 23.81%, $\chi^2 = 5.055$, $p = 0.025$), but no statistically significant difference in immediate surgical success rate, surgical duration, the proportion of readmitted patients, or the proportion of patients with secondary surgery ($p > 0.05$), as seen in table 2.

The effects of different treatment methods on the patients' SF-36 scores within 12 months were explored using one-way repeated measures analysis of variance. The baseline data presented no statistically significant differences between the two groups ($p > 0.05$), indicating high comparability. The Shapiro–Wilk test suggested that the data of each group followed an approximate normal distribution ($p > 0.05$). According to Mauchly's test of sphericity, the variance–covariance matrix of each group was equal ($p > 0.05$) (Table 2). The results are summarized as follows:

The time treatment interaction effect of the SF-36 score was significant between the two groups ($F_{SF\text{-}36\ interaction} = 45.624$, $p < 0.05$), indicating that different treatment methods have different individual effect sizes on SF-36 scores at 3 time points between the two groups. In addition, the SF-36 scores of both groups increased over time ($F_{SF\text{-}36\ time} = 67.581$, $p < 0.05$), suggesting significant changes in SF-36 score over time. Finally, the effects of different treatment methods on SF-36 score varied ($F_{SF\text{-}36\ treatment} = 43.142$, $p < 0.05$).

Table 2. Comparison of indicators of efficacy between the two groups

Item	High-density mapping group (n = 95)	Routine group (n = 105)	$t/\chi^2/Z$	p
Immediate surgical success rate (%)	100	100	-	1.000[a]
Surgical duration (min, x ± s)	176.83 ± 9.64	168.90 ± 8.20	1.371	0.172
Number of postoperative recurrences (n)	11 (11.58%)	25 (23.81%)	5.055	0.025
3 months	8	13		
6 months	0	6		
12 months	3	6		
Number of readmitted patients (n)	7	15	2.438	0.118
Number of patients with secondary surgery (n)				
SF-36 score (point, x ± s) [b]	4	7	0.579	0.447
Baseline	96.42 ± 4.55	95.62 ± 6.33	1.371	0.252
3 months	106.61 ± 8.53	101.21 ± 6.90	4.532	< 0.001
6 months	118.45 ± 5.67	112.18 ± 6.17	5.443	< 0.001
12 months	124.34 ± 6.54	118.40 ± 6.55	4.695	< 0.001

a: Fisher's exact probability test; b: repeated measures analysis of variance ($F_{interaction}/P_{interaction}$: 45.624/0.001; F_{time}/P_{time}: 67.581/0.001; $F_{treatment}/P_{treatment}$: 43.142/0.001); SF-36: Concise health survey questionnaire.

Table 3. Comparison of adverse reactions

Group	Atrial tachycardia	Pericardial tamponade	Pericardial effusion	Severe bleeding	Stroke	Incidence (%)
High-density mapping group (n = 95)	2	0	0	1	1	4 (4.21)
Routine group (n = 105)	11	0	1	2	0	14 (13.33)
χ^2 value						5.068
p value						0.024

Based on further pairwise comparison of SF-36 scores at 3, 6 and 12 months between the two groups, it was found that SF-36 scores at the 3 time points of both groups were in the same order: the high-density mapping group > the routine group.

Comparison of adverse reactions

In the high-density mapping group, atrial tachycardia occurred in two patients, severe bleeding in one patient, and stroke in one patient. In the routine group, there were 11 patients with atrial tachycardia, one with pericardial effusion, and two with severe bleeding. The incidence of adverse reactions had a statistically significant difference between the two groups (4.21% vs. 13.33%, $\chi^2 = 5.068$, p = 0.024), as shown in table 3.

Univariate and multivariate analysis of influencing factors for recurrence

An univariate logistic regression analysis was conducted on the correlations between recurrence and various factors, revealing that left atrial diameter (odds ratio [OR] = 1.563, 95% confidence interval [CI]: [1.246-1.785], p < 0.001), course of AF (OR = 1.123, 95% CI: [1.043-1.343], p < 0.001) and surgical method (OR = 0.453, 95% CI: [0.342-0.895], p < 0.001) were the influencing factors for recurrence, with statistical significance. The results showed that large left atrial diameter (OR = 1.565, 95% CI: [1.324-1.884], p < 0.001) and long course of AF (OR = 1.145, 95% CI: [1.078-1.653], p < 0.001) were risk factors for recurrence, while surgery guided by high-density substrate mapping (OR = 0.453, 95% CI: [0.232-0.784], p < 0.001) was a protective factor for recurrence, as displayed in table 4.

Predictive value of various factors in recurrence

The results demonstrated that left atrial diameter, course of AF, and surgical method all had certain predictive values for post-operative recurrence. The area under the curve (AUC) of left atrial diameter, course of

Table 4. Univariate and multivariate analysis of influencing factors for recurrence

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	p	OR (95%CI)	p
Age	1.022 (0.981~1.065)	0.291	-	-
Gender	1.154 (0.561~1.453)	0.734	-	-
History of hypertension	0.845 (0.635~1.454)	0.532	-	-
History of diabetes	0.561 (0.353~1.586)	0.125	-	-
History of coronary heart disease	0.784 (0.682~1.583)	0.320	-	-
BMI	0.944 (0.876~1.543)	0.452	-	-
Left atrial diameter	1.563 (1.246~1.785)	< 0.001	1.565 (1.324~1.884)	< 0.001
Course of AF	1.123 (1.043~1.343)	< 0.001	1.145 (1.078~1.653)	< 0.001
Surgical method	0.453 (0.342~0.895)	< 0.001	0.453 (0.232~0.784)	< 0.001

BMI: body mass index; AF: atrial fibrillation.

Table 5. Predictive value of various indicators for postoperative corneal edema in cataract patients

Item	AUC	95% CI	Sensitivity (%)	Specificity (%)
Left atrial diameter	0.743	0.656~0.832	76.31	74.54
Course of AF	0.756	0.701~0.824	80.61	81.70
Surgical method	0.689	0.623~0.711	71.44	73.48
Combined prediction	0.865	0.774~0.887	86.24	85.73

BMI: body mass index; AF: atrial fibrillation; AUC: area under the curve.

AF, and surgical method in predicting post-operative recurrence was 0.743 (95% CI: 0.656-0.832), 0.756 (95% CI: 0.701-0.824), and 0.689 (95% CI: 0.623-0.711), respectively. Their combination showed the highest value in predicting post-operative recurrence, with an AUC of 0.865 (95% CI: 0.774-0.887), as exhibited in table 5.

Discussion

AF occurs based on the changes in pathophysiological substrates of the atrium. The alteration of atrial substrates is currently considered an important factor in AF recurrence and maintenance following a CA procedure. Based on the study of Verma et al.[11], LVA and scar can predict long-term recurrence of AF after PVI. The key to the success of RFA lies in the ability to clarify its electrophysiological mechanisms and accordingly select appropriate ablation plans. Current research has demonstrated that atrial tachycardia after surgery for congenital heart diseases is mainly related to electrophysiological abnormalities caused by surgical scars[19], and it can be further divided into recurrent and focal types. Recurrent atrial tachycardia is more common, and caused by intra-atrial reentry. The formation of reentrant circuits is related to the presence of a slow conduction zone in the atrium, which is caused by the primary heart disease and surgical scar[19]. The origin of focal atrial tachycardia is also near the scar. Unlike the typical reentry mechanism based on CTI atrial tachycardia, this type of patients mostly present surgical scar-related reentry, where surgical scars, patches or sutures in certain areas between the superior and inferior vena cava can form complete blocks. If there is viable myocardium between these tissues and scars, it is possible to form a slow conduction zone, thereby producing stable reentries and resulting in atrial tachycardia[20]. Therefore, atrial substrate mapping is particularly important.

For a long time, scholars generally believed that PVI alone is not enough for the ablation of PsAF, and additional linear ablation and/or CFAE ablation are needed[21]. However, additional ablation significantly prolongs surgical duration, as well as increases the incidence of post-operative atrial tachycardia and severe complications. Therefore, for patients with PsAF, current guidelines do not recommend empirical pulmonary vein ablation[22]. In the present study, high-density mapping was conducted using a PentaRay electrode, which further verifies the

superiority of individualized ablation strategy with left atrial voltage-guided substrate modification. Its success rate is not lower than that of domestic mainstream procedures, with higher post-operative quality of life in patients.

At present, the multi-electrode mapping catheters used in clinical practice for the atrium mainly include annular electrodes, PentaRay electrodes, basket electrodes, and HDGrid electrodes. Basket electrodes are characterized by high point density, but high costs and difficult operation, and the 3D mapping system is not compatible with pressure monitoring ablation catheters. HDGrid electrodes can simultaneously record 32 bipolar signals, which can more realistically, effectively, and accurately identify voltage zones. However, they have not yet been applied in clinical practice in China. The number of points in circular electrode mapping is relatively small and the density is low, resulting in an inability of automatic mapping. Most of the time, manual calibration is required[23]. PentaRay electrodes can reach the entire cardiac cavity, and when combined with confidence software, they can achieve safe and accurate mapping, with fewer anatomical pseudolumens and less manual calibration. Thus, they are significantly superior to circular electrodes.

In the current ablation strategy with voltage-guided substrate modification, bipolar LVA is mainly used as an alternative electrophysiological indicator of atrial fibrosis to guide ablation. In addition, there is still controversy over whether LVA is equivalent to the need for substrate modification. Rolf et al.[24] have found that AF patients with individualized ablation based on LVA have a significantly higher AF-free recurrence rate compared with those with PVI alone. According to the study of Jadidi et al.[25], for patients with PsAF, PVI combined with left atrial LVA-guided ablation is superior to PVI alone, and PVI is only suitable for patients with left atrial LVA (measured under AF attacks) < 10%. There are also research results demonstrating that the AF-free recurrence rate of PVI combined with modified LVA-guided ablation is higher than PVI alone and PVI combined with empirical ablation, the incidence of postoperative atrial tachycardia is lower, as well as the surgical duration, irradiation time and ablation time are significantly reduced[21].

Of course, this study also has some limitations. First, this study is a single-center study with a small sample size and a follow-up time of 1 year. There was a trend of differences in the recurrence-free survival period, but due to the short duration, no differential results were observed. In future research, the sample size can be enlarged and the follow-up time can be prolonged to obtain more results. In addition, the data collection in this study was mainly based on case review, which may lead to recall bias in the course of the disease. If there is a portable ECG recording device in future research, it will provide more effective and accurate information.

Conclusion

For patients with PsAF, more accurate mapping is conducted on the atrial substrate using a PentaRay electrode, which further verifies that the success rate of individualized ablation strategy is like mainstream procedures, and it significantly improves the subsequent health status of patients and reduces their incidence of adverse reactions.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

References

1. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The framingham heart study. JAMA. 1994;271:840-4.
2. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013;34:2746-51.
3. Shi S, Tang Y, Zhao Q, Yan H, Yu B, Zheng Q, et al. Prevalence and risk of atrial fibrillation in China: a national cross-sectional epidemiological study. Lancet Reg Health West Pac. 2022;23:100439.
4. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. Int J Stroke. 2021;16:217-21.
5. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS): the gnosis and management of atrial fibrillation of the European society of cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42: 373-498.
6. Andrade JG, Deyell MW, Macle L, Wells GA, Bennett M, Essebag V, et al. Progression of atrial fibrillation after cryoablation or drug therapy. N Engl J Med. 2023;388:105-16.
7. Ernst S, Schlüter M, Ouyang F, Khanedani A, Cappato R, Hebe J, et al. Modification of the substrate for maintenance of idiopathic human atrial fibrillation: efficacy of radiofrequency ablation using nonfluoroscopic catheter guidance. Circulation. 1999;100:2085-92.
8. Sutter JS, Lokhnygina Y, Daubert JP, Bahnson T, Jackson K, Koontz JI, et al. Safety and efficacy outcomes of left atrial posterior wall isolation compared to pulmonary vein isolation and pulmonary vein isolation with linear ablation for the treatment of persistent atrial fibrillation. Am Heart J. 2020;220:89-96.
9. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995;91:1588-95.
10. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, et al. Electrical remodeling of the atria in congestive heart failure; Electrophysiological and electroanatomic mapping in humans. Circulation. 2003;108:1461-8.
11. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005;45:285.
12. Houck CA, De Groot NM, Kardys I, Niehot CD, Bogers AJ, Mouws EM. Outcomes of atrial arrhythmia surgery in patients with congenital heart disease: a systematic review. J Am Heart Assoc. 2020;9:e016921.
13. Ma W, Lu FM, He L, Zhang F, Wu DY, Xu J. Electroanatomic mapping and radiofrequency catheter ablation of atrial tachycardias after non-right atrial approach to mitral valve replacement. Chin J Cardiac Pacing Electrophysiol. 2021;35:149.
14. Nakao M, Ishibashi Y, Hino Y, Yamauchi K, Kuwaki K. Relationship between menstruation-related experiences and health-related quality of life of Japanese high school students: a cross-sectional study. BMC Womens Health. 2023;23:620.
15. Riahi S, Larsen JM. The 3-month post-atrial fibrillation ablation blanking period: time to redefine? Europace. 2020;22:1759-60.
16. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20:e1-160.
17. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol. 2013;61:1713-23.
18. Andrade JG, Champagne J, Dubuc M, Deyell MW, Verma A, Macle L, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring: a randomized clinical trial. Circulation. 2019;140:1779-88.
19. Kottkamp H, Bender R, Berg J. Catheter ablation of atrial fibrillation: how to modify the substrate? J Am Coll Cardiol. 2015;65:196-206.
20. Adachi T, Yoshida K, Takeyasu N, Masuda K, Sekiguchi Y, Sato A, et al. Left septal atrial tachycardia after open-heart surgery: relevance to surgical approach, anatomical and electrophysiological characteristics associated with catheter ablation, and procedural outcomes. Circ Arrhythm Electrophysiol. 2015;8:59.
21. Jiang LY, Xia XJ, Liu S. Effectiveness and safety of catheter ablation in treatment of atrial fibrillation combined with coronary heart disease. J Clin Internal Med. 2018;35:184-6.
22. Correction to: Association of left atrial high-resolution late gadolinium enhancement on cardiac magnetic resonance with electrogram abnormalities beyond voltage in patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2023;16:e000087.
23. Li T, Zhan XZ, Xue YM, Fang XH, Liao HT, Wu SL. Voltage substrate of the left atrial in patients with atrial fibrillation. Chin J Cardiac Pacing Electrophysiol. 2017;31:224-8.
24. Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014;7:825-33.
25. Jadidi AS, Lehrmann H, Keyl C, Sorrel J, Markstein V, Minners J, et al. Ablation of persistent atrial fibrillation targeting low-voltage areas with selective activation characteristics. Circ Arrhythm Electrophysiol. 2016;9:e002962.

ORIGINAL ARTICLE

Model for analysis of actors in divergence or convergence of strategic health objectives

Modelo para análisis de actores en divergencia o convergencia de objetivos estratégicos sanitarios

Martha K. Torres-Salgado

Sección de Investigación y Posgrado, Unidad Profesional Interdisciplinaria de Ingeniería, Ciencias Sociales y Administrativas, Instituto Politécnico Nacional, Mexico City, Mexico

Abstract

Objective: *Correlate methods to analyze and identify the effectiveness of the objectives in actors with maps of strategic power.* **Method:** *It is a conceptual study, analytical and with deductive reasoning, of explanatory scope in correlation of convergent and divergent strategic objectives to health processes.* **Results:** *Understanding the importance of analyzing and understanding the prospective in the decision-making of the actors that impact their strategic, tactical and operational deployment of hospital medical care with the proposals of models with alignment in the health system and comprehensive practicality and analytical architecture modeling of how the hierarchical levels of actors can be concentrated according to the objectives with indicators and committed goals.* **Conclusions:** *The prospective analysis of actors makes it easier to evaluate health leaders according to the effectiveness of their established objectives through the collection of information in matrices, MACTOR (Method, Actors, Objectives, Force Results) and mapping of health objectives. It is relevant in favor of ensuring strategic alignment in health institutions until reaching hospitals and giving continuity to the objectives and improving conflict management for the benefit of medical care.*

Keywords: *Actors and objectives. Priority of objectives. Maps.*

Resumen

Objetivo: *Correlacionar métodos para analizar e identificar la eficacia de los objetivos en actores con mapas del poder estratégico.* **Método:** *Estudio conceptual, analítico y con razonamiento deductivo, de alcance explicativo en correlación de objetivos estratégicos convergentes y divergentes a los procesos de salud.* **Resultados:** *Comprender la importancia de analizar y entender la prospectiva en la toma de decisiones de los actores que impactan es su despliegue estratégico, táctico y opera- tivo eficaz a la atención médica hospitalaria con las propuestas de modelos con alineamiento en el sistema de salud y la practicidad integral y analítica del modelado de arquitectura de objetivos cómo se pueden concentrar los niveles jerárquicos de actores de acuerdo con los objetivos con indicadores y metas comprometidas.* **Conclusiones:** *El análisis prospectivo de actores facilita evaluar a los líderes de salud de acuerdo con la eficacia de sus objetivos establecidos a través de recolección de información en matrices, MACTOR (Método, Actores, Objetivos, Resultados de Fuerza) y mapeo de objetivos de salud que tiene relevancia en pro de lograr garantizar un alineamiento estratégico en las instituciones de salud hasta llegar a los hospi- tales, y dar continuidad a los objetivos y mejorar la administración del conflicto en beneficio de la atención médica.*

Palabras clave: *Actores y objetivos. Prioridad de objetivos. Mapas.*

Correspondence:
Martha K. Torres-Salgado
E-mail: katty_torres_salgado@hotmail.com

Date of reception: 07-08-2023
Date of acceptance: 16-01-2024
DOI: 10.24875/CIRUE.M24000771

Cir Cir (Eng). 2024;92(6):708-717
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

To provide effective and quality health care, the convergence of key stakeholders and leaders is required, from regulators, payers, providers of goods or services, and intermediaries, to the suppliers in the health care value chain. This convergence is now a priority to improve and reinvent process models and health indicators of stakeholders and evaluate the strategic deployment of performance in achieving the objectives and strategies by decision-makers in public health policies, in order to deliver quality services on time to the greatest number of patients while minimizing costs, with convergence in the intelligent reaction of the intervening actors and their interrelations[1] in four interconnected environments: social, political, economic, and technological; which are in constant change and have an impact on the health care map of the health sector value chain[2]. Therefore, it is reiterated that strategic and global planning is a sequence of logical, ordered, functional activities, with strategic deployment and continuity, aimed at establishing a realizable global vision for the responsible actors. It is part of clarifying the fundamental mission or purpose of the departments to project it into a desirable, achievable future, guided by their values; a process that allows for the integral visualization of the future of institutions, understood as the process of guiding the strategic alignment of objectives, strategies, and public policies to health care entities from where they are and what they are in the present to where they should be and what they should be in the future. With a cross-sectional vision based on the processes of the departments, it integrates the efforts of stakeholders around a common objective, understands the dynamics and interactions that occur among companies, clients, suppliers, and key actors, and aligns organizational performance with the strategy and objectives of the health sector[3].

Likewise, organizations are created vertically, based on specialization to fulfill the various functions they perform. Thus, the responsibility for the expected results is established on the function and not on the processes that develop transversally across organizational units[4]. On the other hand, evaluation is part of the strategic planning process, which is a valuable tool for achieving the mission and global vision that guarantees continuous improvement. Finally, performance indicators, in turn, serve to indicate, which comes from the Latin *indicare*, meaning to show or signify something, with clues and signals, and performance indicates the capacity of the processes within organizations in the value chain to manage their resources and meet the efficient and effective objectives and goals established[3,4]. Through performance measurement, 2 priority aspects are addressed: the first is measuring efficiency and the second is effectiveness. Efficiency is defined as the result of benefit relative to cost, and effectiveness is what is performed or executed in relation to what was planned within the established time frame. Thus, productivity is efficiency multiplied by effectiveness[5], as well as coordination with relevant actors who intervene in addressing risk factors and health determinants, including monitoring trends in diseases and their impact on public health, to promote efficiency and equity in resource allocation[6].

Therefore, the health sector needs to respond to how to identify global actors who make decisions on effective strategic objectives that are decisive and key in their strategic alignment in health care.

Method

In the actor analysis to identify the political opposition and support that the health reform process and strategy implementation will face, it is necessary to use methodologies that allow for the identification, analysis of stakeholder participation in health processes, and evaluation with indicators. This study presents three proposals: the first, without using software for structural actor analysis; the second, with the application of MACTOR (Method, Actors, Objectives, Results of Force), as well as the design of effective strategies aimed at intervening with these actors to increase their political feasibility; and the third, modeling architecture for actors and performance indicators (KPI).

Strategic analysis mapping of health reform actors

This is one of the tools for studying the implementation of health sector reform, and it is the first step in a political feasibility analysis, which should be complemented by the design of other tools that allow for the evaluation of the impact of applying the strategies. One way to do this is offered by the Policy Maker tool[7], and its integration with formats is visualized in figure 1, which allows for the implementation, estimation, and

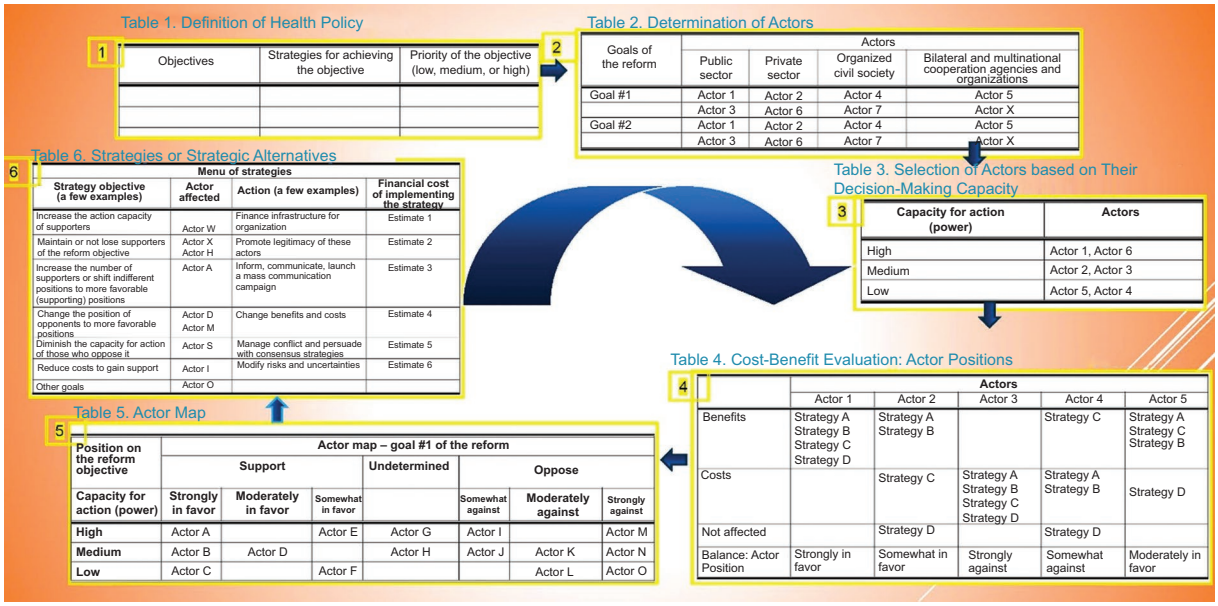

Figure 1. *Basic matrix layout for actor and strategy analysis. The 6 stages of matrices for performing actor analysis are visible, noting that for the large-scale health care process, a substantial volume of global and regional information would need to be processed for its application and analysis. (Source: adaptation of Strategic Actor Analysis Mapping for Health Reforms[8]).*

introduction of costs and the potential success of each strategy, with the goal of calculating the final probability and total cost of various intervention packages or participations in the strategic alignment of health. Table 1 details the purpose of each stage[8].

Analysis of stakeholder strategies

Part of the actor's game is defined as individuals who make decisions and take specific positions in the environment, with significance for the performance of processes and potential impact on decision-making. This leads to analysis to understand the health governance system. It is known that individuals defend their interests, and each actor has justified reasons for their actions, which is known as "methodological individualism," where the actor is either individual-unipersonal or collective-collegial and will try to do everything that benefits them to achieve their goals. Additionally, if there is alignment between those interests, alliances will be formed. But if there is divergence in interests, conflict can arise due to the differences in their interests. In other words, power will arise relatively from the actors and will influence the characteristics that favor alliances or conflicts[9].

Another perspective is in the potential system that the actors in the environment find themselves in. Their surroundings (habitus) are decisive in their behavior. Each individual behaves according to how they have been formed through learned social culture and daily life throughout their life, which limits their freedom of action, as it depends on social systems. However, in contrast, although conflicts occur in the environment and groups emerge that question the system, these actors promote changes and evolve the reality, thus avoiding this deterministic approach in the social sphere[10]. Therefore, understanding the structure of relationships between its elements provides insight into the system's behavior and its constant change, where the interconnection or network of relationships between elements is crucial for understanding them[11].

The stages in the analysis of intervention and participation of actors for their possible effects and consequences on systems are[11]:

- Identify and descriptively characterize the external and internal actors participating in the system or its environment.
- Describe the objectives, motivations, and intentions of each actor, creating a chart where each actor recognizes their goals and strategies in terms of maximizing their benefit or developing their motivations.
- Evaluate and weigh the relationships between actors, i.e., the influence that each actor (individual or collective) can exert over the other actors.

Table 1. Actor Method for Health Reforms

Stage	Purpose
1. Definition of Content-Policy	Identify prioritized specific objectives and the definition of the strategies or means that have been designed to achieve the proposed objectives, with prior analysis of technical and financial feasibility.
2. Identification of the Actors Participating in the Process	Analyze and locate the participation of each actor in relation to the identified objectives of the reform and health strategies.
3. Evaluation of the Action Capacity of All Actors	Select a limited number of actors with greater power who support or oppose the objective, through simulation with the technical team leading the reform, with in-depth knowledge of the sector and its actors within the analytical framework of guidelines.
4. Costs and Benefits	Conduct a cost-benefit analysis related to the implementation of health objectives through interviews to understand each actor's position on each reform objective and the reasons that justify or explain their position (the costs and benefits the actor associates with the reform's objectives).
5. Preparation of Political Maps of the Actors	Determine the political map of the actors, identifying the support or obstacles each one represents for the reform process, and generate strategies to induce mobilization and change of position regarding the reform or change.
6. Strength of Actors Participating in Strategic Objectives	Once the actions arising from the correlation of forces of actors directly participating in each reform objective are identified, recognize the opportunities and threats arising from transitions and changes in the political, social, economic, and environmental context of the reform. These changes are independent of the action and beyond the control of the reform leader (s). In this phase, strategies (objectives and actions) are defined to seize opportunities and overcome obstacles hindering the achievement of reform objectives.

It is evident that applying this methodology with the actor map and strategies designed increases the political feasibility of reform objectives. The technical team presents the strategies to the leaders of the process in relation to the relevant actors, and through simulation work, selects the actors to focus on and the appropriate strategies to influence the direction of the health sector reform.

Source: Self-created, adapted from ref. 8.

– Understand the positioning of actors regarding objectives. Describe the current attitude of each actor towards each objective (opposed, neutral, indifferent, or favorable). Represent a matrix of actors × objectives.
– Understand the degree of convergence and divergence between actors and the plane of the distance between the different objectives of the system.

To develop the structural analysis of actors, on the one hand, a document detailing the identity of each actor is created, listing their objectives, ongoing projects, and their maturation (preferences), motivations, obligations, and internal means of action (coherence), along with their past strategic behavior (attitude). On the other hand, the means of action available to each actor over others to carry out their projects are examined.

Evaluation of the power relations of the actors

It is conducted through the Matrix of Direct Influence (MID) of Actors, in which the actors are distinguished on the ordinate (y) axis and values are assigned to the abscissa (x) axis to weigh the interrelationship of strength between them, with the relationship being represented at each intersection of the matrix. The result obtained allows for the understanding of the role and interrelationships of actors in the performance of the management and governance process. They are weighted by experts for recording in the actors' influence matrix. The relationships are weighted on a scale from 0 to 4, where the higher the number, the greater the influence of one actor over another. Each actor has their own means or strategies of action that allow them to achieve their goals and influence, to some degree, other actors. For the categorization of actor influence (Table 2), after the matrix calculation of relationships between actors, a graph called a plane or map is obtained (Fig. 2), which consists of two axes—ordinate and abscissa—and as a result, 4 quadrants are observed:

– Dominant actors: highly influential and not very dependent within the process.
– Subordinate actors: not very influential and highly dependent within the process.
– Actors conditioned by results: as influential as they are dependent on the processes.
– Autonomous actors: neither influential nor dependent in relation to the analyzed process.

Table 2. Categorization of Actor Influence

Value	Relationship
0	Assigned when there is no influence of one actor over another, meaning that the interaction does not result in changes in decision-making or actions of the actors, nor does it have consequences from the change.
1	Indicates a weak relationship, where the influencing actor modifies certain activities or processes in which the actor is involved.
2	Indicates a medium-strength relationship, where one actor has the ability to change entire or specific projects of the actor receiving the influence.
3	Refers to a strong relationship between actors. In this mode, the first actor influences the other radically enough to nullify the reason for the existence of the other actor. The consequences are of high impact. The task assigned as the mission of the actor receiving or affected by the interaction is committed.
4	This weighting is given for categorical influence, to the point where it threatens the existence of the actor receiving the influence and may even manifest as a risk to the integrity of the actors affected by the influence.

Table 2 shows that the weighting is defined according to the degree of influence, with 5 levels of relationships between actors: (0) an actor has little or no influence over another; (1) an actor can pose a limited risk to the processes of another actor; (2) an actor can put the success of another actor's processes at risk; (3) the fulfillment of their missions; or (4) their own existence. The different actors are placed in an influence and dependency plane. The analysis of power relationships highlights the strengths and weaknesses of each actor, their ability to freeze a situation, and other circumstances. In conclusion, the weighting evaluates direct influences between actors using a categorized weighting through a mutual influence box, known as the actor×actor matrix (MAA).
Source: Self-created, adapted from ref. 11.

Integration in the convergent and divergent analysis of actors

In this phase, the positioning of the actors is analyzed in relation to their strategic objectives from the previous structural analysis of MICMAC (Matrix-based Multiplication Applied to Classification) through another matrix of the valued position (MAO), in which the actors are associated with the objectives. The result shows the map of alliances and conflicts. This is achieved through the matrix description of potential alliances to all positions of coincident or favorable actors regarding certain strategic objectives. Similarly, divergent and opposing positions between different actors concerning the strategic objectives are interpreted as conflictual. Likewise, the weighting of the effects of the objectives on the intentions of the actors is observed in reverse or divergent terms.

The mechanism, in short, is through matrix calculation, which is defined by using the MACTOR application and distinguished in the following phases:

– Associate or correlate the preferences identified between the actors and their strategic objectives in the system or process.
– Locate the actors in relation to the objectives or strategic challenges based on the importance of perceiving whether they are allies, in conflict, or neutral.
– Quantitatively weigh the relationship that occurs, with the applicable scale recording different signs in the evaluations according to the actor's behavior regarding the objective, or conversely, the impact of the objective on the actor's interests. The sign distinction in the scales is verified through neutral, positive, or negative values[12]:
  - Neutral valuation (value 0): reflects that the actor is indifferent to the objective, and at the same time, the objectives do not change the actor's interests.
  - Positive and negative valuations of the actor in favor of the objectives (Table 3).

Actor objectives architecture model

The mapping of actors as an interdisciplinary and transversal adaptation consists of creating objective maps, which visualize the path that allows progress toward the maturity route for optimizing the achievement of the objective (Fig. 3). It is an interdisciplinary diagram because various actors participate in the process, guiding and describing their contributions to the deployment of the health care process. They are the graphical representation of the sequence of objectives that integrate a process. It describes movement or flow (which occurs over time) by various actors or owners of the process, and it describes what objective each actor aims to achieve, using symbols or drawings made on an electronic sheet[13,14,15] (Fig. 4).

Consequently, once mapped, the construction of KPIs and indicator dashboards is established in six stages[3,14,15]:

Table 3. Positive (+) and Negative (−) Evaluations of the Actor in Support of the Objectives

Value (+)	Objective	Value (−)	Objective
+1	Essential for the development of the actor's processes	−1	Risk to the actor's processes
+2	Priority for achieving the expected processes and programs of the actor	−2	Risk to the success of the actor's processes and programs
+3	Indispensable to the actor's mission	−3	Risk to the fulfillment of the actor's mission
+4	Indispensable for the actor's existence and continuity	−4	Risk to the actor's very existence

These scales are applied for weighting and are incorporated into an actor positioning chart for each strategic objective. This information helps decision-makers in health management and allows understanding possible alliances or oppositions; ultimately, it facilitates proposing strategies with alignment and alliances between actors to address key variables and associated strategic objectives.
Source: Self-created, adapted from ref. 12.

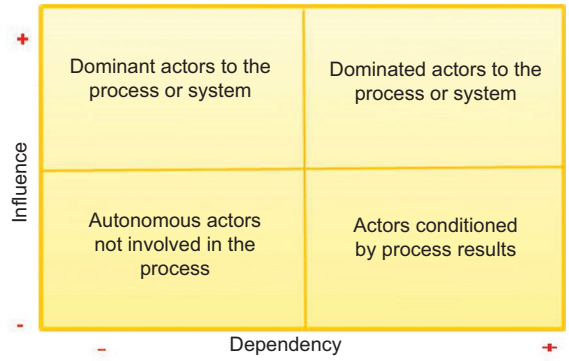

Figure 2. *Actors' influence and dependence map. This shows that the map consists of 4 key positions: dominant actors (highly influential and minimally dependent), dominated actors (minimally influential and highly dependent), actors conditioned to results (equally influential and dependent), and autonomous actors (neither influential nor dependent on the system or process analyzed). (Source: self-created, adapted from ref. 12).*

- *Identification of indicators:* For the construction of the indicator architecture in priority processes of specific activities, it is based on processes, subprocesses, and stages in obtaining process maps.
- *Selection of priority activities in the mappings:* The most important activity within the process is selected, not necessarily in the inputs or outputs of the process for priority or specific activities. This allows for a preventive guarantee of the expected result of the good or service. Priority activities are clearly identified in the value chain as unique and distinctive activities that satisfactorily deliver the good or service. Otherwise, these activities become a bottleneck that impacts the delivery of an unsatisfactory good or service and leads to conflicts between people[3,16].
- *Definition of indicators:* Defining KPIs that provide useful, accurate, correct, and important measurements is key to ensuring good strategy and making relevant decisions. The KPI offers visualization of activities to anticipate results and make decisions from any functional area where the activity is located.
- *Implementation of indicators and validation:* This is formalized through documentation that allows for standardization of the main elements that integrate the indicator. The design of a template for indicators is created, which allows for tracking through monitoring by the responsible actor or owner of reporting progress. It also validates if the established control is ideal and works to collect statistical information for consolidating its adjustment and implementation, incorporating it as part of the dashboard for the operational group, middle management, or senior management.
- *Indicator perspectives:* Categorization will allow grouping them based on specific criteria to visualize the progress of the objectives of each group of indicators in a timely manner[3,17]:
  - Profitability (productivity): Refers to recovering the investment and obtaining financial benefits in cost/benefit terms. For hospitals, it is common to use productivity, referring to results in health care services.
  - Activities: The priority link in the value chain for obtaining a good or service.
  - Patient safety: A classification used for indicators that monitor the use of best preventive practices to reduce failures, which are causes of adverse events, in providing patient care[18].
  - Offer: The value propositions offered to the client or user in their products/services.
  - Quality: Covers customer or user satisfaction with the goods or services received.

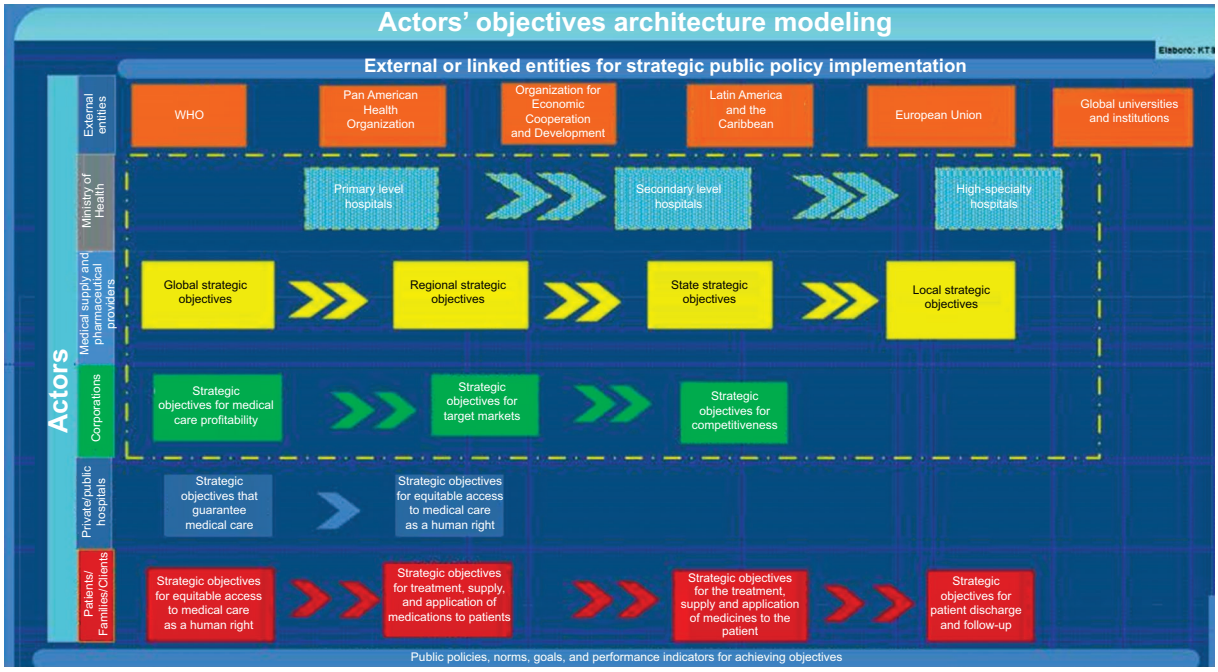

Figure 3. *Actors' objectives architecture modeling. It is a map that integrates actors, with the advantage that it allows visualization of the beginning and end of the public policy implementation process, priority objectives, transitioning to flat, horizontal structures where the names or positions of responsible individuals within the health care structure do not appear, allowing for a conflict-free diagnosis among actors and visualizing divergence that can be measured before and during the process to deliver expected results at strategic, tactical, and operational levels. (Source: self-created, adapted from refs. 3 and 19).*

- Health regulatory bodies[18]: Indicate and add mandatory indicators designated by external health entities and compliance monitoring, for the benefit of the quality and safety provided to the patient.

– *Performance KPIs for middle management and senior management*[3,14,15]: Strategic KPI dashboards are a tool designed in a matrix structure. On the lateral side of the matrix, the various categorization hierarchies, called "perspectives," are established, selected by the process actors. On the upper right side, the relevant KPI data intended to be visualized after being measured are included. The description of its structural design is as follows:
  - Strategic alignment perspective: Allows for categorizing profitability (productivity), activities, patient safety, offer, quality, and health regulatory bodies, among others, according to the scenario, global, regional, or sectorial.
  - Medical areas: Specifies the area within the organizational structure of the position.
  - Objective: Identifies and qualitatively expresses the goals of the actors towards which resources, efforts, and activities of the organization must be directed to fulfill its mission and vision.
  - Strategy: The initiative that establishes the means the actors will employ to achieve the objective and goal they aim for, to obtain the expected results.
  - Indicator: A means, link, or variable used to measure values on a measurement scale derived from a series of observed events in the priority activities of the processes.
  - Indicator results: Make sense according to the established objectives (expected results), from which a series of activities are organized to achieve them. These include:
    - Goal: A quantitative element of the objective in time.
    - Status: The parameterization according to the progress of results, assigned the color green, red, or yellow, depending on the maximum or minimum permissible limit.
    - Graph: Illustrates trends in the performance indicator visually to analyze, understand, and make comparisons, among other benefits.

Discussion

This research contributes to the importance of the individuals who lead, prioritize, and decisively

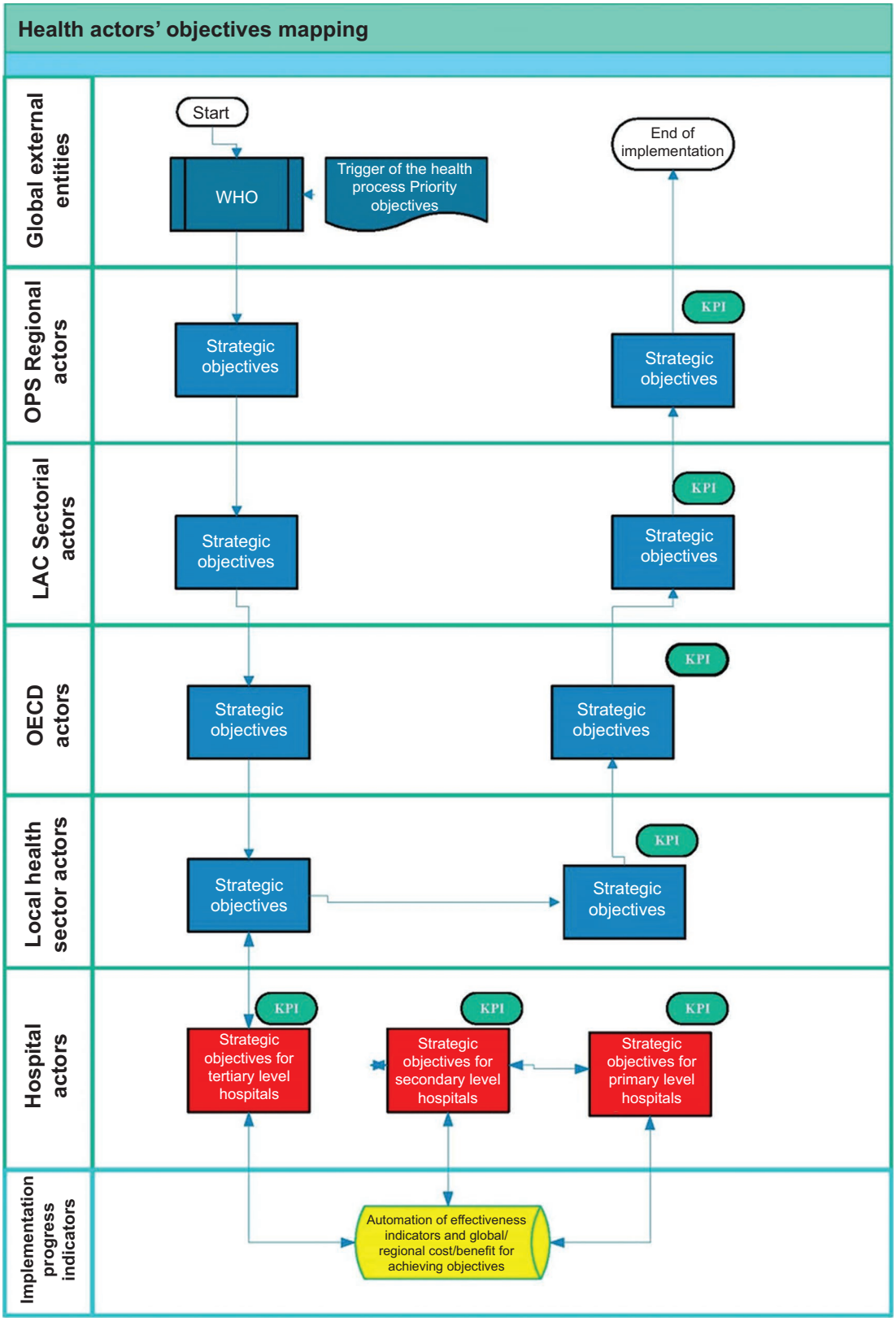

Figure 4. *Health actors' objectives mapping. The interdisciplinary diagram is subdivided into 3 main parts and 1 supporting part: 1) external global entities, which is the space to link client-provider entities, such as units, directions, or external organizations to the health care process or subprocess; 2) regional or local health actors, who participate in synchronized objectives until the implementation of strategic deployment for the delivery of medical care services; 3) implementation progress indicators, used to create the database for concentrating information and monitoring indicator measurement. (Source: self-created, adapted from refs. 3 and 19).*

influence, and are key in fulfilling and ensuring the continuation of the goals of public health policies for providing medical care in hospitals. The opportunity was afforded to present simple and innovative methodologies in this study, highlighting structural, strategic, and prospective analysis to identify the role of actors in their strategic alignment, and even evaluate, with KPIs, the follow-up on global, regional, or sectoral convergence or divergence in effectively achieving strategic, tactical, and operational objectives in the health care sector's value chain, where health care actors perform the health care operations to achieve the expected outcomes in medical care.

The first method involves understanding and identifying the political opposition and support that the health reform process will face. The second prioritizes factors in the MICMAC software that are determinative and sets the stage to continue with the research line of actor analysis and the construction of actor maps in relation to achieving strategic objectives with the MACTOR software, allowing for the observation of the various strategic leaders applying resources in different health care sector scenarios. In the actor objectives architecture model, both the theoretical and practical use of Microsoft Visio[19] software are linked in actor mapping to visualize the actor game, while also observing, through the dashboard, the KPIs that allow measurement of the convergence in achieving effective objectives and strategies used to achieve the goals, at strategic, tactical, and operational levels.

The study presents the perspective of implementing alignment at strategic, tactical, and operational hierarchical levels in the corresponding control dashboards, with the establishment and implementation of KPIs for objectives, strategies, and goals according to their priorities, and the realization of activities with KPIs that ensure the mission, vision, and strategic objectives. In certain cases, the lines of action or corresponding initiatives are implemented in time, enabling the adjustment of strategic actions towards the expected results in the production of hospital medical goods and services.

Conclusions

Strategic actor mappings using matrices and interdisciplinary health actor objectives maps are associated with the structured quantitative analysis, based on the identification of priority variables from MICMAC and MACTOR, prioritizing strategic actions to ensure coherent strategic alignment in health care institutions, extending to hospitals to ensure continuity of effective and efficient objectives in providing the best medical care, fostering healthy interaction and intelligent management of political interest conflicts based on the analyses performed on processes or activities.

The study, through the use of actor diagnostics, is a contribution, and its interpretation in MACTOR, along with mapping and the evaluation of process owners through KPIs, affirms the research question: Yes, global actors who make decisions can be identified, along with strategic alignment, and even the effectiveness of the various strategic levels —tactical and operational— up to hospital managers who lead the provision of medical care.

The significant involvement of actors is validated through the use of analysis methods and the MACTOR software and mapping, which can be learned in the health and hospital sector to develop disruptive proposals and strategies, preparing hospital administrators to present results based on KPIs obtained for feedback in future global or regional public health policies.

Finally, the actor analysis anticipates and visualizes in a prioritization map, convergence, and strategic power, which will impact hospitals in the future, ensuring an efficient vision of hospital medical care due to the multiple global factors and leading actors that will affect the health sector and globally in the long term.

Acknowledgments

The author thanks the National System of Researchers and UPIICSA for their support in this research.

Funding

This research has received a postdoctoral grant from CONAHCyT.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The author declares that this article does not contain any patient data.

Right to privacy and informed consent. The author declares that this article does not contain any patient data.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence in the drafting of this manuscript, nor for the creation of figures, graphics, tables, or their corresponding footnotes.

References

1. Organización de Estados Americanos. Planificación del Desarrollo Regional Integrado: Directrices y Estudios de Casos Extraídos de la Experiencia de la OEA 1984. Departamento de Desarrollo Regional. Secretaría Ejecutiva para Asuntos Económicos y Sociales. Organización de los Estados Americanos. Washington, D.C.; enero de 1984.
2. Doing Business in México. Guía para una inversión inteligente. Convergencia y Oportunidades en el Sector Salud. PwC México; junio de 2012.
3. Torres-Salgado MK. Indicadores de desempeño de procesos médicos con alineamiento estratégico en la atención al paciente. Cir Cir. 2021;89:403-10.
4. Armijo M, Bonnefoy J. Indicadores de desempeño del sector público. Publicación de las Naciones Unidas; 2005.
5. Gutiérrez Pulido H. Calidad total y productividad. México: Mc Graw Hill; 2010.
6. Plan Estratégico de la Organización Panamericana de la Salud 2020-2025. La equidad, el corazón de la salud. Documento oficial: 359. Washington, D.C.: Organización Panamericana de la Salud; 2020. Licencia: CC BY-NC-SA 3.0 IGO.
7. Reich M, Cooper D. Policy maker. Computer-aided political analysis: improving the art of the feasible. Version 2.2 PoliMap. (1995-1998); 1996.
8. Infante A. Lineamientos para la realización de análisis estratégicos de los actores de la reforma sectorial en salud. Programa de Organización y Gestión de Sistemas y Servicios de Salud de la División de Desarrollo de Sistemas y Servicios de Salud de la OPS/OMS, por los investigadores del Centro de Políticas Públicas del Instituto de Estudios Superiores de Administración de Caracas, Venezuela, María Helena Jaén y Daniel Paravisini. Caracas, Venezuela: Organización Panamericana de la Salud; 2000.
9. Boudon R. La lógica de lo social. Madrid: Rialp; 1984.
10. Bourdieu P. Homo academicus. 3.ª ed. Madrid: Siglo XXI; 2008.
11. Godet M, Durance P. Prospectiva estratégica para las empresas y los territorios. París: Organización de las Naciones Unidas para la Educación, la Ciencia y la Cultura (UNESCO); 2011.
12. Godet M. De la anticipación a la acción. Manual de prospectiva estratégica. Barcelona: Marcombo Boixareu; 1993.
13. Godet M. El método MACTOR, Estratégico. Revista de la Fundación para Estudios de la Defensa Nacional, junio de 1996.
14. Torres Salgado MK. Process architecture with strategic indicators in outpatient medical services in highly specialized hospital. Gac Med Mex. 2020;155:1-9.
15. Torres-Salgado MK. Arquitectura de procesos para hospitales: construcción de modelado estratégico de indicadores. Rev Hospital Juárez Mex. 2022;89:136-45.
16. Porter ME. What is strategy. Harvard Business Review. 1996;(60-78).
17. Simon D, Fischbach K, Schoder D. Enterprise architecture management and its role in corporate strategic management. Information Systems and e-Business Management. 2013;12:5-42.
18. Meena K, Thakkar J. Development of balanced scorecard for healthcare using interpretive structural modeling and analytic network orocess. J Adv Manag Res. 2014;11:232-56.
19. Todo sobre Microsoft Visio® para diagramas. ¿Qué quieres hacer con tus diagramas? Lucidchart, Lucid Software. Disponible en: https://www.lucidchart.com/pages/es/que-es-microsoft-visio.

ORIGINAL ARTICLE

Animal experimental study of 3D-printed titanium implants based on magnesium-zinc ion surface modification to promote oral soft-tissue closure

Estudio experimental en animales de implantes de titanio impresos en 3D basados en la modificación iónica de la superficie de magnesio/zinc para promover el cierre del tejido blando oral

*Shuo Huang, Fang Guo, Ning Liu, Kaijin Hu, and Changkui Liu**

College of Stomatology, Xi'an Medical University, The Third Affiliated Hospital of Xi'an Medical University, Research Center for Tooth and Maxillofacial Tissue Regeneration and Restoration, Xi'an, Shaanxi, 710021, China

Abstract

Objective: *The study aimed to investigate whether 3D-printed titanium implants modified with magnesium and zinc ion surfaces can promote oral soft-tissue closure.* **Method:** *New Zealand Great White rabbits were selected as experimental animals, and the left and right side mandibular teeth of each animal were randomly divided into an experimental group and control group, each with 18 cases, and the bilateral first premolar teeth were extracted after general anesthesia, and implants were implanted into the magnesium/zinc ionized surface-treated and the surface-untreated groups, respectively.* **Results:** *Under naked-eye observation, the combination of implant material and surrounding soft tissue in the experimental group was significantly better than that in the control group; fluorescence staining showed that the fluorescence density value of the experimental group was significantly higher than that of the control group ($p < 0.05$).* **Conclusions:** *3D-printed titanium implants based on magnesium–zinc ion surface modification promote oral soft-tissue closure with significant results.*

Keywords: *Magnesium-zinc ion surface modification. 3D printing. Titanium implants. Soft tissue closure. Animal experiments.*

Resumen

Objetivo: *Investigar si los implantes de titanio impresos en 3D modificados con superficies de iones de magnesio y zinc pueden promover el cierre de tejidos blandos orales.* **Método:** *Se seleccionaron conejos grandes blancos de Nueva Zelanda como animales experimentales, y los dientes mandibulares izquierdo y derecho de cada animal se dividieron al azar en grupo experimental y grupo control, cada uno con 18 casos. Se extrajeron los primeros premolares bilaterales después de administrar anestesia general y se colocaron implantes en los grupos tratados con y sin modificación iónica de la superficie de magnesio/zinc.* **Resultados:** *Bajo observación a simple vista, la combinación del material del implante y el tejido blando circundante en el grupo experimental fue significativamente mejor que en el grupo de control. La tinción de fluorescencia mostró que el valor de densidad de fluorescencia del grupo experimental fue significativamente mayor que el del grupo control ($p < 0.05$).* **Conclusiones:** *Los implantes de titanio impresos en 3D basados en la modificación iónica de la superficie de magnesio/zinc promueven el cierre de los tejidos blandos orales con resultados significativos.*

Palabras clave: *Modificación iónica de la superficie de magnesio/zinc. Impresión 3D. Implantes de titanio. Cierre de partes blandas. Experimentos con animales.*

***Correspondence:**
Changkui Liu
E-mail: liuchangkui@xiyi.edu.cn

Date of reception: 26-12-2023
Date of acceptance: 18-03-2024
DOI: 10.24875/CIRUE.M24000796

Cir Cir (Eng). 2024;92(6):718-724
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Peri-implantitis is a common complication of oral implantation, which arises mainly due to the failure to form a stable soft tissue closure between the implant and the soft tissues, and although local antibiotics can control the infection to a certain extent, it is often difficult to remove the chronic foci of infection[1]. The presence of inflammation in the soft tissue of the neck of the implant affects the combination of gingival soft tissue and the smooth neck of the implant, and the inflammation gradually and continuously develops downward from the neck of the implant, resulting in the formation of a fibrous parcel on the surface of the implant, and the implant then loosens and falls off[2]. In the case of natural teeth, the soft-tissue closure consists of epithelium and connective tissue that penetrates the mucosal area to protect the submucosal tissues against external disturbing factors. Dental implants in contact with the epithelium and connective tissue form a closure similar to that of a natural tooth. However, compared to natural teeth, implant epithelial and connective tissues are weakly attached and susceptible to damage by external factors, leading to higher rates of implant infection[3,4]. Therefore, it is important to seek an effective method to strengthen the bond between soft tissues and the implant neck to resolve peri-implantitis and maintain the long-term stability of implants. 3D-printed personalized titanium implants are increasingly being studied as a new alternative to immediate implantation in the posterior region; however, due to the fact that the soft tissues around the implant are in a bacterial environment in the oral cavity, cases of poor closure of the implant with the surrounding soft tissues are common due to the effects of the rejection reaction and inflammatory response[5]. Relevant studies have shown that implant surface modification can effectively improve the surface properties of implants and enhance the ability of titanium surface and soft-tissue binding[6], and magnesium and zinc as a commonly used preparation for oral soft tissue healing, based on this background, this paper is to build a 3D-printed titanium implant modified with magnesium and zinc ions, and implanted in the oral cavity of New Zealand great white rabbits, to explore whether it can promote the closure of the oral soft tissues, with the aim of opening up new ways to provide a number of theoretical theories for the clinical development of The purpose of this paper is to provide some theoretical references for clinical development of new ways of oral implantation.

Method

Laboratory animal

Eighteen 6-month-old healthy adult New Zealand Large White rabbits, male and female, with a body mass of 2.5-3.5 kg, were selected as experimental animals, provided by the Animal Experiment Center of Xi'an Jiaotong University, and kept in the Animal Room of the Animal Experiment Center of the Department of Medicine of Xi'an Jiaotong University.

Main reagents

S-3000N scanning electron microscope (SEM; Hitachi, Japan), E300CP/400CS hard tissue cutting and grinding system (EX-AKT Vertriebs GmH, Germany), TCS.SP8 laser scanning confocal microscope (Leica, Germany), the C43.104 electronic universal testing machine (MTS type, Shenzhen Meters Company, China). Pentobarbital sodium, calcineurin cell viability kit (Eimage Technology Co., Ltd., China).

Personalized implant design and fabrication

A computed tomography of rabbit head was taken and the obtained DICOM data were imported into the medical image processing software MIMICS 15.0 to obtain a 3D geometric surface model of the jawbone and teeth. The 3D geometric surface model of the mandible with teeth was exported as a point cloud file in STL format and imported into Geomagic 12.0 inverse software, and personalized root-shaped titanium implants were designed according to the morphology of the bilateral mandibular first premolar teeth, which were printed out using 3D printing technology (SLM, EOS-M290, Germany, average particle size of 20 μm), and a mixed-acid wash solution (HF: HNO_3: H_2O = 1:5:4 Vol) was diluted 4 times with ultrapure water and used to acid-wash the titanium-based material under ultrasound 3 times for 5 min each time to remove the surface oxide film. Subsequently, the samples were rinsed with ultrapure water until the surface was smooth and clean without residual traces of mixed acid wash solution, dried naturally in the air, and the samples were labeled as Ti. The above pre-treated materials were placed on the target stage of the vacuum chamber of the plasma immersion ion implantation (PIII) equipment, and the magnesium, and zinc ions were injected individually and the magnesium/zinc ions were

co-injected when the vacuum degree was up to 5 × 10-2 Pa. Finally, they were washed with distilled water, autoclaved, and dried and preserved for use[1]. and dried and preserved for use[7].

Experimental grouping and treatments

The left and right mandibular teeth of each experimental animal were randomly divided into two groups, and the bilateral first premolar teeth were extracted after general anesthesia, one implant was implanted in each of the magnesium/zinc ion surface-treated group (experimental group) and the surface-untreated group (control group), respectively, and a total of 36 implants were implanted, i.e., 18 implants in the experimental group and 18 implants in the control group. The specific methods of soft tissue implant surgery were as follows: 3% sodium pentobarbital at a dose of 1 mL/kg was used to perform auricular marginal intravenous general anesthesia, perioral skin preparation was performed after anesthesia became evident, and in accordance with aseptic surgical practices, intra and extraoral 1% povidone-iodine disinfection was performed, and routine toweling was performed. Minimally, invasive extraction of bilateral mandibular first premolar, implantation of the sterilized implant, mattress suture method to close the gingiva and implant. Postoperatively, penicillin 800,000 U was given intramuscularly once a day for 5 d to prevent infection in the operative area. Feeding and observation under routine conditions were performed to closely observe whether there was any wound infection after surgery. The sutures of the wound were removed 10d after the operation. The operation methods were all standardized to ensure that there was no significant difference between each group of experimental subjects before the test observation. The experimental animals in each group were executed by air embolization of the marginal ear vein at 2 and 4 weeks after the operation, and bilateral mandibular specimens were taken for observation and testing.

Fluorescent staining test

After the animals were executed at 2-4-weeks postoperatively, the mandibular specimens with implants were taken and fluorescently labeled with a calcein yellow chlorophyll kit, while the specimens were dehydrated, fixed, and fabricated into implant bone abrasions, which were observed under a laser scanning confocal microscope, and the fluorescence density values of the fluorescent bands were measured. The entire staining and observation process should be carried out under light protection to prevent premature quenching of fluorescence. The relevant operations were performed in strict accordance with the instructions of the reagents and instruments.

Observation indicators

(1) At 2 weeks and 4 weeks after implantation, the bonding of the implant material with the host soft tissue of the two groups was compared by visual observation and the bonding of the implant material with the host soft tissue of the two groups was evaluated by fluorescence staining. (2) Observe the fluorescence staining graphs of the two groups 2 weeks and 4 weeks after implantation and compare the fluorescence density values of the two groups.

Statistical method

Data were analyzed using the statistical analysis software Statistical Package for the Social Sciences (SPSS) 17.0, and measurements were expressed as arithmetic mean ± standard deviation and statistically tested using one-way analysis of variance (ANOVA). Each group of variables contained at least three valid values, and the significant difference level was set at $p < 0.05$ to indicate that the data were statistically significantly different.

Results

Observation by naked eye

After 2 and 4 weeks of implantation, under naked eye observation, the combination of the implant material and the surrounding soft tissues in the experimental group had almost no gaps and was tighter than that of the control group, and the surrounding tissues were red and glossy, and no obvious inflammatory reaction was seen; in the control group, the combination of the implant material and the surrounding soft tissues had numerous gaps, and the surrounding tissues were poorly blooded and glossy, and there was an obvious inflammatory reaction, which was a poor result. The combination of the implant material with the surrounding soft tissue in the experimental group was significantly better than that in the control group figure 1.

Fluorescent staining test results

The area labeled with calcein xanthophyll showed green fluorescent bands. Since calcein xanthophyll can combine with calcified new bone and fluoresce under ultraviolet irradiation, the amount of fluorescent labeling can suggest the active degree of bone metabolism and bone proliferation in the tissues around the implant after surgery, and thus, it has been widely used in the restoration research of bone tissues. After 2 and 4 weeks of implantation, the fluorescence density values of the experimental group were (94.48 ± 33.40) and (30.78 ± 11.22), and the fluorescence density values of the control group were (68.44 ± 22.41) and (21.94 ± 7.97), respectively, and the measured data were analyzed by one-way ANOVA with SPSS 17.0 software.: At 4 weeks of planting, the fluorescence density values of both groups were significantly higher than those of this group at 2 weeks ($p < 0.05$); at 2 and 4 weeks of planting, the fluorescence density values of the experimental group were significantly higher than those of the control group ($p < 0.05$) figure 2 and table 1.

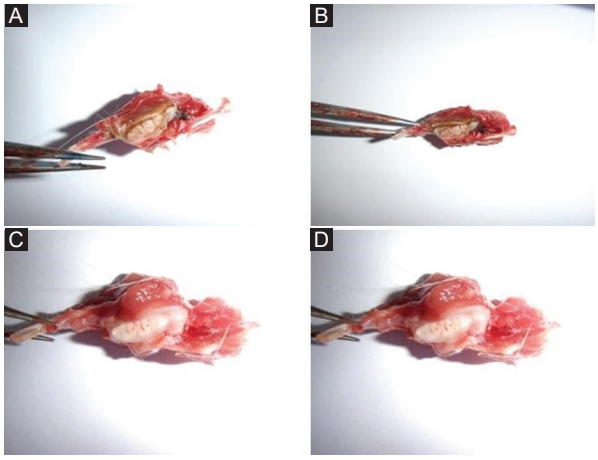

Figure 1. A*: sample pictures of the control group after 2 weeks.* **B:** *sample pictures of the control group after 4 weeks.* **C:** *sample pictures of the experimental group after 2 weeks.* **D:** *sample pictures of the experimental group after 4 weeks.*

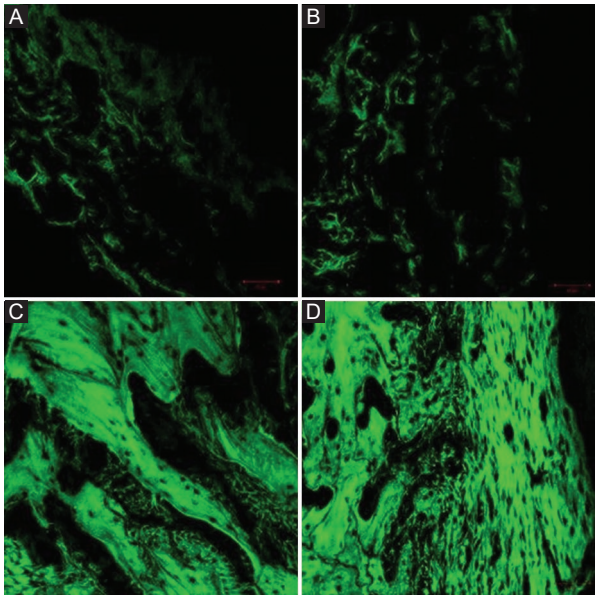

Figure 2. A: *fluorescence staining pictures of the control group after 2 weeks.* **B:** *fluorescence staining pictures of the control group after 4 weeks.* **C:** *fluorescence staining pictures of the experimental group after 2 weeks.* **D:** *fluorescence staining pictures of the experimental group after 4 weeks.*

Discussion

Peri-implant soft-tissue closure consists of two parts: epithelial attachment and connective tissue attachment. Epithelial attachment is the first layer of soft-tissue closure and is the front line of defense against external risk factors[8]. The tooth-epithelial bonding interface is formed at the perforating gingival site immediately after the eruption of a natural tooth, and its stability depends on the binding epithelium. The binding epithelium is a lowly differentiated non-keratinized complex squamous epithelium, which is stably attached to the tooth surface by epithelial adherens and forms a closed interface against harmful biological factors[9]. The epithelial attachment apparatus consists of two layers, including the basal layer where the inner basement membrane binds to the outer connective tissue and the suprabasal layer where the inner basement membrane and hemibridges come into direct contact with the tooth surface. The peri-implant epithelium is also directly attached to the abutment surface through the inner basement membrane and hemi-bridging granules, but this attachment structure is distributed only in the root-side portion of the epithelial attachment interface, whereas in the natural peri-implant periodontal area, the inner basement membrane and hemi-bridging granules are widely distributed throughout the epithelial-tooth interface. Therefore, the epithelial attachment strength of implants is lower than that of the natural periodontium and is more susceptible to destruction by external forces or biological factors[10-12]. In addition, when inflammatory manifestations were present in the soft tissues, the tendency of the inflammatory infiltration bands on the outer side of the pocket wall cells to

Table 1. Comparison of fluorescence density values between the two groups ($\bar{x}$ ± s)

Groups	Number of examples	Control group	Experimental group	F	p
2 week	18	21.94 ± 7.97	30.78 ± 11.22	2.725	0.010
4 week	18	68.44 ± 22.41	94.48 ± 33.40	2.747	0.010
F		8.294	7.670		
p		0.000	0.000		

spread toward the root side was more pronounced in the implant periodontium compared with the natural periodontium, with a greater total extent, a higher density of inflammatory cells in the soft tissues, and the neutrophils in the natural periodontium were mainly clustered in the epithelium of the pocket wall, whereas those in the implant periodontium were also distributed in the perivascular area around the root far away from the pocket wall[13,14]. Animal model studies have shown that compared with periodontitis, the connective tissue of peri-implant pockets often lacks an epithelial barrier to plaque, and its inflammatory infiltration is more extensive and closer to the top of the alveolar ridge, with more neutrophils and osteoclasts, and more severe resorption of the alveolar ridge; after removing inflammatory predisposing factors, the inflammatory response in the natural periodontium is self-limiting, while peri-implant lesions can still continue to progress, triggering extensive bone resorption[15,16]. This shows that the inflammatory destructive capacity of the implant periodontium is higher than that of natural teeth once symptoms of infection appear. Clinical studies have also confirmed that the progression of peri-implantitis tends to increase in a non-linear fashion and progresses faster than periodontitis[17]. Therefore, improving the sealing properties of the implant to the oral soft tissues is crucial for preventing infections and improving the long-term success rate of implants. Most of the current implant materials are commercially pure titanium or titanium alloys, and although this untreated titanium implant material has a certain soft-tissue bonding ability, its pure metal surface inhibits cell proliferation and migration to a certain extent, thus affecting tissue healing, and its limitations presented in the field of oral implantation have become increasingly prominent[18]. Relevant studies have shown that the attachment of suitable concentrations of magnesium and zinc ions to the surface of titanium materials by PIII technology is important for the proliferation and migration of human gingival fibroblasts (HGFs), which is expected to influence the ability of implant binding to oral soft tissues to a considerable extent[19]. Therefore, the present study was conducted to investigate whether 3D-printed titanium implants based on surface modification of magnesium and zinc ions could promote oral soft-tissue closure using New Zealand Large White Rabbits, and the results were as follows.

In this study, it was found that after 2 and 4 weeks of implantation, the combination of implant material and surrounding soft tissues in the experimental group was significantly better than that in the control group under naked-eye observation; fluorescence staining analysis showed that the fluorescence density values of the experimental group at 2 and 4 weeks of implantation were (94.48 ± 33.40) and (30.78 ± 11.22), respectively, which were significantly higher than those of the control group of (68.44 ± 22.41), (21.94 ± 7.97), and the differences were all statistically significant. (21.94 ± 7.97), and the differences were statistically significant, suggesting that 3D printed titanium implants based on surface modification of magnesium and zinc ions can effectively promote the combination of the implant and its periodontal tissues, and the closure effect is remarkable. Analyzing the reasons, on the one hand, the surface modification of magnesium and zinc ions can increase the biocompatibility of titanium implants. Titanium is a commonly used implant material, but there is often a certain tissue reaction at the interface between it and the soft tissue, resulting in incomplete closure of the soft tissue to the titanium implant. By introducing magnesium and zinc ions on the titanium surface, the compatibility between the implant and the surrounding tissues can be increased and the tissue reaction to the titanium can be reduced, thus promoting the closure of the soft tissues[20]. In addition, HGFs are the main cells involved in soft-tissue regeneration and closure, providing the basis for the formation of the keratinocyte layer, which plays a key role in oral wound healing and soft-tissue regeneration. The number and activity of HGFs at the implant-soft tissue interface are important for the formation of a solid closure between the implant and the soft tissue[21]. Relevant studies have shown that surface modification means to adjust the surface morphology and chemical composition of titanium have a significant effect on the behavior of HGFs adhesion spreading, migration, and proliferation, which suggests that changes in the physicochemical

properties of titanium surfaces can affect their soft-tissue closure properties[22]. It has been found that both magnesium and zinc ions have a certain promotion effect on the proliferation and activation of oral soft-tissue cells[23]. Magnesium ions can promote the migration and proliferation of soft-tissue cells and accelerate the closure process. Zinc ions have antioxidant and anti-inflammatory effects, which can promote tissue repair and healing, and further promote soft-tissue closure[24]. On the other hand, magnesium, a common agent in dental clinical treatment, has a significant effect on the behavior of HGFs. Ionization of magnesium into titanium surfaces by plasma immersion can effectively improve the adhesion and spreading of HGFs on the material surface and increase the potential of the material to promote soft-tissue closure. The study of the migration rate of HGFs on pure magnesium surfaces revealed that a specific concentration of magnesium ions could significantly enhance the adhesion of HGFs on the material surface although it had no significant effect on the proliferation and activity of HGFs[25]. Xiao et al.,[26] studied and discussed the effect of magnesium ion concentration on the directional migration ability of human fibroblasts and found that this property was related to integrins in extracellular matrix proteins. Zinc is also commonly used in oral therapy, where it effectively promotes soft-tissue regeneration and facilitates wound healing. Zinc also has an important effect on the behavior of HGFs. Zogheib et al.[27] cultured HGFs in a zinc-free medium and found that zinc deficiency significantly reduced HGFs migration, proliferation, and DNA synthesis, and affected cell morphology and intracellular oxidative stress levels. The addition of exogenous zinc as a supplement eliminated these conditions. Zinc has strong antimicrobial activity, implant-released zinc is effective in preventing post-operative infections, and plasma-immersed ion-incorporated zinc on titanium surfaces is effective in improving osteogenic properties and inhibiting bacterial growth. In addition, magnesium and zinc synergize to achieve complementary effects. Observations on the surface of titanium samples chelated with both magnesium and zinc ions revealed that magnesium ions can promote cell proliferation and differentiation, and facilitate the bonding of the implant with the surrounding soft tissues, while zinc ions can be highly effective in antimicrobial activity, and improve the stability and durability of the bonding of the implant with the surrounding soft tissues[28]. Hong[29] injected magnesium and zinc simultaneously into the surface of medical titanium, and the osteogenic proliferation and differentiation of rat bone marrow MSCs could be induced by the synergistic effect of magnesium and zinc ions, and this result fits with the conclusion of the present study. In addition, it has been shown[30] that magnesium and zinc ions can also affect angiogenesis in oral soft tissues. Angiogenesis is an important part of the soft-tissue repair and closure process, while magnesium and zinc ions can regulate the proliferation of vascular endothelial cells and the release of angiogenic factors, promote blood vessel growth and repair, and provide a better blood supply and nutrient support for the closure of the soft tissues, thus promoting the closure of oral soft tissues.

There are still some limitations of this study. For example, the sample size of this study is small, the study population is single, it is a single-center design, and the mechanism related to oral soft-tissue closure is relatively insufficient. All of these limitations constrain the generalization of the results of this study, and a more definitive and comprehensive conclusion of the study needs to be further confirmed by multi-sample and multi-center studies.

Conclusion

3D-printed titanium implants based on magnesium and zinc ion surface modification can promote oral soft-tissue closure with significant effect in this animal experiment.

Funding

Innovative team for disease mechanism and prevention of oral and maxillofacial system (No. 2022TD-54); General project of Key R&D Plan of Science and Technology Department of Shaanxi Province (No. 2023-YBSF-097); Xi'a Medical University 2022 Research Capacity Improvement Plan Project (No. 2022NLTS090); The Youth Innovation Team of Shaanxi Universities (no number).

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical

research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Ethics approval and consent to participate

The ethics approval was reviewed and approved by The College of Stomatology, Xi'an Medical University, Research Center for Tooth and Maxillofacial Tissue Regeneration and Restoration.

References

1. Liu JY, Lin YC, Chang GS, Li HH, Yang YT, Matsuyama YC, et al. Flame-sprayed strontium-and magnesium-doped hydroxyapatite on titanium implants for osseointegration enhancement. Surf Coat Technol. 2020;21:945-8.
2. Lee UL, Yun S, Lee H. Osseointegration of 3D-printed titanium implants with surface and structure modifications. Dent Mater. 2022;19:1105-9.
3. Alali A, Abdal-Hay A, Gulati K, Ivanovski S, Fournier BP, Lee RS. Influence of bioinspired lithium-doped titanium implants on gingival fibroblast bioactivity and biofilm adhesion. Nanomaterials (Basel). 2021;22:1358-61.
4. van Hengel IA, Putra NE, Tierolf MW, Minneboo M, Fluit AC, Fratila-Apachitei LE, et al. Biofunctionalization of selective laser melted porous titanium using silver and zinc nanoparticles to prevent infections by antibiotic-resistant bacteria. Acta Biomater. 2020;29:72-5.
5. Choe HC. Acceleration of bone formation and adhesion ability on dental implant surface via plasma electrolytic oxidation in a solution containing bone ions. Metals. 2021;48:246-57.
6. Abar B, Kelly CN, Allen NB. Influence of Topography on 3D Printed Titanium Foot and Ankle Implants. Vol. 34. Los Angeles, CA: SAGE Publications Sage CA; 2020. p. 15-8.
7. Zheng J, Zhang L, Yang X. A study on the coordination of cyclohexanocucurbit [6] uril with copper, zinc, and magnesium ions. Green Process Synth. 2021;23:4-7.
8. Wang N, Maskomani S, Meenashisundaram GK, Fuh JY, Dheen ST, Anantharajan SK. A study of titanium and magnesium particle-induced oxidative stress and toxicity to human osteoblasts. Mater Sci Eng C Mater Biol Appl. 2020;45:158-62.
9. Zhao H, Wang W, Liu F. Electrochemical insertion of zinc ions into self-organized titanium dioxide nanotube arrays to achieve strong osseointegration with titanium implants. Adv Mater Interfaces. 2022;112: 138-42.
10. Cao J, Lian R, Jiang X. Magnesium and fluoride doped hydroxyapatite coatings grown by pulsed laser deposition for promoting titanium implant cytocompatibility. Appl Surf Sci. 2020;102:178-81.
11. Timofeeva SN, Kadikov IR, Korchemkin AA. The effects of zinc and magnesium ingestion on essential trace-element accumulation in the organs of white rats upon cadmium exposure. Bio Web Conf. 2020;22:536-7.
12. Shah K, Mestry J, Rangnekar S. The role and importance of lipoproteins, vitamin D3, vitamin K and magnesium in the osseointegration of titanium dental implants. IOSR J Dent Med Sci. 2021;112:138-42.
13. Liu DW, Zuo C, Su KQ, Li P, Xiao LB, Cheng GY, et al. Strontium-zinc phosphate chemical conversion coating improves the osseointegration of titanium implants by regulating macrophage polarization. Chem Eng J. 2021;48:1-3.
14. Garamus VM, Limberg W, Serdechnova M. Degradation of titanium sintered with magnesium: effect of hydrogen uptake. Metals Open Access Metal J. 2021;16:106-7.
15. Zhao DW, Liu C, Zuo KQ. Strontium-zinc phosphate chemical conversion coating improves the osseointegration of titanium implants by regulating macrophage polarization. Chem Eng J. 2020;43:1708-10.
16. Shah K, Mestry J, Rangnekar S. The role and importance of lipoproteins, vitamin D3, vitamin K and magnesium in the osseointegration of titanium dental implants. IOSR J Dent Med Sci. 2021;35:15-7.
17. Awadly TA, Wu G, Ayad M, Radi IA, Wismeijer D, El Fetouh HA, et al. A histomorphometric study on treated and untreated ceramic filled PEEK implants versus titanium implants: preclinical *in vivo* study. Clin Oral Implants Res. 2020;56:94-100.
18. Wu S, Xu J, Zou L, Luo S, Yao R, Zheng B, et al. Long-lasting renewable antibacterial porous polymeric coatings enable titanium biomaterials to prevent and treat peri-implant infection. Nat Commun. 2021;12:3303.
19. Chernohorskyi DM, Chepurnyi YV, Vasiliev OS, Voller MV, Kopchak AV. Evaluation of the accuracy of surgical reconstruction of mandibular defects when using navigation templates and patient-specific titanium implants. J Educ Health Sport. 2021;81:444-9.
20. Charoenkwan P, Kanthawong S, Nantasenamat C, Hasan M, Shoombuatong W. iAMY-SCM: improved prediction and analysis of amyloid proteins using a scoring card method with propensity scores of dipeptides. Genomics. 2021;14:2300-4.
21. Sharp AL, Pallegadda R, Baecker A, Park S, Nassery N, Hassoon A, et al. Are mental health and substance use disorders risk factors for missed acute myocardial infarction diagnoses among chest pain or dyspnea encounters in the emergency department?. Ann Emerg Med. 2022;32:116-9.
22. Amara HB, Martinez DC, Shah FA. Magnesium implant degradation provides immunomodulatory and proangiogenic effects and attenuates peri-implant fibrosis in soft tissues. Bioact Mater. 2023;21:1042-6.
23. Goodson AM, Parmar S, Ganesh S, Zakai D, Shafi A, Wicks C, et al. Printed titanium implants in UK craniomaxillofacial surgery. Part II: perceived performance (outcomes, logistics, and costs). Br J Oral Maxillofac Surg. 2021;59:320-8.
24. Watanabe T, Nakagawa E, Saito K. Differences in healing patterns of the bone-implant interface between immediately and delayed-placed titanium implants in mouse maxillae. Clin Implant Dent Relat Res. 2020;25:1205-8.
25. Altuna P, Fernández‐Villar S, Barroso‐Panella A, Ortiz-Puigpelat O, Hernández-Alfaro F, Nart J. Narrow diameter titanium–zirconium tissue‐level implants supporting multi‐unit FDPs in the anterior area: a 5‐year prospective study. Clin Oral Implants Res. 2023;29:710-25.
26. Xiao W, Chen Y, Chu C, Dard MM, Man Y. Influence of implant location on titanium-zirconium alloy narrow-diameter implants: a 1-year prospective study in smoking and nonsmoking populations. J Prosthet Dent. 2021;35:66-9.
27. Zogheib T, Walter-Solana A, Iglesia FL. Do titanium mini-implants have the same quality of finishing and degree of contamination before and after different manipulations? An *in vitro* study. Metals Open Access Metal J. 2021;49:72-6.
28. Borgonovo AE, Censi R, Vavassori V. A possible relationship between peri-implantitis, titanium hypersensitivity, and external tooth resorption: metal-free alternative to titanium implants. Case Rep Dent. 2021;45:1512-3.
29. Hong MH. Comparison of stress distribution in bone and implant-supported dental prosthesis with zirconia and titanium implants: a 3-dimensional finite element analysis. J Korean Acad Dent Technol. 2020;44:617-22.
30. Chacun D, Lafon A, Courtois N. Compared osseointegration of a novel zirconia material and titanium on blasted implants in dogs. Clin Oral Implants Res. 2020;25:7694-701.

ORIGINAL ARTICLE

Extranodal Rosai-Dorfman disease in the breast: a literature review from 1969 to 2023

Enfermedad de Rosai-Dorfman extraganglionar en la mama: una revisión de la literatura de 1969 a 2023

Jorge S. Haro-Cruz[1], Laura M. Rodríguez-Barrios[1], Ana C. Díaz-Degollado[2], Guillermo Álvarez-Sánchez[1], Marisol Guitián-González[1], Claudio D. Rojas-Gutiérrez[1], Erick Zuñiga-Garza[1], Israel Salgado-Adame[1], Ruddy F. Canaan-Figueroa[1], Allan F. Delcid-Morazán[1], Sara I. Rodríguez-Barrios[3], and Daniel Chacón-Galvis[1]*

[1]Departamento de Cirugía Plástica y Reconstructiva, Centro Médico Nacional "20 de noviembre," Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; [2]Hospital de Oncología, Centro Médico Nacional Siglo "XXI", Instituto Mexicano del Seguro Social. Ciudad de México, México; [3]Departamento de Cirugía General, Hospital Santo Tomás, Ciudad de Panamá, Panamá

Abstract

Objective: *Reviewing available literature regarding extranodal Rosai–Dorfman disease in the breast to explore the clinical characteristics of this disease, the described therapeutic options, and their outcomes.* **Method:** *In January 2024, the PubMed, SpringerOpen, and Scopus databases were searched with the keywords "Rosai," "Dorfman," and "Breast." Forty-two studies were included in the final analysis, obtaining a total of 70 reported cases of extranodal Rosai–Dorfman disease affecting the breast. Patient characteristics, mammogram descriptions, therapeutic management, and outcomes were reviewed for statistical analysis.* **Results:** *The main population consisted of females in their sixth decade of life (93%), presenting with a firm, non-tender nodule (65.7%), generally localized to one breast (72%). About 18.6% of patients had nodal or extranodal disease in other areas. Excisional biopsy was the main treatment strategy (63%) and surgical excision showed a lesser association with recurrence than incisional biopsy (p = 0.049). Most instances of disease recurrence or progression were diagnosed within the first 2 years.* **Conclusions:** *This study revealed that surgical excision showed less association with disease recurrence or progression than expectant management. Follow-up can be conducted with a mammogram and physical examination since recurrence tends to occur locally within 2 years.*

Keywords: *Breast. Extranodal. Rosai–Dorfman disease. Management. Systematic review.*

Resumen

Objetivo: *Revisar la literatura disponible respecto a la enfermedad de Rosai-Dorfman en la mama para explorar sus características clínicas, las opciones terapéuticas descritas y sus desenlaces.* **Método:** *En enero de 2024 se realizó una revisión en las bases de datos PubMed, SpringerOpen y Scopus con las palabras clave "Rosai", "Dorfman" y "Breast". Se incluyeron en el análisis 42 estudios, obteniendo un total de 70 casos reportados de enfermedad de Rosai Dorfman extraganglionar en la mama. Las características de los pacientes, las mastografías, los manejos y los desenlaces se incluyeron en el análisis estadístico.* **Resultados:** *La población principal consistió en mujeres en la sexta década de la vida (93%), debutando con un nódulo firme, no doloroso (65.7%), generalmente localizado en una sola mama (72%). El 18.6% presentaron enfermedad en otros sitios. La biopsia escisional fue el principal manejo (63%), y la escisión quirúrgica mostró menor asociación con recurrencia que la biopsia incisional (p = 0.049). La mayoría de las recurrencias ocurrieron en los primeros 2 años.*

***Correspondence:**
Jorge S. Haro-Cruz
E-mail: jorgeharocruz@gmail.com

Date of reception: 01-04-2024
Date of acceptance: 12-05-2024
DOI: 10.24875/CIRUE.M24000797

Cir Cir (Eng). 2024;92(6):725-734
Contents available at PubMed
www.cirugiaycirujanos.com

Conclusiones: *Este estudio reveló que la escisión quirúrgica se asocia a menor recurrencia que el manejo expectante. El seguimiento debe mantenerse por al menos 2 años con un enfoque en las recurrencias locales.*

Palabras clave: *Extraganglionar. Mama. Enfermedad de Rosai-Dorfman. Manejo. Revisión sistemática.*

Introduction

Rosai–Dorfman disease (RDD), sometimes referred to as "Rosai–Dorfman–Destombes disease," represents a rare, idiopathic, and generally benign pathological entity which most commonly manifests as a massive, bilateral lymphadenopathy in the head and neck region of males between their second and third decade of life[1]. It was first described in 1959 by Pierre-Paul Louis Lucien Destombes but was not recognized as its own pathological entity until pathologists Juan Rosai and Ronald Dorfman's work in 1969[2,3]. Although initially described as a sinus histiocytosis with massive lymphadenopathy, it is currently classified as a type of non-Langerhans cell histiocytosis[4,5]. Less than half of afflicted patients present an extranodal variety of this disease, with some studies citing somewhere between 50 and 90 cases of sole breast affection[5].

Clinically, breast affection is most frequently reported as a firm non-tender nodule in one or both breasts. Confirmatory diagnosis is achieved through histopathological analysis, while core biopsy has been reported to be more reliable in comparison to fine-needle aspiration; excisional biopsy remains the mainstay for definitive diagnosis[6]. Finding proliferative histiocytes with emperipolesis is deemed to be pathognomonic of Rosai–Dorfman, with emperipolesis consisting of the presence of an intact cell within the cytoplasm of another cell[7]. The interiorized cell remains viable and is capable of exiting the other cell at any time without causing structural or functional compromise[8]. Another characteristic that guides diagnosis is its immunohistochemical profile which stains positive for S100 and CD68, and negative for CD1a[9]. While most cases have been associated with a benign prognosis, recurrence, and progression, both at a local and systemic level have been described and data on long-term follow-up is scarce[10]. Despite its low incidence, this pathology tends to mimic breast malignancy on clinical and radiological examination and with no current guidelines regarding a diagnostic and therapeutic gold standard, patients are often managed on a case by case basis[1,5,10].

The following systematic review aims to look at every case currently published in medical literature, gathering information on patient characteristics, presentation, management, and outcome in hopes of acting as a guide for future clinicians faced with this infrequent clinical entity.

Method

For the present systematic review, we selected all published original articles reporting cases of histologically confirmed extranodal Rosai–Dorfman disease with breast affection. We conducted a literature search in January 2024 using the PubMed, SpringerOpen, and Scopus databases with the keywords "Rosai–Dorfman" and "Breast." All articles including the established keywords published since 1969 were initially considered, with most of them corresponding to case reports and literature reviews. Inclusion criteria encompassed all articles detailing patients with a histologically confirmed diagnosis of Rosai–Dorfman in the breast with or without the involvement of other sites. Exclusion criteria included articles which were inaccessible, reports of Rosai–Dorfman outside of the breast, or cases that did not include at least four of the nine items detailed on our checklist. We initially identified 67 possible studies of which only 55 were assessed for eligibility. After a full review of each article, 42 were included in our review with eight being literature reviews and the rest being case reports and case series (Fig. 1). Among the articles included, clinical data were collected including demographic characteristics of patients, use of mammogram, BIRADS, management, length of follow-up, and recurrence. Whenever an article included data on patients previously reported by another author, only new patients were considered toward our final patient count, but any data missing from the previous reports were still compiled. Only articles including previously unreported patients among their series were included in the study. Statistical analysis was conducted with the Statistical Package for the Social Sciences version 25.0 statistical software. Findings were presented as mean ± standard deviation for numerical variables and frequency (%) for categorical

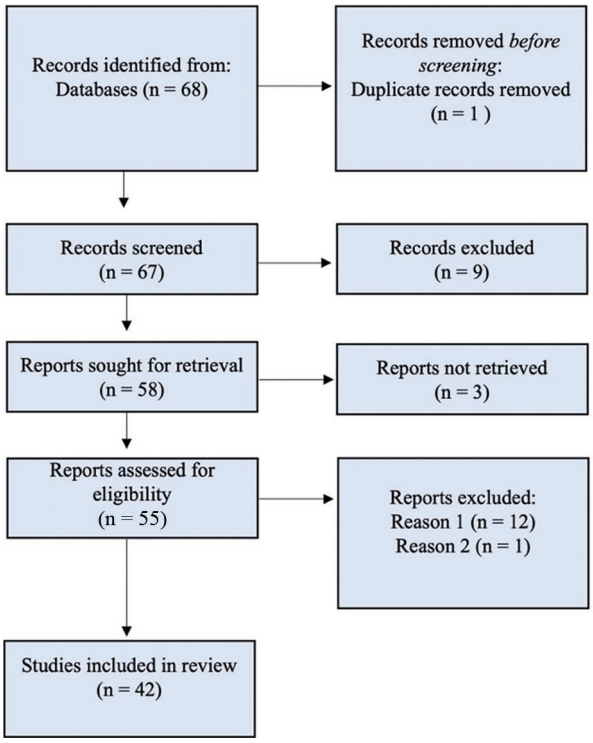

Figure 1. *Algorithm for article selection. Reason 1: Article did not describe a case of extranodal breast Rosai–Dorfman disease. Reason 2: Article described a case of extranodal breast Rosai–Dorfman disease but did not include enough data regarding the patient and management.*

variables. χ^2 and Fisher's exact test were utilized. Statistical significance was deemed as $p < 0.05$.

Results

After a careful review of each of the articles included in our study, we identified a total of 70 cases of extranodal Rosai–Dorfman disease (RDD) of the breast across 42 reports (Table 1). We observed a gender distribution of five males and 65 females (7% vs. 93%), with a generalized age range of 15-84 years and a mean age of 54 (± 15), implying a relatively mature demographic. On gender analysis, a mean age of 54 (± 15) and 44 (± 15) were found among females and males, respectively. Out of 68 patients in whom the initial clinical presentation was reported, the most frequently described scenario consisted of a palpable, non-tender nodule (n = 46, 65.7%). Twelve patients (17.1%) were asymptomatic and had incidental discoveries after a routine imaging study, 4 (5.7%) had bilateral nodules, 3 (4.3%) presented with multiple nodules in one breast, and 3 (4.3%) debuted with mastalgia. Data on clinical presentation were missing on 2 (2.9%) cases. A single breast was affected in 51 cases (72.9%), with bilateral affection in 9 (12.9%) reports. The right breast was most commonly affected (n = 31, 44.2%), while the remaining patients did not have laterality reported (n = 10, 14.2%). Most debuted with a localized breast affection (n = 56, 80%) versus a smaller proportion of patients who had some degree of nodal or extranodal disease in other areas of their bodies (n = 13, 18.6%).

While not all patients underwent radiologic studies, the one most frequently mentioned as part of the diagnostic workup was a mammogram (n = 50, 71.4%). Among these patients, the most commonly reported findings were poorly defined solid nodules classified as BIRADS 4 (n = 40, 80%). The remaining cases were classified as BIRADS 5 (n = 5, 10%), BIRADS 3 (n = 3, 6%), and BIRADS 0 (n = 2, 4%).

In regard to management, the most frequently reported procedure was an excisional biopsy (n = 44, 63%) followed by an incisional biopsy with subsequent expectant management (n = 13, 18.6%). Of the remaining patients, 6 (8.5%) underwent more extensive surgical procedures before diagnosis such as a partial mastectomy (n = 3, 4.3%), quadrantectomy (n = 2, 2.9%), and lumpectomy (n = 1, 1.4%). One of the reports combined an excisional biopsy with oral steroids, while another reported an incidental diagnosis made after a reduction mammoplasty. The remaining reports did not describe management (n = 6, 8.5%).

Follow-up was mentioned in 43 (61.4%) cases. The length of follow-up ranged from 2 months to 14 years, with an average of 20 months. Out of these patients, disease progression or recurrence was shown on 12 (17.1%), presenting as early as 2 months and up to 4 years after initial diagnosis, with an average of 16 months. Roughly half of these occurred locally in the affected breast, with the other half presenting mainly in the subcutaneous tissue of other sites of the body without a particular discernible pattern. Out of the included 70 cases, only one death (1.4%) was reported and directly attributed to disease progression.

On statistical analysis, gender did not appear to impact outcome when comparing recurrence between men and women ($p = 0.82$), debuting with bilateral disease was found to be associated with extranodal disease ($p = 0.007$). In regard to recurrence or progression, extramammary disease at diagnosis showed a stronger association in comparison to isolated

Table 1. Case reports reviewed and findings

Author	Age	Gender	Clinical presentation	Affected Breast	Extension	Mammogram/BIRADS*	Management	Outcome
Rosai and Dorfman[11] (1969)	25	F	-	Bilateral	Regional LN, CNS, soft-tissues, liver	-	Excisional biopsy	Persistent lymphadenopathy
	17	F	-	-	Axillary LN	-	Excisional biopsy	-
Pérez Guillermo et al.[12] (1993)	71	F	Nodule	Bilateral	EBA	LB: Solid well-defined mass (4) RB: Solid poorly defined mass (4)	LB: Excisional biopsy/ RB: Quadrantectomy	-
Hammond et al.[13] (1996)	67	F	Nodule	-	EBA	Solid poorly defined mass (4)	Excisional biopsy	Disease-free at 6 months
Govender and Chetty[14] (1997)	34	F	Nodule	-	EBA	-	-	-
Green et al.[15] (1997)	15	F	Bilateral nodules	Bilateral	Regional LN	(4)	Excisional biopsy	-
	84	F	Asymptomatic	Bilateral	Axillary LN	(4)	Excisional biopsy	Deceased 2 months after surgery due to systemic progression
	56	F	Bilateral nodules	Left	Mediastinal LN	(4)	Excisional biopsy	Disease-free at 5 years
	69	F	Nodule	Right	EBA	(4)	Excisional biopsy	-
	48	F	Nodule	Right	EBA	(4)	Excisional biopsy	Disease-free at 12 months
	54	F	Nodule	Right	EBA	(4)	Excisional biopsy	Disease-free at 12 months
	71	F	Nodule	-	EBA	(4)	Excisional biopsy	-
Soares et al.[16] (1999)	65	F	Multiple bilateral nodules	Bilateral	EBA	Multiple bilateral solid masses (4)	Excisional biopsy	-
Hummel et al.[17] (1999)	52	F	Nodule	Left	EBA	Poorly defined mass (5)	-	-
Ng et al.[18] (2000)	61	F	Nodule	Right	EBA	Not performed	Excisional biopsy	Disease-free at 6 months
	40	F	Mastalgia	Right	EBA	Poorly defined mass (4)	Excisional biopsy	Disease-free at 1 month
Kuzmiak et al.[19] (2003)	30	F	Nodule	Right	EBA	Poorly defined mass (4)	Excisional biopsy	-
Pham et al.[20] (2005)	53	F	Nodule	Left	EBA	Poorly defined mass (4)	Incisional biopsy	Disease-free at publication
Da Silva et al.[21] (2007)	50	F	Nodule	Left	EBA	Poorly defined mass (4)	Excisional biopsy	Disease-free at 5 years
Perera et al.[22] (2007)	23	M	Nodule	Left	EBA	Poorly defined mass (5)	Excisional biopsy	Disease-free at 3 months
Dahlgren et al.[23] (2008)	64	F	Asymptomatic	Bilateral	Parotid and cervical LN	- -	Excisional biopsy	-

(Continues)

Table 1. Case reports reviewed and findings *(continued)*

Author	Age	Gender	Clinical presentation	Affected Breast	Extension	Mammogram/BIRADS*	Management	Outcome
Franco-Odio et al.[24] (2009)	59	F	Nodule	Right	EBA	Poorly defined mass (5)	Excisional biopsy	-
Morkowski et al.[25] (2010)	53	F	Asymptomatic	Left	EBA	Irregular dense mass (4)	Excisional biopsy	Initially presented with a negative incisional biopsy, progressed locally after 4 years, underwent excision, and remains disease-free at 5 years and 10 months
	45	F	Asymptomatic	Left	EBA	Poorly defined mass (4)	Excisional biopsy	Disease-free at 14 months
	54	F	Asymptomatic	Right	EBA	Irregular mass (4)	Excisional biopsy	Disease-free at 4 years
Wu et al.[26] (2010)	33	F	Nodule	Right	EBA	-	Lumpectomy	Disease-free at 2 years
Bansal et al.[27] (2010)	35	M	Nodule	Right	EBA	-	Incisional biopsy	Disease-free at 18 months
Picón-Coronel et al.[28] (2010)	67	F	Nodule	Right	EBA	Poorly defined mass (4)	Excisional biopsy	-
Noordzij et al.[29] (2011)	75	F	Nodule	Right	EBA	Multiple solid masses	Excisional biopsy	-
Gwin et al.[30] (2011)	68	F	Asymptomatic	Bilateral	EBA	Multiple small bilateral masses (4)	Incisional biopsy	-
Tenny et al.[31] (2011)	64	F	Nodule	Right	Axillary LN	Poorly defined mass (4)	Incisional biopsy	Local recurrence at 6 months, contralateral breast mass at 7 months, left flank SCT mass at 11 months (after initial biopsy)
Fu et al.[32] (2012)	78	F	Nodule	Right	EBA	-	Excisional biopsy	-
Cha et al.[33] (2012)	62	F	Nodule	Right	EBA	Poorly defined mass (3)	Incisional biopsy	Disease-free at 10 months
Baladandapani et al.[34] (2012)	59	M	Multiple unilateral nodules	Left	EBA	Poorly defined lobulated mass (5)	Excisional biopsy	-
Parkin et al.[35] (2015)	56	F	Asymptomatic	Left	EBA	Solid well-defined mass (4)	Incisional biopsy	Disease-free at 11 months
Ibáñez et al.[36] (2015)	69	F	Nodule	Right	EBA	Poorly defined mass (4)	Partial mastectomy	Disease-free at 3 years
Mantilla et al.[37] (2016)	59	F	Mastalgia	-	EBA	Non-definitive findings (0)	Incisional biopsy	New nodule in SCT of left thigh at 3 years of follow-up
	67	F	Nodule	-	EBA	-	-	-
Simmons et al.[38] (2016)	41	F	Nodule	Right	EBA	Heterogeneous lobulated mass (4)	Excisional biopsy	Disease-free at 9 months

(Continues)

Table 1. Case reports reviewed and findings *(continued)*

Author	Age	Gender	Clinical presentation	Affected Breast	Extension	Mammogram/BIRADS*	Management	Outcome
Jorns[39] (2016)	-	F	Asymptomatic	-	EBA	Poorly defined mass (4)	Incisional biopsy	Disease-free at publication
Zhou[40] (2016)	71	F	Multiple unilateral nodules	Left	EBA	Poorly defined mass (4)	Excisional biopsy	-
El-Attrache et al.[2] (2017)	55	M	Nodule	Right	EBA	Poorly defined mass (4)	Excisional biopsy	-
Delaney et al.[41] (2017)	63	F	Nodule	Right	EBA	Poorly defined mass (4)	Incisional biopsy	New breast nodule at 7 months of follow-up, no further progression at publication
De Mello et al.[42] (2018)	55	F	Nodule	Left	EBA	Irregular poorly defined nodule (4)	Incisional biopsy	Development of 2 new nodules at 2 months of follow-up (SCT of leg and SCT of biopsy site), underwent excision of all three sites afterward
Araújo et al.[43] (2018)	46	F	Nodule	Left	EBA	Solid nodule (0)	Quadrantectomy	Disease-free at 4 years
Liu et al.[44] (2018)	65	F	Nodule	Right	EBA	- -	Excisional biopsy	Disease-free at 40 months
	78	F	Nodule	Right	EBA	- -	Excisional biopsy	Disease-free at 39 months
	53	F	Nodule	Left	EBA	- -	Excisional biopsy	Disease-free at 13 years
	45	F	Nodule	Left	EBA	- -	Excisional biopsy	Disease-free at 7 years
Goldbach et al.[45] (2018)	44	F	Nodule	Right	SCT of abdomen	Poorly defined mass (4)	Excisional biopsy	Disease-free at publication
Shin et al.[46] (2019)	54	F	Mastalgia	Right	EBA	- -	Excisional biopsy	Local recurrence at 6 months post-surgery
Dai et al.[47] (2019)	42	F	Asymptomatic	Left	EBA	Poorly defined mass (4)	Excisional biopsy	Disease-free at 3 years
Shetty et al.[48] (2020)	52	F	Asymptomatic	Right	EBA	Macromastia (3)	Incidental finding after reduction mammoplasty	Disease-free at 13 months
	54	F	Nodule	Right	EBA	(3)	Partial mastectomy	Disease-free at 14 months
	58	F	Nodule	Right	EBA	- -	Excisional biopsy	-
	63	F	Nodule	Right	Axillary LN	Poorly defined complex cystic masses (4)	Partial mastectomy	Systemic recurrence at 12 months post-surgery

(Continues)

Table 1. Case reports reviewed and findings *(continued)*

Author	Age	Gender	Clinical presentation	Affected Breast	Extension	Mammogram/BIRADS*	Management	Outcome
Elshikh et al.[49] (2020)	64	F	Nodule	-	SCT of breast	- -	-	-
	65	F	Nodule	-	EBA	- -	-	-
	50	F	Nodule	-	SCT of breast and parotid	Solid mass (4)	-	-
Vaidya et al.[50] (2020)	43	F	Nodule	Left	EBA	Spiculated solid mass (5)	Excisional biopsy	-
Battle et al.[51] (2020)	49	F	Multiple unilateral nodules	Right	EBA	Poorly defined mass (4)	Incisional biopsy	Remitting and recurring plaques and papules in affected breast during the 12 months of follow-up
Reddy et al.[8] (2021)	36	F	Nodule	Left	EBA	Spiculated mass (4)	Excisional biopsy	Disease-free at 2 years
	58	F	Asymptomatic	Left	Axillary, cervical and pectoral LN, humerus, sternum, bilateral clavicle, D4 vertebrae, bilateral femur, multiple bilateral pulmonary nodules	Poorly defined mass (4)	Excisional biopsy + Oral steroids	Disease-free at 11 months
Choo et al.[52] (2021)	52	F	Nodule	Left	EBA	Poorly defined mass (4)	Excisional biopsy	Disease-free at 4 years
	37	F	Nodule	Left	EBA	Poorly defined mass (4)	Incisional biopsy	-
Maldonado Marcos et al.[9] (2021)	50	M	Nodule	Right	SCT of breast	- -	Excisional biopsy	Disease-free at 2 years
Iancu et al.[5] (2021)	63	F	Multiple bilateral nodules	Bilateral	EBA	Poorly defined mass (4)	Incisional biopsy	Nodule involution at 6 months of follow-up, disease-free at 12 months
Ingole et al.[10] (2022)	21	F	Nodule	Right	EBA	- -	Excisional biopsy	-
Sumner et al.[53] (2023)	59	F	Asymptomatic	Bilateral	EBA	Solid round mass in RB (4), focal asymmetry in medial LB (4)	Excisional biopsy	-
Díaz-Degollado et al.[1] (2023)	67	F	Nodule	Right	EBA	Poorly defined mass (4)	Excisional biopsy	Disease-free at 5 years

*BIRADS score is described in parentheses; mammogram findings are included when described in their respective reports.
LN: lymph node; CNS: central nervous system; EBA: exclusive breast affection; SCT: subcutaneous tissue; LB: left breast; RB: right breast.

Table 2. Recurrence or progression comparison among patients with exclusive breast affection versus extramammary disease

Disease extension at diagnosis	Outcome		Total (%)
	Recurrence or progression (%)	Disease-free (%)	
Exclusive breast affection	58 (7)	90 (28)	81 (35)
Extramammary disease	42 (5)	10 (3)	19 (8)

p = 0.015612.

Table 3. Recurrence or progression comparison among patients with unilateral versus bilateral breast affection

Disease extension at diagnosis	Outcome		Total (%)
	Recurrence or progression (%)	Disease-free (%)	
Unilateral disease	82 (9)	86 (42)	85 (51)
Bilateral disease	18 (2)	14 (7)	15 (9)

p = 0.743641.

breast affection (p = 0.015) (Table 2), but bilateral disease in comparison to unilateral disease did not seem to show such an association (p = 0.74) (Table 3). BIRADS score did not seem to affect outcome when comparing BIRADS 4 versus other scores (p = 0.63). When comparing management strategies, incisional biopsy with subsequent observation seemed to show a stronger association with recurrence than excisional biopsy, but the analysis did not show statistical significance (p = 0.06) (Table 4); nonetheless, when adjusting for all cases of surgical management against incisional biopsy, a significant association was found (p = 0.049) (Table 5).

Table 4. Recurrence or progression comparison among patients with excisional versus incisional biopsy

Disease extension at diagnosis	Outcome		Total (%)
	Recurrence or progression (%)	Disease-free (%)	
Excisional biopsy	44 (4)	78 (21)	69 (25)
Incisional biopsy	56 (5)	22 (6)	31 (11)

p = 0.060103.

Table 5. Recurrence or progression comparison among patients with surgical versus expectant management

Disease extension at diagnosis	Outcome		Total (%)
	Recurrence or progression (%)	Disease-free (%)	
Surgical management	50 (5)	81 (26)	74 (31)
Incisional biopsy	50 (5)	19 (6)	26 (11)

p = 0.060103.

Discussion

Rosai–Dorfman–Destombes disease (RDD) is a rare, proliferative, and inflammatory idiopathic disorder with a pathogenesis that remains unknown. Breast affection alone is particularly rare, with most reviews citing a prevalence of < 1% of cases[1,2,5,41,44,53]. Most reports consist of women over 50 years of age who present with an asymptomatic non-tender, firm, and palpable nodule which on radiologic examination presents as a poorly defined rounded mass in mammograms and a hypoechoic mass in ultrasound[48]. Due to the affected demography and its imaging characteristics, this presentations tends to elicit a high suspicion of breast malignancy and start the patient on a diagnostic workup which may ultimately guide them to the operating room[1,5,10].

Our review showed demographic findings consistent with those previously described in other articles with a predominance of females in their sixth decade of life. Affected males seemed to debut an average of 10 years before their female counterparts, but no significant impact in outcome was found on statistical analysis. While a variety of clinical presentations were reported, the most common one was a single non-tender, firm, palpable nodule affecting a single breast, a finding previously reported in multiple literature reviews[5,41]. The second most common presentation was an asymptomatic nodule detected through routine screening. In regards to such radiologic studies, the one most frequently mentioned was a mammogram reporting findings deemed as BIRADS 4, but no significant association was found between reported BIRADS score and outcomes in our analysis.

While most patients presented with purely extranodal breast disease without systemic compromise, almost a fifth had some degree of non-breast affection which ranged from local and regional lymph nodes to distant organs and subcutaneous tissue. Cervical and axillary nodes were the most commonly reported sites. Our analysis found an association between those patients who debuted with extramammary

disease and those who presented recurrence during follow-up. When conducting the same analysis on unilateral versus bilateral disease no such association was found, nonetheless, bilateral disease was found to be associated with extramammary disease, therefore indirectly granting a slightly higher risk of disease recurrence.

Regarding management, excisional biopsies were found to be the most frequently described procedure both in previous reviews and in ours[2,44]. The second most frequently reported management option was vigilance after diagnostic confirmation with an incisional biopsy. Most reports of nodal and extranodal RDD describe benign outcomes without intervention, with only a small percentage of patients presenting further progression[5,41]. Our review found that among patients with breast RDD when comparing excisional and incisional biopsies with the available data, no significant association was found with disease progression or recurrence. Nevertheless, when adjusting the parameters to include all patients who received a surgical intervention (excisional biopsy, mastectomy, quadrantectomy, lumpectomy, and a patient who underwent a breast reduction), the statistical analysis produced a significant association which may show a slight decrease in recurrence among those who received some kind of surgical excision.

When dealing with recurrence or progression, half of these presented locally in the affected breast, with the remaining half manifesting either regionally or distantly, such as two patients whose recurrence appeared in the subcutaneous tissue of their leg, and another in whom the new lesion presented in the left flank. These findings show that while follow-up examinations must include the breast, they cannot be restricted to it and should include a general assessment as well.

While lacking, available data on follow-up suggest that disease progression or recurrence tends to take place within the first 2 years and rarely before 6 months. While more data are required to establish an adequate protocol for outpatient observation, a yearly mammogram and physical examination seem to be an adequate option. Mortality is rarely reported as a result of breast RDD in the literature, being mentioned only in 1 of the cases found on review.[11]

Conclusion

Rosai–Dorfman disease is a very infrequent pathology, one with an exquisitely rare disposition to present as a solitary breast nodule. Such presentation steps outside the borders of the population that we normally associate with RDD and seems to favor both a different gender and age group. Among these patients, the clinical presentation of extranodal breast RDD tends to mimic malignancy, making differential diagnosis difficult for those unfamiliar with this pathology. Due to its low incidence, guidelines for management do not currently exist, and more evidence is required to generate appropriate ones; in spite of this, our review lead us to find important aspects of this disease's behavior that we have chosen to sum up in the following points: (1) Imaging studies tend to present findings that can be most frequently reported as BIRADS4. (2) Diagnosis can only be obtained through histopathological analysis of a biopsy sample and requires a strong clinical suspicion. (3) Surgical excision, by excisional biopsy or a larger procedure, seemed to show less association with disease recurrence or progression when compared with expectant management. (4) Excisional biopsy seems to be associated with the same outcomes as more extensive surgical procedures. (5) Follow-up is important as almost a fifth of patients showed some sign of disease progression or recurrence. (6) Breast imaging is an important part of patient monitorization, but not the sole foundation of it since only half of the recorded cases of progression or recurrence occurred locally. (7) Follow-up should be maintained for at least 2 years since most instances of recurrence or progression were detected within the first 16 months.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Díaz-Degollado AC, Haro-Cruz JS, Rojas-Gutiérrez CD. Extranodal rosai-dorfman disease presenting as a suspicious breast lump: an infrequent but elusive differential diagnosis. A case report. Rev Senol Patol Mam. 2024;37:100559.
2. El-Attrache B, Kapenhas E, Morgani J, Ahmed T. A rarity in breast pathology: a male case of Rosai-Dorfman disease and literature review. Int J Surg Case Rep. 2017;37:1-3.
3. Navarro-Olvera JL, Parra-Romero G, Cruz-Cruz A, Gómez-Apo E, Chávez-Macias L, Carrillo-Ruiz JD. Intracranial Rosai Dorfman disease - A rare differential diagnosis of multiple meningiomas: a case report. Cir Cir. 2023;92:542-6.
4. Cheng X, Cheng JL, Gao AK. A study on clinical characteristics and magnetic resonance imaging manifestations on systemic Rosai-Dorfman disease. Chin Med J. 2018;131:440-7.
5. Iancu G, Gica N, Mustata LM, Panaitescu AM, Vasile D, Peltecu G. Rosai-Dorfman disease: breast involvement-case report and literature review. Medicina (Kaunas). 2021;57:1167.
6. Chen X. Rosai-Dorfman disease of the breast mimicking fat necrosis on core biopsy. Am J Clin Pathol. 2018;149:S42-53.
7. Rastogi V, Sharma R, Misra S, Yadav L, Sharma V. Emperipolesis - a review. J Clin Diagn Res. 2014;8:ZM01-2.
8. Reddy A, Joshi S, Popat P, Shet T. Rare presentations and literature review of Rosai Dorfman disease of the breast. Hum Pathol Case Rep. 2021;24:1-5.
9. Maldonado Marcos E, Tuca Rodríguez F, Rodríguez-Hermosa JI, Artigau Nieto E, Delisau Puig O, Farrés Pla C, et al. Afectación mamaria recidivante por enfermedad de Rosai-Dorfman en paciente varón. Cir Esp. 2021;99:832.
10. Ingole S, Pavithra V, Sundaram S, Joseph LD, Hussain SA, Dev B. The false alarm: rosai-dorfman disease of breast: case report. Egypt J Radiol Nucl Med. 2022;53:83.
11. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. Arch Pathol. 1969;87:63-70.
12. Pérez-Guillermo M, Sola-Pérez J, Rodríguez-Bermejo M. Malacoplakia and Rosai-Dorfman disease: two entities of histiocytic origin infrequently localized in the female breast--the cytologic aspect in aspirates obtained via fine-needle aspiration cytology. Diagn Cytopathol. 1993;9:698-704.
13. Hammond LA, Keh C, Rowlands DC. Rosai-Dorfman disease in the breast. Histopathology. 1996;29:582-4.
14. Govender D, Chetty R. Rosai-Dorfman disease of the breast. Histopathology. 1997;31:483-4.
15. Green I, Dorfman RF, Rosai J. Breast involvement by extranodal Rosai-Dorfman disease: report of seven cases. Am J Surg Pathol. 1997;21:664-8.
16. Soares FA, Llorach-Velludo MA, Andrade JM. Rosai-Dorfman's disease of the breast. Am J Surg Pathol. 1999;23:359-60.
17. Hummel P, Waisman J, Chhieng D, Yan Z, Cohen JM, Cangiarella J. Fine-needle aspiration cytology of Rosai-Dorfman disease of the breast: a case report. Diagn Cytopathol. 1999;21:287-91.
18. Ng SB, Tan LH, Tan PH. Rosai-Dorfman disease of the breast: a mimic of breast malignancy. Pathology. 2000;32:10-5.
19. Kuzmiak CM, Koomen M, Lininger R, Pisano E. Rosai-Dorfman disease presenting as a suspicious breast mass. AJR Am J Roentgenol. 2003;180:1740-2.
20. Pham CB, Abruzzo LV, Cook E, Whitman GJ, Stephens TW. Rosai-Dorfman disease of the breast. AJR Am J Roentgenol. 2005;185:971-2.
21. Da Silva BB, Lopes-Costa PV, Pires CG, Moura CS, Borges RS, da Silva RG. Rosai-Dorfman disease of the breast mimicking cancer. Pathol Res Pract. 2007;203:741-4.
22. Perera AS, Keleher AJ, Nath M. Rosai-Dorfman disease presenting as a male breast mass. Am Surg. 2007;73:294-5.
23. Dahlgren M, Smetherman DH, Wang J, Corsetti RL. Rosai-Dorfman disease of the breast and parotid gland. J La State Med Soc. 2008;160:35-8.
24. Franco-Odio SO, Fuentes-Peláez A, Rodríguez-Díaz R, Jiménez-Galainena J. Enfermedad de Rosai-Dorfman en mama. Informe de un caso. Rev Inf Cient. 2009;62(2):1-7.
25. Morkowski JJ, Nguyen CV, Lin P, Farr M, Abraham SC, Gilcrease MZ, et al. Rosai-Dorfman disease confined to the breast. Ann Diagn Pathol. 2010;14:81-7.
26. Wu YC, Hsieh TC, Kao CH, Chang HW, Wang CH, Lin YY, et al. A mimic of breast lymphoma: extranodal Rosai-Dorfman disease. Am J Med Sci. 2010;339:282-4.
27. Bansal P, Chakraborti S, Krishnanand G, Bansal R. Rosai-Dorfman disease of the breast in a male: a case report. Acta Cytol. 2010;54:349-52.
28. Picón-Coronel G, Palmerín-Bucio ME, Méndez-Pérez V, Alvarado-Cabrero I. Enfermedad de Rosai-Dorfman en glándula mamaria. Informe de un caso y revisión de la literatura [Mammary gland Rosai Dorfman disease. A case report and literature review]. Gac Med Mex. 2010;146:212-5.
29. Noordzij W, Weernink EE, van Imhoff GW, Kluin PM, de Haan LD. Benigne histiocytose: ziekte van Rosai-Dorfman [Benign histiocytosis: rosai-Dorfman disease]. Ned Tijdschr Geneeskd. 2011;155:A3176.
30. Gwin K, Cipriani N, Zhang X, Schmidt R, Hyjek E. Bilateral breast involvement by disseminated extranodal Rosai-Dorfman disease. Breast J. 2011;17:309-11.
31. Tenny SO, McGinness M, Zhang D, Damjanov I, Fan F. Rosai-Dorfman disease presenting as a breast mass and enlarged axillary lymph node mimicking malignancy: a case report and review of the literature. Breast J. 2011;17:516-20.
32. Fu L, Liu M, Song Z, Xu B, Tian J. 18F-fluoro-deoxyglucose positron emission tomography/computed tomography scan findings in Rosai-Dorfman disease with IgG4-positive plasma cell infiltration mimicking breast malignancy: a case report and literature review. J Med Case Rep. 2012;6:411.
33. Cha YJ, Yang WI, Park SH, Koo JS. Rosai-Dorfman disease in the breast with increased IgG4 expressing plasma cells: a case report. Korean J Pathol. 2012;46:489-93.
34. Baladandapani P, Hu Y, Kapoor K, Merriam L, Fisher PR. Rosai-Dorfman disease presenting as multiple breast masses in an otherwise asymptomatic male patient. Clin Radiol. 2012;67:393-5.
35. Parkin CK, Keevil C, Howe M, Maxwell AJ. Rosai-Dorfman disease of the breast. BJR Case Rep. 2015;1:20150010.
36. Ibáñez RG, Chávez MO, Jara CR, Figueroa GM, Olguín HF, Molina CC. Enfermedad de Rosai-Dorfman mamario. Rev Chil Cir. 2015;67:65-9.
37. Mantilla JG, Goldberg-Stein S, Wang Y. Extranodal Rosai-Dorfman disease: clinicopathologic series of 10 patients with radiologic correlation and review of the literature. Am J Clin Pathol. 2016;145:211-21.
38. Simmons NR, Xu ML, Tavassoli FA, Geisel J, Killelea B, Philpotts LE. A rare presentation of Rosai-Dorfman disease as a breast mass. Breast J. 2016;22:581-3.
39. Jorns JM. Extranodal Rosai-Dorfman disease of the breast. Breast J. 2017;23:105-7.
40. Zhou Q, Ansari U, Keshav N, Davis F, Cundiff M. Extranodal manifestation of Rosai-Dorfman disease in the breast tissue. Radiol Case Rep. 2016;11:125-8.
41. Delaney EE, Larkin A, MacMaster S, Sakhdari A, DeBenedectis CM. Rosai-Dorfman Disease of the breast. Cureus. 2017;9:e1153.
42. De Mello Tucunduva TC, Gaziero A, Tostes VS, Chaves MC, Stiepcich MM, Torres US, et al. Extranodal Rosai-Dorfman disease manifesting with breast involvement: imaging and histopathological findings. Breast J. 2019;25:1266-7.
43. Araújo JL, Cavalcanti BS, Soares MC, Sousa UW, Medeiros GP. Rosai Dorfman's disease in breast simulating cancer - A case report. Cancer Rep Rev. 2018;2:1-3.
44. Liu M, Li X, Li Y, Wang Z, Cheng L, Song X, et al. Rosai-Dorfman disease with features of IgG4-related disease in the breast: cases report and literature review. Asian Pac J Allergy Immunol. 2018;36:51-7.
45. Goldbach AR, Hava S, Caroline D, Zhao X, Bains A, Pascarella S. Rosai-Dorfman disease of the breast: A potential marker of systemic disease. Breast J. 2019;25:134-7.
46. Shin GW, Park YM, Heo YJ, Baek JW, Lee YJ, Han JY, et al. Sonographic features of Rosai-Dorfman disease in the breast: a case report. J Clin Ultrasound. 2020;48:108-10.
47. Dai D, Cai Q, Vohra NA, Wong J, Therien ZP, Hewan-Lowe K, et al. Rosai-Dorfman disease presenting as a breast mass. Arch Pathol Clin Res. 2019;3:8-14.
48. Shetty S, Sharma N, Booth CN, Oshilaja O, Downs-Kelly EP, McKenney JK, et al. Mammary extranodal Rosai-Dorfman disease with and without associated axillary lymphadenopathy: insights for practitioners of breast pathology. Int J Surg Pathol. 2020;28:541-8.
49. Elshikh M, Schellingerhout D, Rayan J, Taher A, Elsayes AK, Mujtaba B, et al. Disease characteristics, radiologic patterns, comorbid diseases, and ethnic differences in 32 patients with Rosai-Dorfman disease. J Comput Assist Tomogr. 2020;44:450-61.
50. Vaidya T, Mahajan A, Rane S. Multimodality imaging manifestations of Rosai-Dorfman disease. Acta Radiol Open. 2020;9:(8).
51. Battle B, McIntire P, Babagbemi K, Mema E. Extranodal multifocal Rosai-Dorfman disease of the breast: a case report. Clin Imaging. 2021;71:49-51.
52. Choo PZ, Loh AH, Selvarajan S, Tan PH, Tan VK, Yong WS, et al. Breast-related extranodal Rosai-Dorfman disease presenting as subcutaneous masses with thick hyperechoic rim, with review of the literature. Breast J. 2021;27:883-6.
53. Sumner C, Salem K, Abunimer L, Ewaz A, Zhang L, Monsrud A, et al. Bilateral breast Rosai-Dorfman disease screen detected by mammography. Clin Case Rep. 2023;11:e6983.

ORIGINAL ARTICLE

Comparing costs and timing of ankle sprain care in two first-tier care systems

Comparación de costos y oportunidad de la atención del esguince de tobillo en dos sistemas de atención de primer nivel

Arlette R. Ordóñez-Flores[1], José J. Rivera-Sánchez[2], M. Valeria Jiménez-Baez[3], David Rojano-Mejía[4], Macedonia G. Moreno-Tovar[5], and Alma I. Guerrero-Martínez[6]*

[1]Servicio de Rehabilitación, Hospital General de Zona No. 197, Instituto Mexicano del Seguro Social (IMSS), Órgano de Operación Administrativa Desconcentrada Estado de México Oriente, Texcoco de Mora, Estado de México; [2]Servicio de Geriatría, Hospital General de México Dr. Eduardo Liceaga, Mexico City; [3]Coordinación de Planeación y Enlace, Órgano de Operación Administrativa Desconcentrada Quintana Roo, Cancún, Quintana Roo; [4]Coordinación de Investigación en Salud, IMSS, Mexico City; [5]Coordinación Clínica de Educación e Investigación en Salud, Unidad de Medicina Familiar No. 41, Órgano de Operación Administrativa Desconcentrada Mexico City Sur, Mexico City; [6]Coordinación Clínica de Turno, Hospital General de Zona No. 48, Órgano de Operación Administrativa Desconcentrada Mexico City Sur, Mexico City. Mexico

Abstract

Objective: *To compare the costs of care and the opportunity of care for the management of grade I-II ankle sprain in two Family Medicine Units, one with rehabilitation service (FMU 13) and one without rehabilitation service (FMU 41).* **Method:** *Observational analytical study, records with diagnosis of grade I-II ankle sprain attended at the FMU were included January-November 2021. Consultations were recorded in the emergency department, family medicine, rehabilitation, cabinet studies and time to grant the appointment in the rehabilitation service (opportunity of care), the Mann-Whitney U test was used to compare costs of care and timeliness of care.* **Results:** *In FMU 41, care costs were higher compared to FMU 13 ($13,990 vs $8,063); however, this difference was not significant, as was the cost of care in family medicine, rehabilitation, and opportunity of care.* **Conclusions:** *The costs of care and the opportunity of care were similar in both models of care (FMU 13-FMU 41) of grade I-II ankle sprain.*

Keywords: *Ankle sprain. Cost of care. Cost analysis. Rehabilitation.*

Resumen

Objetivo: *Comparar los costos de atención y la oportunidad de la atención del manejo del esguince de tobillo de grado I-II en dos Unidades de Medicina Familiar, una con servicio de rehabilitación (UMF 13) y otra sin servicio de rehabilitación (UMF 41).* **Método:** *Estudio observacional analítico en el que se incluyeron expedientes con diagnóstico de esguince de tobillo de grado I-II atendidos en las UMF 13 y 41, de enero a noviembre de 2021. Se registraron las consultas en los servicios de urgencias, medicina familiar y rehabilitación, los estudios de gabinete y el tiempo en otorgar la consulta en el servicio de rehabilitación (oportunidad de la atención). Para comparar los costos en la atención y la oportunidad de la atención se utilizó la prueba de U de Mann-Whitney.* **Resultados:** *En la UMF 41, los costos en la atención fueron mayores en comparación con la UMF 13 ($13,990 vs. $8,063); sin embargo, esta diferencia no fue estadísticamente significativa, al igual que en el costo de atención en medicina familiar y rehabilitación y la oportunidad de la atención.* **Conclusiones:** *Los costos de la atención y la oportunidad de la atención fueron similares en ambos modelos (UMF 13-UMF 41) para la atención del esguince de tobillo de grado I-II.*

Palabras clave: *Esguince de tobillo. Costo de atención. Análisis de costos. Rehabilitación.*

Correspondence:
David Rojano-Mejía
E-mail: rojanodavid@gmail.com

Date of reception: 13-01-2023
Date of acceptance: 03-10-2023
DOI: 10.24875/CIRUE.M23000772

Cir Cir (Eng). 2024;92(6):735-740
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Ankle sprain is one of the most common musculoskeletal injuries. In the United States, 2 million acute sprains occur annually[1], and emergency services report an incidence rate of 2 to 7 per 100 people per year[2], resulting in high costs for treatment both in emergency services and in primary care units[3,4]. In Mexico, it is also one of the main reasons for consultation in rehabilitation services[5].

In 2004, the Instituto Mexicano del Seguro Social (IMSS) implemented rehabilitation services at the primary care level to provide more timely care to patients with ankle sprains and other low-complexity diseases[6].

To determine the timeliness of care and the costs of treating the main musculoskeletal conditions in the rehabilitation service at the primary care level, a study was conducted back in 2008. This study demonstrated that the timeliness of care was faster in Family Medicine Units (UMFs) with rehabilitation services, and costs were lower vs a UMF without rehabilitation services at the primary care level[7]. One of the conditions studied was ankle sprain, but we consider that the sample of the study was limited and that the current conditions of health care services[8] may differ from those previously reported. Therefore, the objective of this study is as follows: to compare health care costs and the timeliness of care for people with grade I-II ankle sprain in a UMF with rehabilitation services at the primary care level versus another UMF without rehabilitation services at the primary care level.

Method

We conducted an observational analytical study from January through November 2021 in 2 UMFs: UMF 13, which has rehabilitation services, and UMF 41, which does not have rehabilitation services. The sample was obtained through non-probabilistic consecutive case sampling in both UMFs, including records of patients over 18 years old who consulted for acute grade I-II ankle sprain. Patients with a history of sprain in the past year, who reported data on osteoarthritis or previous surgical procedures in the evaluated limb, peripheral vascular insufficiency, neuropathy, or joint instability, were excluded.

Patient information was obtained from the electronic health record. General data collected included age, sex, body mass index (BMI), diagnosis, days of incapacity, type of incapacity, consultations in emergency services, family medicine, and rehabilitation, imaging modalities, and the time taken to provide the consultation in the rehabilitation medicine service (timeliness of care) and exercise prescription.

The costs for the analysis were obtained from the 2021 Official Journal of the Federation for first and third-level care[9]. The data on accumulated incapacity days and the type of incapacity were obtained from the family clinic database, and the costs of consultations and imaging modalities were obtained from the IMSS procurement portal[10]. The costs were categorized as follows:

- Total cost of emergency service: Sum of the cost for consultation in emergency services at the first or third level, as appropriate, plus the cost of imaging studies (in all cases, simple radiographs).
- Total cost of care at the UMF: Cost for the number of consultations provided at the UMF.
- Total cost of care in the rehabilitation service: Cost for the number of rehabilitation medicine consultations plus the cost for the number of physiotherapy sessions.
- Total cost of general care: Total cost of the emergency service plus the total cost at the UMF plus the total cost of care in the rehabilitation service.

Statistical Analysis

Quantitative variables were summarized using measures of central tendency and dispersion: mean and standard deviation if they met the normality assumption, and median and interquartile range if they did not meet the assumption. For inferential analysis, since the cost variables did not meet the normality criteria, medians were compared using the non-parametric Mann-Whitney U test, and the chi-square test was used for nominal variables.

Ethical Considerations

The study was submitted to the national research committee and the ethics committee, obtaining the registration number R-2021-785-016.

Results

A total of 256 patients were included, with 128 patients from each UMF. The mean age in UMF 13 was 38.7 years, while in UMF 41 it was 34 years. In both groups, more than 50% were male, over 70% had overweight or obesity, grade I ankle sprain was

Table 1. Demographic Characteristics

Variable	UMF 41 (no rehabilitation) (n = 128)		UMF 13 (with rehabilitation) (n = 128)		p
	n o X	SD (%)	n o X	SD (%)	
Age (Mean ± SD)	34.31	(11.49)	38.76	13.14	0.004
Male Sex	76	59.40%	71	55.50%	0.52
Female Sex	52	40.60%	57	44.50%	0.52
Body Mass Index (BMI)					
Normal	28	21%	38	29.70%	
Overweight	54	42.20%	58	45.30%	
Obesity Grade I	33	25.80%	32	25%	0.002
Obesity Grade II	13	10.20%	0	0%	
Ankle Sprain Grade I	64	50%	64	50%	
Ankle Sprain Grade II	64	50%	64	50%	1
Type of Disability					
General Illness	71	55.50%	61	47.70%	
Work Risk	31	24.20%	50	39.10%	
Commute Risk	26	20.30%	17	13.30%	0.029

SD: Standard Deviation.

Table 2. Total Emergency Costs in Mexican Pesos

Variable	UMF 41 (n = 113)		UMF 13 (n = 110)		p
	Median	Range CI	Median	Range CI	
Emergency Consultation Cost	3258	3258-3258	3258	671-3258	0.512
X-ray Cost	570	570-570	570	360-570	0.762
Total Emergency Cost	3828	3838-3828	3828	1031-3828	0.512

CI: confidence interval.

the most frequent, and most of the disabilities were due to general illness (Table 1).

Regarding emergency service costs, the costs were similar in both UMFs (Table 2).

There were no statistically significant differences in total days of disability, number of family doctor consultations, total cost per UMF consultation, and total care cost, with equal medians in both UMFs (Table 3).

Regarding the percentage of patients referred to a physical medicine and rehabilitation unit, it was identified that in UMF 41, 24.2% of patients were referred vs 19.5% in UMF 13. Of the total patients treated, 64% in UMF 41 received instructions to do home exercises, and 60% in UMF 13 received such instructions.

Regarding rehabilitation service care, no statistically significant differences were found in both clinics for variables such as timeliness of care, number of consultations with a rehabilitation specialist, number of physical therapy sessions, and cost per session, with similar medians for timeliness of care, showing only a difference of 2 days (greater in UMF 13). The total rehabilitation cost was higher in UMF 41, as patients were referred to a third-level care unit; however, the difference was not statistically significant (Table 4).

The overall care cost included the total emergency service cost, the overall care cost at the UMF, and the overall rehabilitation service cost, with an increase in costs at UMF 41, though no statistically significant differences were observed (Table 5).

Discussion

In our study, no statistically significant differences were found in the costs of care or the timeliness of rehabilitation services between UMF13 and UMF41 in patients with grade I-II ankle sprains.

In the studied sample, the prevalence of ankle sprains was slightly higher in men vs women (57.4 vs 42.6), which is similar to what has been reported by some studies[11,12]; however, it differs from the findings

Table 3. Cost in Mexican Pesos in the UMF

Variable	UMF 41 (no rehabilitation) (n = 128)		UMF 13 (with rehabilitation referral) (n = 128)		p
	Median	Range CI	Median	Range CI	
Total days of disability	14	3-71	14	4-71	0.344
Number of consultations by family doctor	3	1-7	3	1-6	0.214
Total consultation costs by UMF	2511.27	831-5914	2511	837.09-5914	0.24

CI: confidence interval.

Table 4. Comparison of Medians Between Both Groups with Rehabilitation Referral (n = 56)

Variable	UMF 41 (no rehabilitation) (n = 31)		UMF 13 (with rehabilitation) (n = 25)		p
	Median	Rango IC	Mediana	Rango IC	
Opportunity for care (number of days)	6	1-12	8	3-15	0.098
Number of consultations	1	1-2	1	1-2	0.457
Number of rehabilitation sessions	1	1-4	1	1-4	0.098
Cost per rehabilitation session	2831	2831-11,324	1162	1162-4648	0.077
Total rehabilitation cost in Mexican Pesos	5140	2309-15,942	2324	6972-2324	0.098

CI: confidence interval.

of other studies[2,13], due to differences in the studied populations. In these latter studies, individuals with high physical activity (athletes and military personnel) were included, and in this population, women suffer a higher number of sprains vs men, in contrast to our population, where most individuals are sedentary, thus reducing the risk of sprains in women[14].

The BMI was similar to that reported in another study[13], where 75% of the population had overweight and obesity. This is important since it has been demonstrated that female sex and overweight are the most significant risk factors for the development of post-traumatic ankle osteoarthritis; therefore, considering the characteristics of our population, early rehabilitation programs should be strengthened for individuals with risk factors[11].

The age of onset of ankle sprains reported in the literature is higher in children vs adolescents, and higher in adolescents vs adults[11-13]; however, in our study, due to the characteristics of the study population and the inclusion criteria, the mean age of onset was 36 years because ankle sprains are considered injuries associated with physical activity, and these are more frequent at younger ages[2,15].

More than 50% of the disabilities were issued for general illness, which may be related to the high incidence of ankle sprains during extracurricular activities, such as sports[14]. It is suggested that future studies consider the activity being performed at the time of the ankle sprain.

Table 5. Total Costs in Mexican Pesos (Emergency Service, UMF, and Rehabilitation Service)

Variable	UMF 41		UMF 13		p
	Median	Rango IC	Median	Rango IC	
Total Costs	13,990	(837.10-20,155)	8063	(1674-15,822.54)	0.241

CI: confidence interval.

Regarding emergency service costs, a higher cost was identified in UMF 41, as patients with ankle sprains were directly referred to third-level care, resulting in the highest costs; however, this difference was not statistically significant. Also, 21 ankle sprain patients from UMF 13 attended both the UMF emergency service and the trauma hospital, generating double expenses for the same service. This may have contributed to the lack of statistically significant differences in costs between both care models, despite the expectation that patients using the UMF emergency service would incur lower care costs (UMF 13). This is important because with proper clinical evaluation, clinical conditions requiring referral to second or third-level care can be ruled out[16], which is why we believe

that training family doctors at the first level of care in the timely diagnosis of grade I or II sprains will help save resources and time, benefiting both the patient and IMSS[4].

As for the costs of care at the UMF, no differences were found between the two UMFs, and similarly, the days of disability and number of consultations were very similar. However, the costs differ from those reported by Sánchez-Hernández et al.[7], who found that in the UMF with rehabilitation services, the number of disability days and the average cost were lower compared to the UMF without rehabilitation services, likely due to better timeliness of care (shorter waiting times) for accessing rehabilitation services.

Once patients with ankle sprains (24.2%) from UMF 41 were referred to the physical medicine and rehabilitation unit, they received an average consultation in which a home exercise program was provided to improve ankle functionality. Similarly, patients from UMF 13 referred to the rehabilitation unit at the first level of care (19.5%) received a consultation and a home program. The referral of ankle sprain patients from the first level of care to rehabilitation services in our study differs from a study conducted in the United States, in which only 6.8% of patients with ankle sprains were referred to rehabilitation services[17]. Regarding timeliness of care, it was similar in both UMFs, in contrast to what was found by Sánchez-Hernández et al.[7] in their study.

Prescribing exercise programs by the primary care physician is key to functional recovery. Scientific evidence has shown that therapeutic exercise is one of the most effective interventions for restoring functionality[16,18]; however, in this study, exercise was only prescribed by UMF doctors in 65% of cases, which is why we believe it is important to train family doctors to prescribe therapeutic exercises early and reduce the need for rehabilitation referrals. This could improve the patient's functional recovery and reduce health care costs.

This is important because various studies have demonstrated that early physical therapy intervention in patients with different musculoskeletal problems reduces hospital stay time, promotes early discharge and functional recovery, and improves the patients' quality of life who receive rehabilitation programs compared to those who do not or who do not start early; additionally, with a reduction in costs[19,20].

To improve the care of musculoskeletal problems at first-level care units, different models have been implemented; for example, in Sweden, in recent years, a model adapted from triage systems used in emergency services for classifying and caring for patients with musculoskeletal problems commonly seen in primary care services has been implemented[21]. The triage model aims to provide immediate contact with physical therapists for an initial examination and treatment, reducing the burden on first-level care physicians, decreasing waiting times, and ensuring rapid access to evaluations, suggestions, and effective treatments[19,22].

In this study, no statistically significant differences were observed in the variables studied, but it allows us to observe that the care times in both rehabilitation services are very similar, as is the type of therapy provided and the number of sessions administerd for the treatment of grade I-II ankle sprains. Therefore, we believe it is necessary to maintain continuous training for first-level care doctors in ankle sprain management, emphasizing diagnosis and early prescription of exercise. Likewise, new care models for low-complexity conditions in first-level care can be implemented.

Limitations

Since data were obtained from the electronic health records, it was not possible to evaluate the functional condition of the ankle at discharge, know the effectiveness of both first-level care systems, or perform a cost-effectiveness analysis. It is also likely that exercise prescription was underestimated, as some doctors may not have recorded the intervention in the health record.

Strengths

This study provides insight into the care process for patients with ankle sprains from the emergency service to discharge from medical services, as well as identifying referral times to rehabilitation services in both care models and the costs associated with ankle sprain care until the patient returns to work. It also lays the foundations for continuing this line of research with comprehensive economic evaluations of cost-effectiveness or cost-utility for new care models at the first-level medical care.

Implications for Clinical Practice

This study identifies areas of opportunity in the care process for patients with ankle sprains, specifically the evaluation by the emergency service and the lack of early exercise prescriptions in more than 30% of

patients. Continuous training programs in the diagnosis and treatment of ankle sprains should be strengthened for first-level care physicians to improve functional recovery, reduce medical care costs, and avoid overloading emergency services with low-complexity conditions.

Conclusions

The costs of care and the timeliness of care in rehabilitation services were similar in both care models (UMF 13 and UMF 41) for grade I-II ankle sprains.

References

1. Waterman BR, Owens BD, Davey S, Zacchilli MA, Belmont PJ Jr. The epidemiology of ankle sprains in the United States. J Bone Joint Surg Am. 2010;92:2279-84.
2. Herzog MM, Kerr ZY, Marshall SW, Wikstrom EA. Epidemiology of ankle sprains and chronic ankle instability. J Athl Train. 2019;54:603-10.
3. Menz HB, Williams CM, Lazzarini PA, Gordon J, Harrison C. Foot, ankle, and leg problems in Australian primary care: consultation patterns, management practices, and costs. Fam Pract. 2022 Nov 2:cmac122. doi: 10.1093/fampra/cmac122. Online ahead of print.
4. Shah S, Thomas AC, Noone JM, Blanchette CM, Wikstrom EA. Incidence and cost of ankle sprains in United States emergency departments. Sports Health. 2016;8:547-52.
5. Lomelí-Rivas A, Rivero-Garduño ME, Rovelo-Wegener Y, Herrada-Chávez CR. Perfil epidemiológico del servicio de medicina de rehabilitación de médica sur. Médica Sur. 2018;21:62-7.
6. González JMG. Servicios de rehabilitación en unidades de medicina familiar. Rev Med IMSS. 2004;42:369.
7. Sánchez-Hernández MA, Ibarra-Ramírez CT, del Rosario Vilchis-Aguado M, Montesano-Delfín JR, Guízar-Mendoza JM, Loya-García BE. Impacto del servicio de rehabilitación en el primer nivel de atención. Rev Med IMSS. 2008;46:391-6.
8. Juárez-Ramírez C, Reyes-Morales H, Gutiérrez-Alba G, Reartes-Peñafiel DL, Flores-Hernández S, Muños-Hernández JA, et al. Local health systems resilience in managing the COVID-19 pandemic: lessons from Mexico. Health Policy Plan. 2022;37:1278-94.
9. Diario Oficial de la Federación de México (2019, 12 de noviembre). Acuerdo número ACDO.AS3.HCT.301120/310.P.DF dictado por el H. Consejo Técnico, en sesión ordinaria de 30 de noviembre de 2020, relativo a la Aprobación de los Costos Unitarios por Nivel de Atención Médica actualizados al año 2021. Ciudad de México: Instituto Mexicano del Seguro Social, Honorable Consejo Técnico. Disponible en: https://www.dof.gob.mx/nota_detalle.php?codigo=5608945&fecha=28/12/2020#gsc.tab=0.
10. Instituto Mexicano del Seguro Social. Portal de compras del IMSS. (Consultado el 10-11-2022.) Disponible en: http://compras.imss.gob.mx/.
11. Lee S, Song K, Lee SY. Epidemiological study of post-traumatic ankle osteoarthritis after ankle sprain in 195,393 individuals over middle age using the National Health Insurance Database: a retrospective design. J Sci Med Sport. 2022;25:129-33.
12. Al Bimani SA, Gates LS, Warner M, Ewings S, Crouch R, Bowen C. Characteristics of patients with ankle sprain presenting to an emergency department in the South of England (UK): a seven-month review. Int Emerg Nurs. 2018;41:38-44.
13. Doherty C, Delahunt E, Caulfield B, Hertel J, Ryan J, Bleakley C. The incidence and prevalence of ankle sprain injury: a systematic review and meta-analysis of prospective epidemiological studies. Sports Med (Auckland, NZ). 2014;44:123-40.
14. Manderson L, Jewett S. Risk, lifestyle and non-communicable diseases of poverty. Global Health. 2023;19:13.
15. Fraser JJ, MacGregor AJ, Ryans CP, Dreyer MA, Gibboney MD, Rhon DI. Sex and occupation are salient factors associated with lateral ankle sprain risk in military tactical athletes. J Sci Med Sport. 2021;24:677-82.
16. Vuurberg G, Hoorntje A, Wink LM, van der Doelen BFW, van den Bekerom MP, Dekker R, et al. Diagnosis, treatment and prevention of ankle sprains: update of an evidence-based clinical guideline. Br J Sports Med. 2018;52:956.
17. Feger MA, Glaviano NR, Donovan L, Hart JM, Saliba SA, Park JS, et al. Current trends in the management of lateral ankle sprain in the United States. Clin J Sport Med. 2017;27:145-52.
18. Doherty C, Bleakley C, Delahunt E, Holden S. Treatment and prevention of acute and recurrent ankle sprain: an overview of systematic reviews with meta-analysis. Br J Sports Med. 2017;51:113-25.
19. Bornhöft L, Larsson ME, Nordeman L, Eggertsen R, Thorn J. Health effects of direct triaging to physiotherapists in primary care for patients with musculoskeletal disorders: a pragmatic randomized controlled trial. Ther Adv Musculoskelet Dis. 2019;11:1759720X19827504.
20. Marks D, Comans T, Bisset L, Scuffham PA. Substitution of doctors with physiotherapists in the management of common musculoskeletal disorders: a systematic review. Physiotherapy. 2017;103:341-51.
21. O'Farrell S, Smart KM, Caffrey A, Daly O, Doody C. Orthopaedic triage at a physiotherapist-led 'Musculoskeletal Assessment Clinic': a seven-month service evaluation of outcomes. Ir J Med Sci. 2014;183:565-71.
22. Ludvigsson ML, Enthoven P. Evaluation of physiotherapists as primary assessors of patients with musculoskeletal disorders seeking primary health care. Physiotherapy. 2012;98:131-7.

ORIGINAL ARTICLE

Visual and refractive outcomes after SMILE vs FS-LASIK: a paired-eye study

Resultados visuales y refractivos posterior a SMILE versus FS-LASIK: estudio de ojos pareados

Arturo Ramirez-Miranda[1], Angie De-la Mota[1], Guillermo García-De la Rosa[1,2], Juan C. Serna-Ojeda[1], Jorge E. Valdez-García[2], Daniela Fábregas-Sánchez-Woodworth[1], Alejandro Navas[1], Aida Jiménez-Corona[1], and Enrique O. Graue-Hernandez[1]*

[1]Departamento de Córnea y Cirugía Refractiva, Instituto de Oftalmología Conde de Valenciana, Ciudad de México; [2]Escuela de Medicina y Ciencias de la Salud, Instituto de Oftalmología y Ciencias Visuales, Tecnológico de Monterrey, Monterrey, Nuevo León. Mexico

Abstract

Objective: *To compare visual acuity, refraction, Schirmer test, tear break-up time (TBUT), esthesiometry, optical quality, higher order aberrations and posterior corneal elevation measurements before and after small-incision lenticule extraction (SMILE) and femtosecond laser-assisted in situ keratomileusis (FS-LASIK).* **Method:** *Paired eye, randomized, cohort study. Follow-up was performed at days 1 and 7, and at months 1, 3, 6 and 12.* **Results:** *Forty-two eyes were enrolled in the study. Over time, a difference in posterior corneal elevation was statistically significant ($p < 0.01$) with a greater change in patients treated with SMILE. There was no difference in corrected distance visual acuity and uncorrected distance visual acuity and cylinder between the two techniques; however, there was a statistical significant difference in spherical error and spherical equivalent ($p < 0.01$). There was no difference between the eyes with FS-LASIK and SMILE in the assessment regarding the TBUT, the Schirmer test and esthesiometry.* **Conclusions:** *SMILE showed more changes in the posterior elevation with a progressive backward shift throughout time during follow-up. SMILE and FS-LASIK provides similar results in myopic patients regarding visual acuity, refraction, Schirmer test, TBUT and esthesiometry.*

Keywords: *SMILE. FS-LASIK. Myopia. Refractive surgery. Cornea. Aberrometry.*

Resumen

Objetivo: *Comparar la agudeza visual, la refracción, la prueba de Schirmer, el tiempo de ruptura lagrimal (TBUT), la estesio- metría, la calidad óptica, las aberraciones de alto orden y las medidas de elevación corneal posterior antes y después de la extracción de lentícula por pequeña incisión (SMILE) y de queratomileusis in situ asistida por láser femtosegundo (FS-LASIK).* **Método:** *Estudio de cohorte, aleatorizado, de ojo pareados. El seguimiento se realizó en los días 1 y 7, y en los meses 1, 3, 6 y 12.* **Resultados:** *Se incluyeron 42 ojos en el estudio. Con el tiempo, la diferencia en la elevación posterior de la córnea fue estadísticamente significativa ($p < 0.01$), con un cambio mayor en los pacientes tratados con SMILE. No se observaron diferencias en la agudeza visual con corrección y agudeza visual sin corrección y el cilindro entre las dos técnicas; sin em- bargo, el error esférico y el equivalente esférico tuvieron una diferencia estadísticamente significativa ($p < 0.01$). No se halló diferencia con respecto al TBUT, la prueba de Schirmer ni la estesiometría.* **Conclusiones:** *SMILE mostró más cambios en la elevación posterior, con un desplazamiento posterior progresivo a lo largo del seguimiento. SMILE y FS-LASIK brindan resultados similares en pacientes miopes en cuanto a agudeza visual, refracción, prueba de Schirmer, TBUT y estesiometría.*

Palabras clave: *SMILE. FS-LASIK. Miopía. Cirugía refractiva. Córnea. Aberrometría.*

***Correspondence:**
Arturo Ramírez-Miranda
E-mail: arturorammir@gmail.com

Date of reception: 16-05-2023
Date of acceptance: 20-08-2023
DOI: 10.24875/CIRUE.M23000773

Cir Cir (Eng). 2024;92(6):741-750
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Femtosecond laser-assisted in situ keratomileusis (FS-LASIK) is a blade-free procedure that has become the treatment of choice for refractive errors like myopia. The main advantages of creating flaps with the femtosecond laser compared to the standard technique, which uses a microkeratome, include a thinner and more uniform flap thickness from center to periphery and greater precision and predictability[1,2]. However, dry eye and biomechanical corneal abnormalities remain significant concerns. Excimer laser refractive surgery alters the biomechanical resistance of the cornea by surgically removing tissue[3]. Furthermore, it requires the use of two laser platforms, which increases the time and cost of the procedure.

Small-incision lenticule extraction (SMILE) is a flapless procedure in which a refractive intra-stromal lenticule is manually dissected and removed through a small incision at the periphery of the cornea. This technique reduces the risk of flap-related complications and decreases the effects on corneal hysteresis[4-6]. Potential biomechanical advantages of SMILE have been proposed based on the non-linearity of the stromal tensile force7. Additionally, it theoretically reduces the area of the sub-basal nerve plexus, making the corneal sensitivity and dry eye less affected.

The aim of this study is to compare visual acuity, refraction, Schirmer test, tear break-up time (TBUT), esthesiometry, optical quality, higher-order aberrations (HOA), and posterior corneal elevation measurements before and after performing the SMILE and FS-LASIK procedures on each eye, respectively. Patient follow-up was conducted on days 1 and 7, and months 1, 6, and 12 postoperatively.

Method

We conducted a cohort study at a single center, with a convenience-selected population. The eye pairs of the patients were randomized using version 4.0.2 of the R statistical program (R Core Team, Vienna, Austria) for SMILE in one eye and FS-LASIK in the other eye, for myopia or myopic astigmatism, between January 2012 and December 2013 at *Instituo de Oftalmología Conde de Valenciana* (Mexico City).

Inclusion criteria were patients aged 21 years or older with a normal ophthalmologic examination, a stable refractive error for at least 1 year, overt spherical refraction from 1 to 10 diopters (D), manifest cylinder from 0 to 5 D, and spherical equivalent < 8 D. Patients had to be good candidates for laser vision correction, with a similar refractive error in both eyes (difference < 0.5 D), preoperative pachymetry > 500 μm, and estimated residual stromal bed thickness > 300 μm.

Exclusion criteria were a family history of keratoconus or evidence of corneal diseases or other eye conditions.

All patients underwent a complete ophthalmologic examination before surgery to ensure a normal cornea and anterior segment. Measurements included spherical and cylindrical error, spherical equivalent, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), intraocular pressure, simulated keratometry, posterior keratometry, pachymetry, optical quality, HOA, and posterior corneal elevation.

Patients were masked as to which procedure was performed on each eye. After data collection, this information was unmasked along with the randomization list for statistical analysis.

Follow-up was conducted on days 1 and 7, and months 1, 3, 6, and 12 postoperatively.

Schirmer test

The non-anesthetic test to assess tear secretion was performed by inserting a 30 mm strip (Tear Flow Test Strips, AMCON Laboratories, Missouri, USA) into the inferior fornix at the junction of the middle and lateral third of the lower eyelid margin. The strips remained in this position for 5 minutes with the eyes closed. The degree of wetting was then measured according to the scale provided by the manufacturer.

Tear break-up time

A fluorescein-stained strip (BIO GLO, HUG Pharmaceuticals, California, USA) was placed and moistened with saline solution in the inferior conjunctival sac, and the patient was asked to blink several times. On slit-lamp biomicroscopy with a cobalt blue filter, the time before the first tear film break after a complete blink was observed and recorded as the TBUT. The mean of 3 measurements was calculated.

Corneal esthesiometry

It was measured with a Cochet-Bonnet esthesiometer (Luneau, Paris, France). The instrument was

advanced perpendicular to the central surface of the cornea until contact was made. A positive response was considered if the patient felt the nylon monofilament. Corneal sensitivity was examined three times with each filament length, and the length was sequentially reduced in 5 mm steps. Two positive responses out of three attempts were considered a positive result for each filament length. The corneal sensitivity threshold was considered the result with the longest filament.

Corneal topography

Performed with a Scheimpflug camera and a topographer with Placido disk technology (Sirius; Costruzioni Strumenti Oftalmici, Florence, Italy). Measurements included corneal thickness, simulated keratometry, central 3 mm keratometry, posterior keratometry, HOA, optical quality, and posterior corneal elevation.

Surgical technique

Both procedures were performed under topical anesthesia, after placing standard sterile fields and inserting a blepharostat. Each procedure was performed using the established and described technique[8].

SMILE

The patient's eye was placed under the VisuMax femtosecond laser system (Carl Zeiss Meditec AG, Jena, Germany). The bed was moved to the treatment position under a curved contact lens illuminated for suction. Once proper centration was achieved, the surgeon initiated automatic suction. The laser was activated for photodissection in the following sequence: first, the posterior surface of the refractive lenticule was formed (spirally inward), followed by the anterior surface (spirally outward), and then a small 2-5 mm incision along the circumference of the anterior lenticule surface was made to allow for its extraction.

In all cases, the intended depth of the anterior lenticule surface was 110 μm, with a diameter of 8 mm. Once the femtosecond cutting procedure was completed, the lenticule was dissected, separated through the lateral opening incision (4.0 mm), and manually extracted.

FS-LASIK

The corneal flap was created using the VisuMax femtosecond laser platform (Carl Zeiss Meditec AG, Jena, Germany). The energy of each pulse was set at 140 nJ. The pulse distance was 3 μm for the lamellar flap and 2 μm for the side cut. The side cut was set at 90°, and the flap diameter was fixed at 8.0 mm for all patients. After creating the flap (at a depth of 110 μm), the patient was moved to a Mel-80 excimer laser platform (Carl Zeiss Meditec AG, Jena, Germany) for photoablation. The residual stromal bed was washed with balanced saline solution, and the flap was repositioned.

The postoperative regimen consisted of moxifloxacin drops (Vigamoxi® 0.5%, Alcon, Mexico City, Mexico) every 4 hours for 10 days, fluorometholone (Flumetol® 0.1%, Sophia, Jalisco, Mexico) every 4 hours with a tapering schedule for 3 weeks, and hyaluronic acid 0.4% (Lagricel®, Sophia, Jalisco, Mexico) as needed. Subsequently, only lubricating drops were applied for up to 3 months.

Sample size

The group size of 21 and 21 eyes achieves 7% power to detect non-inferiority using a unilateral independent samples t-test. The non-inferiority margin is 0.0. The true difference between the means should be 0.0. The significance level (alpha) of the test is 0.050. The data are drawn from populations with standard deviations of 0.3 and 0.4.

Statistical analysis

The mean and standard deviation of visual acuity, refraction, Schirmer test, TBUT, esthesiometry, optical quality, HOA, and posterior corneal elevation were determined before and during the follow-up of the SMILE and FS-LASIK surgical procedures.

To compare the means of the mentioned parameters, paired Student's t-test was used for each procedure, and unpaired Student's t-test was used to compare both procedures. A multiple linear regression analysis was conducted independently for SMILE and FS-LASIK to estimate the desired vs the obtained spherical equivalent, and the results are given as regression coefficients (beta) and standard errors. All analyses were performed with Stata/MP 13.1 (Stata Corporation, Texas, USA).

Results

A total of 42 eyes from 21 patients were included; 21 eyes underwent SMILE, and 21 eyes underwent FS-LASIK. The mean age of the patients was 28.3 ± 4.57 years (range: 21 to 31), and 66% of the eyes belonged to female patients. All patients had a mean follow-up of 16.5 ± 3.1 months (range, 13 to 19). No surgical complications were documented, and no eye was diagnosed with corneal ectasia during the follow-up. Pre- and postoperative refractive characteristics are shown in Tables 1 and 2, respectively.

Figure 1 shows the refractive outcomes of the eyes that underwent SMILE at the 12-month follow-up. The mean preoperative UDVA was logMAR 1.39 (Snellen 20/490) and postoperative was logMAR 0.05 (Snellen 20/22) ($p < 0.001$); at the 12-month follow-up, 95% had a UDVA of 20/25 or better (Fig. 1A). The mean preoperative and postoperative CDVA was logMAR −0.006 (Snellen 20/19) and logMAR −0.036 (Snellen 20/18), respectively ($p > 0.001$). In terms of safety, 16 eyes maintained the same CDVA in the postoperative period, and 5 eyes gained 1 line of vision vs preoperative (Fig. 1B). A safety index of 3.0 was achieved.

A strong correlation was found between the desired and obtained spherical equivalent ($R^2 = 0.99941$) (Fig. 1C). The mean preoperative spherical equivalent was −5.49 D, and postoperative, −0.45 D ($p < 0.001$). A total of 90% of the eyes undergoing SMILE had a spherical equivalent of ± 0.50 D, and all eyes in this group remained within ± 1.00 D (Fig. 1D). The pre- and postoperative refractive astigmatism was −1.45 D and −0.66 D, respectively ($p < 0.001$); all eyes had final astigmatism ≤ 1.00 D (Fig. 1E). In long-term follow-up, only 4% of the eyes had a change in spherical equivalent of 0.50 D or more (Fig. 1F).

Figure 2 shows the refractive outcomes of the eyes that underwent FS-LASIK at the 12-month follow-up. In this group, the pre- and postoperative UDVA were logMAR 1.36 (Snellen 20/458) and logMAR 0.07 (20/23), respectively ($p < 0.001$); at the 12-month follow-up, 90% had a UDVA of 20/25 or better (Fig. 2A). The mean pre- and postoperative CDVA was logMAR −0.006 (Snellen 20/19) and logMAR −0.03 (Snellen 20/18) ($p < 0.001$). In terms of safety, 17 eyes maintained the same CDVA in the postoperative period, and 4 eyes gained 1 line of vision (Fig. 2B). Similarly, a safety index of 3.0 was achieved.

A good correlation was found between the desired and obtained spherical equivalent ($R^2 = 0.99762$) (Fig. 2C). The pre- and postoperative spherical equivalent were −4.77 D and 0.245 D, respectively ($p < 0.001$). A postoperative spherical equivalent of ± 0.50 D was achieved in 76% of the eyes, and ± 1.00 D in 90% of the eyes undergoing FS-LASIK (Fig. 2D). The mean preoperative and postoperative refractive astigmatism was −4.47 D and −0.20 D, respectively ($p < 0.001$), with final astigmatism ≤ 1.00 D in 95% of the eyes (Fig. 2E). By the end of the follow-up, the spherical equivalent changed by 0.50 D or more in 15% of the eyes (Fig. 2F).

Table 3 shows the pre- and postoperative topographic measurements of both groups, including pachymetry, simulated keratometry, central 3 mm keratometry, and posterior keratometry. The only statistically significant difference was in postoperative pachymetry, which was lower in the SMILE vs the FS-LASIK group.

On day 1 postoperative, there was no statistically significant difference ($p > 0.58$) in posterior corneal elevation between SMILE and FS-LASIK eyes;

Table 1. Preoperative Refractive Characteristics in Eyes Undergoing SMILE and FS-LASIK

Refractive Characteristic	SMILE (Mean ± SD)	FS-LASIK (Mean ± SD)	p
Overt Spherical Equivalent (D)	−4.49 ± 2.23	−4.47 ± 3.85	> 0.05
Spherical Error (D)	−5.49 ± 2.23	−5.40 ± 2.26	> 0.05
Cylindrical Error (D)	−1.45 ± 1.08	−1.17 ± 1.28	> 0.05
LogMAR UDVA	1.37 ± 0.32	1.35 ± 0.36	> 0.05
LogMAR CDVA	−0.006 ± 0.02	−0.006 ± 0.02	> 0.05

CDVA: corrected distant visual acuity; D: diopters; SD: standard deviation; LogMAR: logarithm of the minimum angle of resolution; UDVA: uncorrected distant visual acuity.

Table 2. Postoperative Refractive Characteristics in Eyes Undergoing SMILE and FS-LASIK 12 Months After Surgery

Refractive Characteristic	SMILE (Mean ± SD)	FS-LASIK (Mean ± SD)	p
Manifest Spherical Equivalent (D)	−0.45 ± 0.50	0.20 ± 0.65	< 0.01
Spherical Error (D)	−0.06 ± 0.56	0.24 ± 0.64	< 0.01
Cylindrical Error (D)	−0.66 ± 0.54	−0.64 ± 0.30	> 0.05
LogMAR UDVA	0.04 ± 0.09	0.03 ± 0.79	> 0.05
LogMAR CDVA	−0.36 ± 0.56	−0.30 ± 0.53	> 0.05

CDVA: corrected distant visual acuity; D: siopters; SD: standard deviation; LogMAR: logarithm of the minimum angle of resolution; UDVA: uncorrected distant visual acuity.

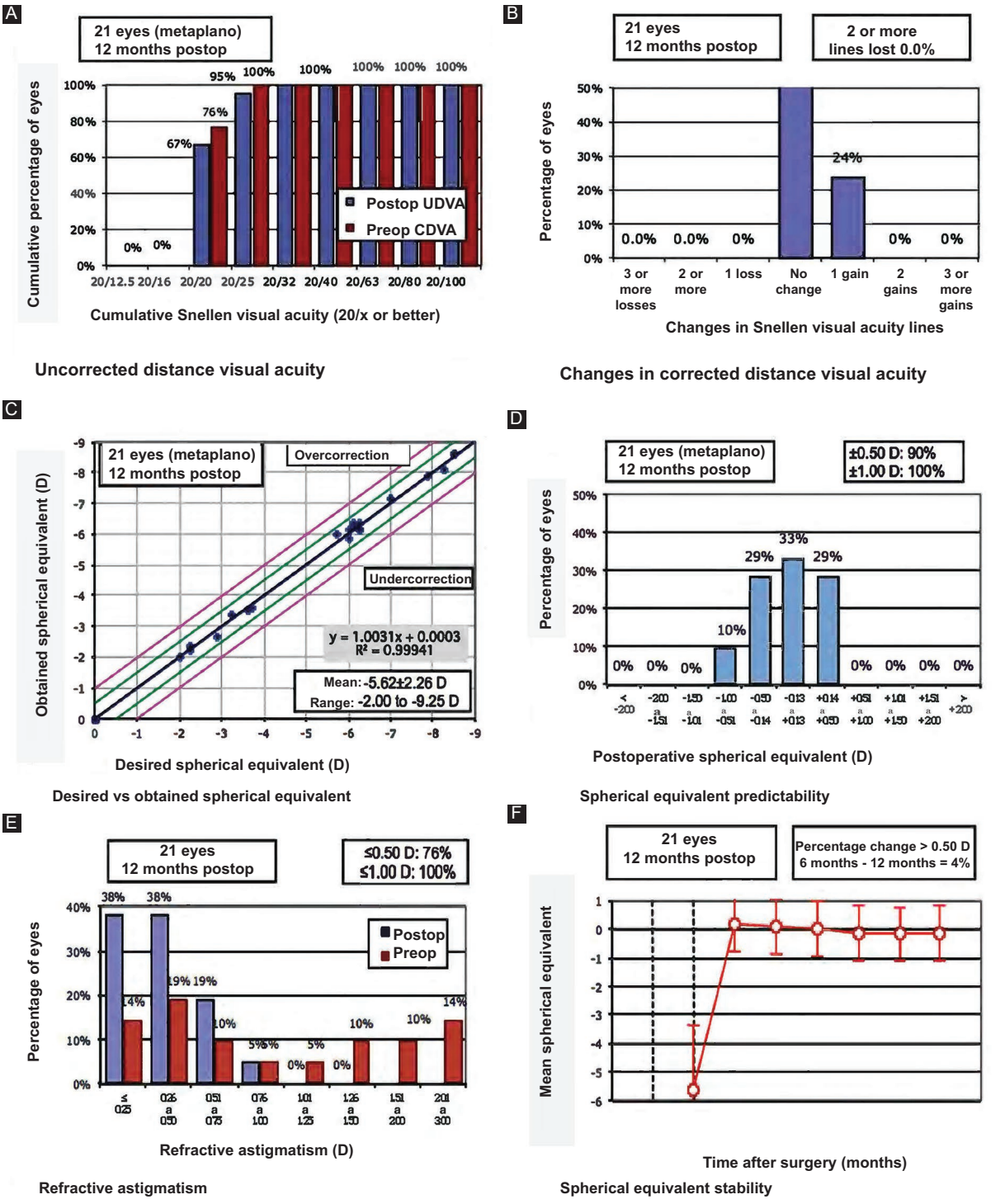

Figure 1. *Refractive outcomes of eyes undergoing SMILE at the 12-months follow-up. These graphs provide detailed information on the accuracy, predictability, safety, and efficacy of the procedure.* **A:** *cumulative uncorrected distant visual acuity graph. Results indicate that 70% of eyes achieved 20/20 vision, 95% reached 20/25, and 100% achieved 20/30.* **B:** *safety graph. The analysis shows that 100% of eyes maintained or improved their uncorrected distant visual acuity after surgery, with no losses observed.* **C:** *spherical equivalent predictability graph. A good correlation was found between the desired and obtained spherical equivalent (R^2 = 0.99941). These results highlight the predictability of the procedure, showing reliable performance in achieving the expected refractive outcomes.* **D:** *spherical equivalent predictability graph. A total of 90% of eyes were within ± 0.50 D, and 100% were within ± 1.00 D of the postoperative spherical equivalent.* **E:** *astigmatism predictability graph. All eyes had final astigmatism ≤ 1.00 D.* **F:** *spherical equivalent stability graph. At long-term follow-up, only 4% of eyes showed a change of 0.50 D or more in spherical equivalent.*

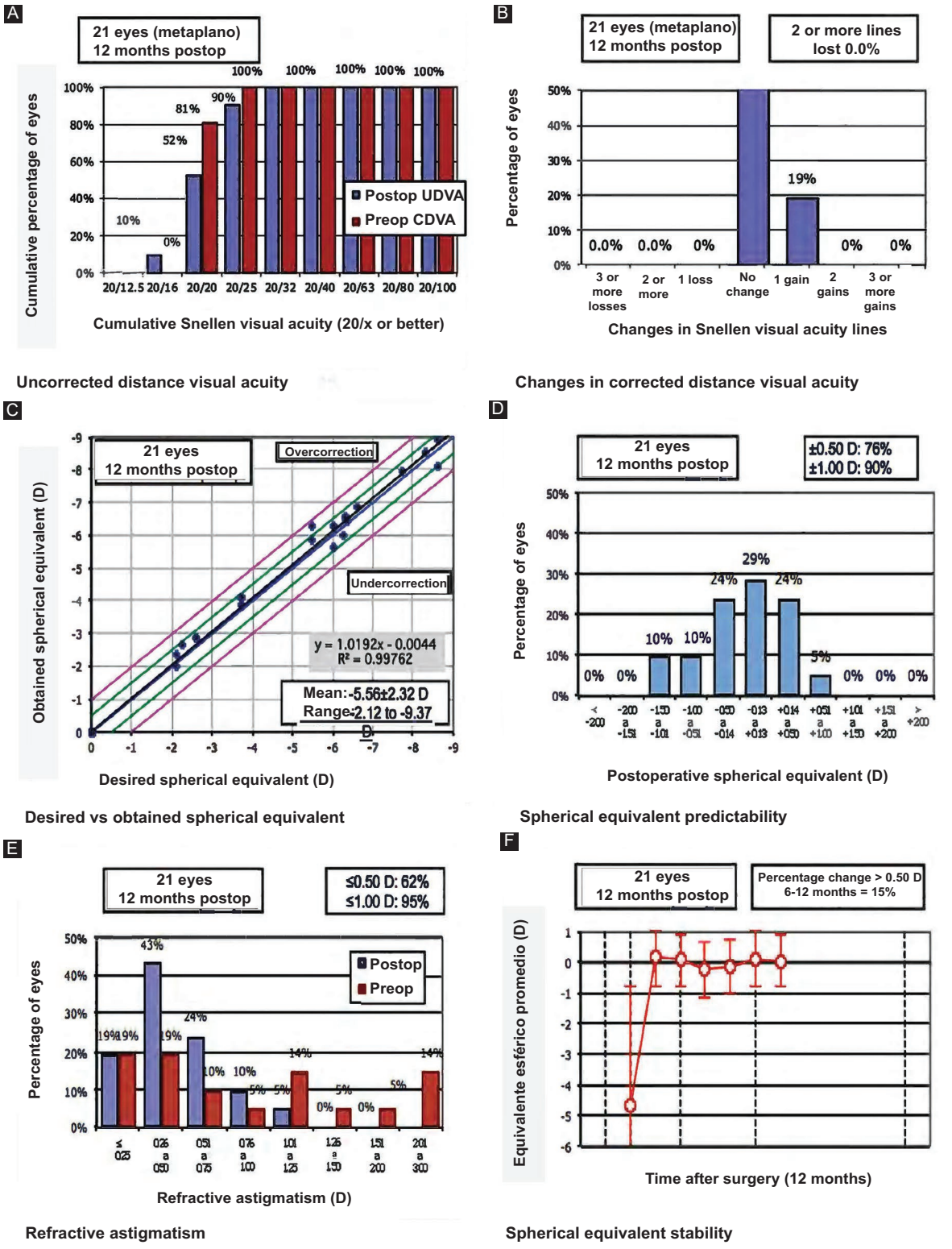

Figure 2. *Refractive outcomes of eyes undergoing FS-LASIK at the 12-months follow-up. These graphs provide detailed information on the accuracy, predictability, safety, and efficacy of the procedure.* **A:** *cumulative uncorrected distant visual acuity graph. Results indicate that 90% had uncorrected distant visual acuity of 20/25 or better.* **B:** *safety graph. The analysis shows that 17 eyes maintained the same uncorrected distant visual acuity post-surgery, and 4 eyes gained 1 line after surgery, with no losses observed.* **C:** *spherical equivalent predictability graph. A good correlation was found between the desired and obtained spherical equivalent ($R^2 = 0.99762$). These results highlight the predictability of the procedure, showing reliable performance in achieving the expected refractive outcomes.* **D:** *spherical equivalent predictability graph. A total of 76% of eyes were within ± 0.50 D, and 90% of eyes were within ± 1.00 D of postoperative spherical equivalent.* **E:** *astigmatism predictability graph. A total of 95% of eyes had final astigmatism ≤ 1.00 D.* **F:** *spherical equivalent stability graph. At the end of follow-up, 15% of eyes showed a change of 0.50 D or more in spherical equivalent.*

Table 3. Pre- and Postoperative Topographic Measurements: Comparison Between the 2 Techniques

Measurement	Preoperative (Mean ± SD)		p	Postoperative (Mean ± SD)		p
	SMILE	FS-LASIK		SMILE	FS-LASIK	
Pachymetry (μm)	522.0 ± 17.6	521.0 ± 17.4	> 0.05	414.8 ± 43.44	449.6 ± 33.7	< 0.01
Simulated Keratometry (D)	43.81 ± 1.25	43.8 ± 1.31	> 0.05	39.37 ± 1.80	40.07 ± 1.6	> 0.05
Keratometry at 3 mm (D)	43.95 ± 1.23	43.9 ± 1.27	> 0.05	39.22 ± 1.92	39.89 ± 1.6	> 0.05
Posterior Keratometry (D)	−6.16 ± 0.19	−6.15 ± 0.2	> 0.05	−6.33 ± 0.60	−6.35 ± 0.25	> 0.05

D: Diopters; SD: Standard Deviation

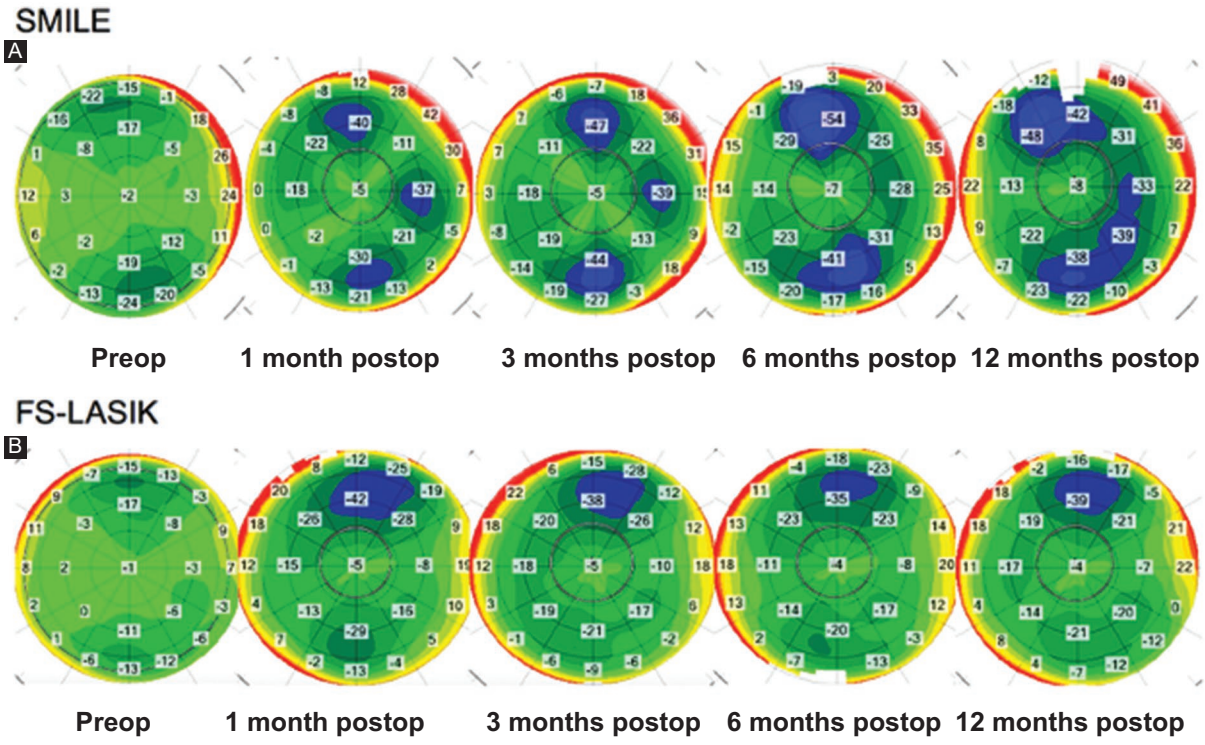

Figure 3. *Changes in posterior corneal elevation over time in 1 eye with SMILE* **(A)** *and 1 eye with FS-LASIK* **(B)**.

however, at the 12-month follow-up, logistic regression analysis showed a statistically significant depression in the posterior elevation map in SMILE eyes ($p < 0.01$) (Fig. 3).

Regarding TBUT, the Schirmer test, and esthesiometry, no significant differences were observed between the 2 groups both preoperatively and at the 12-month follow-up (Table 4). A decrease in corneal sensitivity was observed with both techniques: in the FS-LASIK group, the decrease was from 5.76 ± 0.31 down to 4.79 ± 1.63 after treatment ($p = 0.032$), and in the SMILE group, it was from 5.797 ± 0.30 down to 5.11 ± 1.15 ($p = 0.038$).

Regarding optical quality, there was a higher increase in root mean square (RMS) within the first week of follow-up in the SMILE vs the FS-LASIK group. At the 12-month follow-up, RMS decreased in both groups, with this decrease being statistically significant in the SMILE group. Additionally, an increase in point spread function was observed in both groups, but it was not statistically significant (Table 5).

Finally, a statistically significant decrease in wavefront error, HOA, and astigmatism was found in the SMILE group, while a statistically significant increase in trefoil and coma was found in the FS-LASIK group (Table 6).

Discussion

The femtosecond laser has revolutionized refractive surgery due to its high precision and its ability to make the procedure more reproducible. In this study, we

Table 4. Pre- and Postoperative Values of Tear Breakup Time, Schirmer Test, and Esthesiometry

Measurement	Preoperative (Mean ± SD)			Postoperative (Mean ± SD)		
	FS-LASIK	SMILE	p	FS-LASIK	SMILE	p
TBUT	10.9 ± 2.9	10.0 ± 2.2	> 0.05	8.7 ± 2.37	9.5 ± 2.8	0.151
Schirmer Test	19.3 ± 7.3	19.4 ± 7.5	> 0.05	21.6 ± 10.54	21.4 ± 11.0	0.474
Esthesiometry	5.7 ± 0.3	5.8 ± 0.3	> 0.05	5.9 ± 0.13	5.8 ± 0.2	0.231

SD: Standard Deviation; TBUT: Tear Breakup Time

compared 2 techniques, SMILE and FS-LASIK, in patients who underwent surgery in each eye.

Results regarding visual acuity and refractive characteristics did not differ between the 2 groups, except for the spherical equivalent, which was more favorable in the SMILE group ($p < 0.01$), and the spherical error, where the SMILE group tended to overcorrect, while the FS-LASIK group tended to undercorrect ($p < 0.01$). These results are similar to those reported by Kamiya et al.[9] in a study where 1 eye underwent SMILE and the other lenticular extraction with femtosecond, and they found a trend toward better UDVA and a smaller spherical equivalent in SMILE eyes.

In a prospective, randomized study comparing SMILE and FS-LASIK, the UDVA on postoperative day 1 was higher in the FS-LASIK group, while no statistically significant difference was found at the 6-month follow-up. Similarly, no significant difference was found in terms of CDVA and mean spherical equivalent at the 6-month follow-up between both groups[10]. In a meta-analysis evaluating the clinical outcomes of SMILE and FS-LASIK for myopia correction, no significant difference in final spherical equivalent was found between both procedures[11].

When analyzing topographic measurements, there was a decrease in simulated keratometry and 3 mm central keratometry, with no statistically significant difference between the 2 groups. On the contrary, there was an increase in posterior keratometry with both procedures, which was statistically significant in the FS-LASIK group. An anterior shift in the posterior corneal surface has been reported in patients who underwent LASIK or FS-LASIK; however, some authors have rejected this finding[3,12,13]. Corneal topography is the best index to evaluate the movement of the posterior corneal surface after LASIK[14,15]. This anterior shift can be attributed to the amount of tissue ablated or the thickness of the residual stromal bed. Some studies have shown that progressive corneal deformation is greater when the residual stroma is less than 250 μm[16,17].

Table 5. Optical Quality in the Follow-Up of SMILE and FS-LASIK

	SMILE (Mean ± SD)		FS-LASIK (Mean ± SD)	
	RMS	PSF	RMS	PSF
Preoperative	1.58 ± 0.83	0.09 ± 0.04	1.48 ± 0.80	0.10 ± 0.06
1 Week	1.78 ± 0.99	0.11 ± 0.03	1.25 ± 0.31	0.11 ± 0.03
1 Month	1.40 ± 0.38	0.10 ± 0.03	1.25 ± 0.52	0.12 ± 0.04
3 Months	1.31 ± 0.34	0.11 ± 0.03	1.21 ± 0.40	0.11 ± 0.03
6 Months	1.36 ± 0.51	0.12 ± 0.03	1.28 ± 0.53	0.13 ± 0.03
12 Months	1.27 ± 0.37	0.13 ± 0.04	1.22 ± 0.40	0.12 ± 0.03
p (Preoperative to 12 Months)	0.05	0.10	0.68	0.13

SD: Standard Deviation; PSF: Point Spread Function; RMS: Root Mean Square

Similarly, a statistically significant decrease in posterior corneal elevation was observed in SMILE patients. This group had a posterior corneal shift that remained stable during the follow-up. It has been reported that after SMILE, there are changes in the keratometric power of the posterior cornea[18]. Therefore, these patients may have a protective factor against iatrogenic ectasia or myopic regression, which are related to an increase in posterior corneal elevation[3].

In the present study, similar values were found for TBUT, corneal sensitivity, and the Schirmer test in both groups after surgery. As in other studies, TBUT values decreased after surgery[19]. Some authors have reported advantages of the SMILE technique concerning dry eye and corneal sensitivity. Li et al.[19] demonstrated that SMILE patients were less likely to have corneal staining vs FS-LASIK patients; similarly, SMILE is superior in terms of a smaller reduction in corneal sensitivity. It has been described that SMILE has a lesser impact on the ocular surface and corneal innervation vs LASIK, reducing the incidence of dry eye syndrome[20], which may be influenced by less

Table 6. Pre- and Postoperative Optical Aberrations in Eyes with SMILE and FS-LASIK: Comparison Between Both Techniques

	SMILE		p	F-LASIK		p
	Preoperative	Postperative		Preoperative	Postperative	
WFE	1.37 ± 0.77	1.02 ± 0.44	< 0.05	1.24 ± 0.77	1.04 ± 0.54	> 0.05
HOA	0.40 ± 0.47	0.57 ± 0.23	> 0.05	0.33 ± 0.07	0.65 ± 0.22	> 0.05
Astigmatism	1.24 ± 0.74	0.79 ± 0.41	< 0.01	1.17 ± 0.80	0.7 ± 0.63	> 0.05
Trefoil	0.17 ± 0.25	0.2 ± 0.19	> 0.05	0.12 ± 0.08	0.24 ± 0.12	< 0.05
Coma	0.22 ± 0.30	0.3 ± 0.18	> 0.05	0.20 ± 0.08	0.4 ± 0.22	< 0.05

HOA: Higher Order Aberrations; SD: Standard Deviation; WFE: Wavefront Error

apoptosis, proliferation, and inflammation of keratocytes[21,22]. In a meta-analysis comparing both techniques, it was found that TBUT was longer in SMILE patients 1 and 6 months after surgery, and corneal sensitivity was higher 6 months after surgery[11].

In this study, a reduction in optical quality was observed during the early postoperative period in the SMILE group, with higher RMS, likely due to haze, which is consistent with other studies[23]. However, there was an improvement over time.

A significant increase in trefoil and coma was found in the FS-LASIK group. It has been reported that there is an increase in anterior corneal aberrations after myopic LASIK by creating a flap, either with a mechanical microkeratome or with the femtosecond laser[24]. No increase in aberrations was found after the SMILE procedure, although a slight decentration has been associated with induced coma[25]. In general, postoperative HOAs are smaller after SMILE vs FS-LASIK[25,26].

This study has some limitations. The number of patients should be increased to obtain more precise results, and some analyses show a trend toward 1 of the 2 surgical procedures without reaching statistical significance, possibly due to the small sample size.

This study is the first paired-eye study in the Mexican and Latin American population, as only the Singapore National Eye Centre group has studies with this eye-pairing design in which, with the same sample of 70 patients, predictability and refractive results[27], optical zone functionality and centration[28], as well as visual quality from the patient's point of view[29], are analyzed.

In conclusion, SMILE and FS-LASIK provide similar results in myopic patients regarding visual acuity, refraction, Schirmer test, TBUT, and esthesiometry. SMILE showed more changes in posterior elevation, with a progressive backward shift over time during follow-up.

Acknowledgments

The authors wish to thank Fundación Conde de Valenciana IAP.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors obtained approval from the Ethics Committee for the analysis and publication of clinically obtained data. Informed consent from patients was not required as this is a retrospective observational study.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence in the drafting of this manuscript, nor for the creation of figures, graphics, tables, or their corresponding footnotes.

References

1. Salomão MQ, Wilson SE. Femtosecond laser in laser in situ keratomileusis. J Cataract Refract Surg. 2010;36:1024-32.
2. Soong HK, Malta JB. Femtosecond lasers in ophthalmology. Am J Ophthalmol. 2009;147:189-97.
3. Santhiago MR, Smadja D, Gomes BF, Mello GR, Monteiro ML, Wilson SE, et al. Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal preoperative topography. Am J Ophthalmol. 2014;158:87-95.e1.

4. Moshirfar M, McCaughey MV, Reinstein DZ, Shah R, Santiago-Caban L, Fenzl CR. Small-incision lenticule extraction. J Cataract Refract Surg. 2015;41:652-65.
5. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. Br J Ophthalmol. 2011;95:335-9.
6. Sekundo W, Kunert K, Russmann C, Gille A, Bissmann W, Stobrawa G, et al. First efficacy and safety study of femtosecond lenticule extraction for the correction of myopia: six-month results. J Cataract Refract Surg. 2008;34:1513-20.
7. Reinstein DZ, Archer TJ, Randleman JB. Mathematical model to compare the relative tensile strength of the cornea after PRK, LASIK, and small incision lenticule extraction. J Refract Surg. 2013;29:454-60.
8. Shah R, Shah S, Vogelsangfi H. All-in-one femtosecond laser refractive surgery. Tech Ophthalmology. 2011;9:114-21.
9. Kamiya K, Shimizu K, Igarashi A, Kobashi H. Visual and refractive outcomes of femtosecond lenticule extraction and small-incision lenticule extraction for myopia. Am J Ophthalmol. 2014;157:128-34.
10. Liu M, Chen Y, Wang D, Zhou Y, Zhang X, He J, et al. Clinical outcomes after SMILE and femtosecond laser-assisted LASIK for myopia and myopic astigmatism: a prospective randomized comparative study. Cornea. 2016;35:210-6.
11. Zhang Y, Shen Q, Jia Y, Zhou D, Zhou J. Clinical outcomes of SMILE and FS-LASIK used to treat myopia: a meta-analysis. J Refract Surg. 2016;32:256-65.
12. Hernández-Quintela E, Samapunphong S, Khan BF, González B, Lu PC, Farah SG, et al. Posterior corneal surface changes after refractive surgery. Ophthalmology. 2001;108:1415-22.
13. Nishimura R, Negishi K, Saiki M, Arai H, Shimizu S, Toda I, et al. No forward shifting of posterior corneal surface in eyes undergoing LASIK. Ophthalmology. 2007;114:1104-10.
14. Baek T, Lee K, Kagaya F, Tomidokoro A, Amano S, Oshika T. Factors affecting the forward shift of posterior corneal surface after laser in situ keratomileusis. Ophthalmology. 2001;108:317-20.
15. Maldonado MJ, Nieto JC, Díez-Cuenca M, Piñero DP. Repeatability and reproducibility of posterior corneal curvature measurements by combined scanning-slit and placido-disc topography after LASIK. Ophthalmology. 2006;113:1918-26.
16. Yoshida T, Miyata K, Tokunaga T, Tanabe T, Oshika T. Difference map or single elevation map in the evaluation of corneal forward shift after LASIK. Ophthalmology. 2003;110:1926-30.
17. Sy ME, Ramírez-Miranda A, Zarei-Ghanavati S, Engle J, Danesh J, Hamilton DR. Comparison of posterior corneal imaging before and after LASIK using dual rotating scheimpflug and scanning slit-beam corneal tomography systems. J Refract Surg. 2013;29:96-101.
18. Ganesh S, Patel U, Brar S. Posterior corneal curvature changes following refractive small incision lenticule extraction. Clin Ophthalmol. 2015;9:1359-64.
19. Li M, Zhao J, Shen Y, Li T, He L, Xu H, et al. Comparison of dry eye and corneal sensitivity between small incision lenticule extraction and femtosecond LASIK for myopia. PLoS One. 2013;8:e77797.
20. Denoyer A, Landman E, Trinh L, Faure JF, Auclin F, Baudouin C. Dry eye disease after refractive surgery: comparative outcomes of small incision lenticule extraction versus LASIK. Ophthalmology. 2015;122:669-76.
21. Dong Z, Zhou X, Wu J, Zhang Z, Li T, Zhou Z, et al. Small incision lenticule extraction (SMILE) and femtosecond laser LASIK: comparison of corneal wound healing and inflammation. Br J Ophthalmol. 2014;98:263-9.
22. Gao S, Li S, Liu L, Wang Y, Ding H, Li L, et al. Early changes in ocular surface and tear inflammatory mediators after small-incision lenticule extraction and femtosecond laser-assisted laser in situ keratomileusis. PLoS One. 2014;9:e107370.
23. Kamiya K, Shimizu K, Igarashi A, Kobashi H. Time course of optical quality and intraocular scattering after refractive lenticule extraction. PLoS One. 2013;8:e76738.
24. Muñoz G, Albarrán-Diego C, Ferrer-Blasco T, García-Lázaro S, Cerviño-Expósito A. Long-term comparison of corneal aberration changes after laser in situ keratomileusis: mechanical microkeratome versus femtosecond laser flap creation. J Cataract Refract Surg. 2010;36:1934-44.
25. Li M, Zhao J, Miao H, Shen Y, Sun L, Tian M, et al. Mild decentration measured by a Scheimpflug camera and its impact on visual quality following SMILE in the early learning curve. Invest Ophthalmol Vis Sci. 2014;55:3886-92.
26. Gyldenkerne A, Ivarsen A, Hjortdal JØ. Comparison of corneal shape changes and aberrations induced by FS-LASIK and SMILE for myopia. J Refract Surg. 2015;31:223-9.
27. Ang M, Farook M, Htoon HM, Mehta JS. Randomized clinical trial comparing femtosecond LASIK and small-incision lenticule extraction. J Refract Surg. 2019;35:230-7.
28. Damgaard IB, Ang M, Mahmoud AM, Farook M, Roberts CJ, Mehta JS. Functional optical zone and centration following SMILE and LASIK: a prospective, randomized, contralateral eye study. J Refract Surg. 2019;35:230-7.
29. Damgaard IB, Ang M, Farook M, Htoon HM, Mehta JS. Intraoperative patient experience and postoperative visual quality after SMILE and LASIK in a randomized, paired-eye, controlled study. J Refract Surg. 2018;34:92-9.

ORIGINAL ARTICLE

Characteristics and mortality in patients with cancer and COVID-19

Características y mortalidad en pacientes con cáncer y COVID-19

Alejandro Hernández-Solís[1], Andrea Quintana-Martínez[2], Arturo Reding-Bernal[3], Alejandro Hernández-de la Torriente[1], and Pablo Álvarez-Maldonado[1]*

[1]Servicio de Neumología y Cirugía de Tórax, Hospital General de México Dr. Eduardo Liceaga; [2]Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México; [3]Dirección de Investigación, Hospital General de México Dr. Eduardo Liceaga. Mexico City, Mexico

Abstract

Objective: *Throughout the COVID-19 pandemic, care protocols were created to apply in hospital units and care for the vulner- able populationin. The objetive was to describe clini- cal manifestations, comorbidity and mortality in cancer patients with SARS CoV-2 infection, as well as sanitary measures carried out in COVID centers.* **Method:** *Retrospective study of 1752 patients admitted to a respiratory care unit.* **Results:** *5% of the population studied had a previous diagnosis of cancer; 59.1% were solid neoplasms and 40.9% hematologic neoplasms. Patients with cancer showed lower rates of admission to the intensive care unit (ICU) compared to patients without cancer (8% vs. 17.4%), with no differences in survival.* **Conclusions:** *Oncology patients hospitalized with COVID-19 did not have different survival rates and were less likely to require ICU care compared to non-cancer patients, this is likely due to multidisciplinary teamwork during the pandemic.*

Keywords: *Neoplasm. SARS Cov-2. Mortality.*

Resumen

Objetivo: *Durante la pandemia de COVID-19 se crearon protocolos de atención para aplicar en unidades hospitalarias y atender a las poblaciones vulnerables, el objetivo fue describir las manifestaciones clínicas, la comorbilidad y la mortalidad en pacientes oncológicos con infección por SARS-CoV-2, así como las medidas sanitarias aplicadas por el personal de salud durante la estancia en unidades COVID.* **Método:** *Estudio retrospectivo de 1752 expedientes clínicos de pacientes que ingre- saron a la unidad de cuidados respiratorios de un hospital de tercer nivel en la Ciudad de México de mayo de 2021 a enero de 2022.* **Resultados:** *El 5% de la población estudiada contaba con diagnóstico previo de cáncer; el 59.1% eran neoplasms sólidas y el 40.9% hematológicas. Los pacientes con cáncer mostraron tasas más bajas de ingreso en la unidad de cuidados intensivos (UCI) que los pacientes sin cáncer (8% frente a 17.4%), sin diferencias en la supervivencia.* **Conclusiones:** *Los pacientes oncológicos hospitalizados con COVID-19 no tuvieron tasas de supervivencia diferentes y fueron menos propensos a requerir cuidados en la UCI en comparación con los pacientes sin cáncer; esto se debe probablemente al trabajo en equipo multidisciplinario durante la pandemia.*

Palabras clave: *Cáncer. SARS-CoV-2. Mortalidad.*

Correspondence:
Andrea Quintana-Martínez
E-mail: quma940103@gmail.com

Date of reception: 24-07-2023
Date of acceptance: 14-09-2023
DOI: 10.24875/CIRUE.M23000774

Cir Cir (Eng). 2024;92(6):751-757
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Worldwide, 19.3 million new cancer cases and 10 million cancer-related deaths are reported annually[1]. In Mexico, the *Red Nacional de Registros de Cáncer* (RNRC) reports more than 195,000 new cases and 84,000 deaths from this disease, making it the third leading cause of mortality in the country[2].

The COVID-19 pandemic has significantly impacted cancer patient care, particularly due to the immense workload burdening health care systems, causing delays in diagnosis, treatment administration, and surgical management, leading to disease progression[3,4]. According to a report by Colaterall Global, the true extent of these delays impact may never be fully known[5].

Due to the immunosuppressive effects of underlying cancer and treatments such as chemotherapy, radiotherapy, and surgery, it was initially believed that patients with active cancer were more susceptible to contracting COVID-19 and developing severe disease vs the general population[6,7]. However, cancer does not seem to be a significant risk factor for SARS-CoV-2 infection or its exacerbation, at least not in the same way as other comorbidities such as cardiovascular diseases, diabetes, and chronic lung diseases. Nevertheless, when COVID-19 is acquired, cancer patients are at higher risk for complications[8].

Cancer patients are often older than 60 years and present with comorbidities, which increases their risk of mortality associated with COVID-19 due to immunosenescence and their propensity for exaggerated inflammatory responses caused by a reduction in naïve T cells. The proportion of naïve T cells vs memory T cells is a determining factor in the degree of the adaptive immune response specific to COVID-19, which leads to more severe symptoms in individuals aged 30 to 70 years[9,10].

A key factor in reducing mortality among cancer patients with COVID-19 has been health care professionals, including nurses, doctors, psychologists, and respiratory therapists, who have acted with strict planning from the patient's initial triage to hospital discharge. Health care professionals are involved in every stage of patient care for COVID-19. During the pandemic, the goal was to protect the workforce while prioritizing quality care based on established processes and the experience of other institutions[11,12].

The objective of this study is to describe the clinical characteristics and mortality of cancer patients with COVID-19, as well as the strategies implemented by health care personnel to mitigate the impact of this disease on a respiratory care unit.

Method

We conducted a retrospective study was on 1,752 patient records with SARS-CoV-2, confirmed by a positive polymerase chain reaction test, in the pulmonology unit of Hospital General de México Dr. Eduardo Liceaga from May 1st, 2021 through January 31st, 2022. Statistical analysis was performed using descriptive statistics based on the level of variable measurement. Categorical variables were expressed as frequencies and proportions, while quantitative variables were presented as means with standard deviations or medians with interquartile ranges, depending on data distribution. The chi-square test was used to compare categorical variables across groups (cancer and non-cancer). For continuous quantitative variables, the Student's t-test or Mann-Whitney U test was employed for comparisons between two independent groups. Kaplan-Meier survival analysis (log-rank or Breslow) was utilized. Statistical tests were conducted using SPSS v.26.

Results

A total of 1,752 clinical records were included, 58.7% (1,028) of which corresponded to men and 41.3% (724) to women. The most common age range was 45–55 years, accounting for 24.7% of all hospitalized patients, with an age range spanning from 18 up to 97 years; the mean age was 54.1 years, with a standard deviation of ±15.4 years.

A total of 88 (5%) out of the 1,752 patients studied were diagnosed with neoplasm associated with SARS-CoV-2 infection, while the remaining 95% did not have cancer. Among the cancer cases, a distinction was made between solid and hematological neoplasms: 60.2% were solid tumors, and 39.8% were hematological neoplasms.

Patients with cancer required admission to the respiratory intensive care unit (ICU) at a lower rate than non-cancer patients (8% vs. 17.4%). Additionally, they had a lower proportion of diabetes mellitus diagnoses (19.3% vs. 32.8%) and a lower prevalence of kidney disease (3.4% vs. 10.8%, according to Fisher's exact test) compared to individuals without cancer (Table 1).

Kaplan-Meier survival analysis for hospitalized COVID-19 patients revealed no statistically significant differences in survival between individuals with and without neoplasm. After 50 days of hospitalization, the probability of survival in both groups was approximately 20% (Fig. 1).

Table 1. Sociodemographic and Clinical Characteristics of Patients Hospitalized for COVID-19 With and Without Cancer

Variable	Total (n = 1752)	Without Cancer (n = 1664)	With Cancer (n = 88)	p
Sex, n (%)				
Female	724 (41.3)	684 (41.1)	40 (45.5)	
Male	1028 (58.7)	980 (58.9)	48 (54.5)	0.228[a]
Cancer type, n (%)				
No cancer	1659 (94.7)	1659 (100.0)	0 (0.0)	
Solid	56 (3.2)	0 (0.0)	56 (60.2)	
Hematologic	37 (2.1)	0 (0.0)	37 (39.8)	< 0.001[b]
Outcome, n (%)				
Survived	1247 (71.2)	1185 (71.2)	62 (70.5)	
Died	505 (28.8)	479 (28.8)	26 (29.5)	0.850[a]
ICU admission, n (%)				
No	1448 (83.1)	1367 (82.6)	81 (92.0)	
Yes	294 (16.9)	287 (17.4)	7 (8.0)	0.013[a]
Clinical severity, n (%)				
Mild	222 (12.7)	201 (12.1)	21 (23.9)	
Moderate	1238 (70.7)	1185 (71.3)	53 (60.2)	
Severe	267 (15.2)	253 (15.2)	14 (15.9)	
Critical	24 (1.4)	24 (1.4)	0 (0.0)	0.012[b]
Diabetes mellitus, n (%)				
No	1190 (67.9)	1119 (67.2)	71 (80.7)	
Yes	562 (32.1)	545 (32.8)	17 (19.3)	0.003[a]
Hypertension, n (%)				
No	1218 (69.5)	1152 (69.2)	66 (75.0)	
Yes	534 (30.5)	512 (30.8)	22 (25.0)	0.089[a]
Renal disease, n (%)				
No	1570 (89.6)	1485 (89.2)	85 (96.6)	
Yes	182 (10.4)	179 (10.8)	3 (3.4)	0.008[b]
Age, mean (SD)	54.1 (15.4)	54.3 (15.2)	50.8 (18.5)	0.075[c]
Length of stay (days), mean (SD)	13.1 (11.5)	13.0 (11.1)	15.5 (17.2)	0.161[c]
$SatO_2$, mean (SD)	86.2 (14.8)	86.4 (14.5)	82.0 (18.8)	0.053[c]
D-Dimer, mean (SD)	3525.5 (7680.5)	3525.3 (7734.1)	3528.3 (6647.8)	0.997[c]
Ferritin, mean (SD)	1173.4 (1678.8)	1156.9 (1676.0)	1505.3 (1712.3)	0.103[c]
Troponin, mean (SD)	104.9 (935.5)	108.7 (956.3)	21.1 (50.3)	0.501[c]
Myoglobin, mean (SD)	136.1 (220.6)	137.6 (221.6)	99.5 (194.8)	0.227[c]
CRP, mean (SD)	143.4 (157.0)	143.0 (159.0)	150.8 (109.5)	0.711[c]
Procalcitonin, mean (SD)	3.1 (28.3)	3.3 (29.1)	1.1 (2.9)	0.511[c]
BNP, mean (SD)	191.6 (532.3)	191.3 (530.4)	197.8 (578.7)	0.935[c]

BNP: Brain Natriuretic Peptide; CRP: C-Reactive Protein; SD: Standard Deviation; SatO2: Oxygen Saturation.
[a]Chi-square test
[b]Fisher's exact test
[c]Student's t-test for independent samples.

Similarly, Kaplan-Meier analysis based on the type of neoplasm found no statistically significant differences in survival between patients with solid and hematological neoplasms and SARS-CoV-2 infection (Fig. 2).

Bivariate analyses revealed a statistically significant difference in the clinical presentation between patients with and without neoplasm, with non-cancer patients showing higher prevalence of symptoms such as cough (p = 0.004), fever (p = 0.006), myalgia/

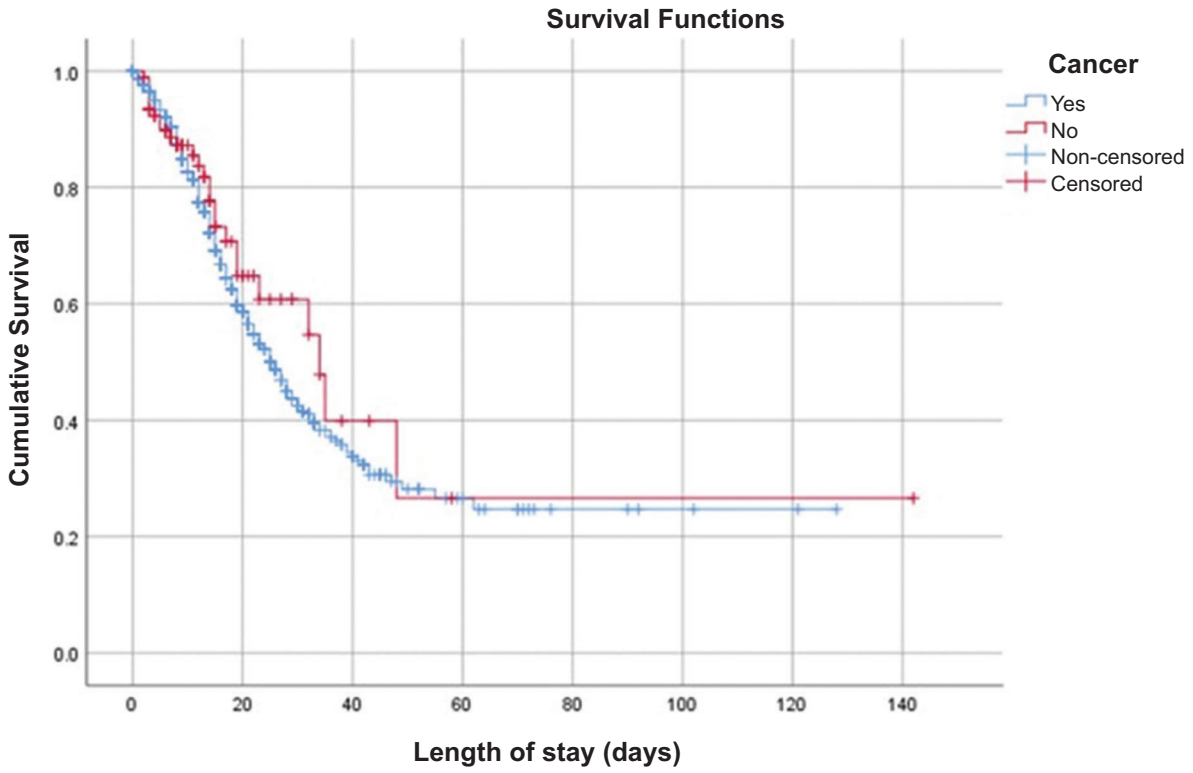

Figure 1. *Kaplan-Meier survival analysis of patients with SARS-CoV-2 infection with and without neoplasm.*

arthralgia (p = 0.006), dyspnea (p < 0.001), and odynophagia (p < 0.001) (Table 2).

The severity of COVID-19 in cancer patients was classified as mild in 23.9% (n = 21), moderate in 60.2% (n = 53), severe in 15.9% (n = 14), and critical in 0% (n = 0).

According to the multiple logistic regression model, for every additional year of age in patients with COVID-19, the likelihood of death increased by 4.5%. The likelihood of death for men was 42% higher vs women. Furthermore, severely and critically ill COVID-19 patients were 2 and 3 times more likely to die than those with mild illness (odds ratio [OR], 2.4 vs. 3.6; p < 0.05) (Table 3).

Discussion

The onset of the global COVID-19 pandemic served as a catalyst for revealing the strengths and weaknesses of health care systems. Patients with various comorbidities, including cancer, were significantly affected, leading to increased mortality, largely due to delays in timely medical care and the rising number of infected patients.

The distribution of COVID-19 patients in our study aligns with other reports, with males being predominant (58.7%) vs females (41.3%), and the most frequently reported age group being 45–55 years (24.7%)[13].

A total of 88 out of all patients were diagnosed with neoplasm and COVID-19, corresponding to 5% vs those without neoplasm (95%). The predominant type of neoplasm was solid tumors, reported in 59.1% of cancer patients, with lung cancer being the most common, followed by GI, breast, and thyroid cancers. Hematological cancers represented 40.9% of neoplasms in our series[14].

The main symptoms in cancer patients were dyspnea (59.1%), cough (47.3%), and fever (44.1%), consistent with findings by Zhang et al.[15], who reported fever (82.1%), cough (81.0%), fatigue (64.3%), and dyspnea (50.0%) as the most common symptoms in cancer patients with COVID-19, along with elevated levels of C-reactive protein, lactate dehydrogenase, lymphocytopenia, anemia, hypoalbuminemia, and leukocytopenia. While symptoms are generally similar in patients with and without cancer, fatigue and dyspnea are more associated with cancer patients,

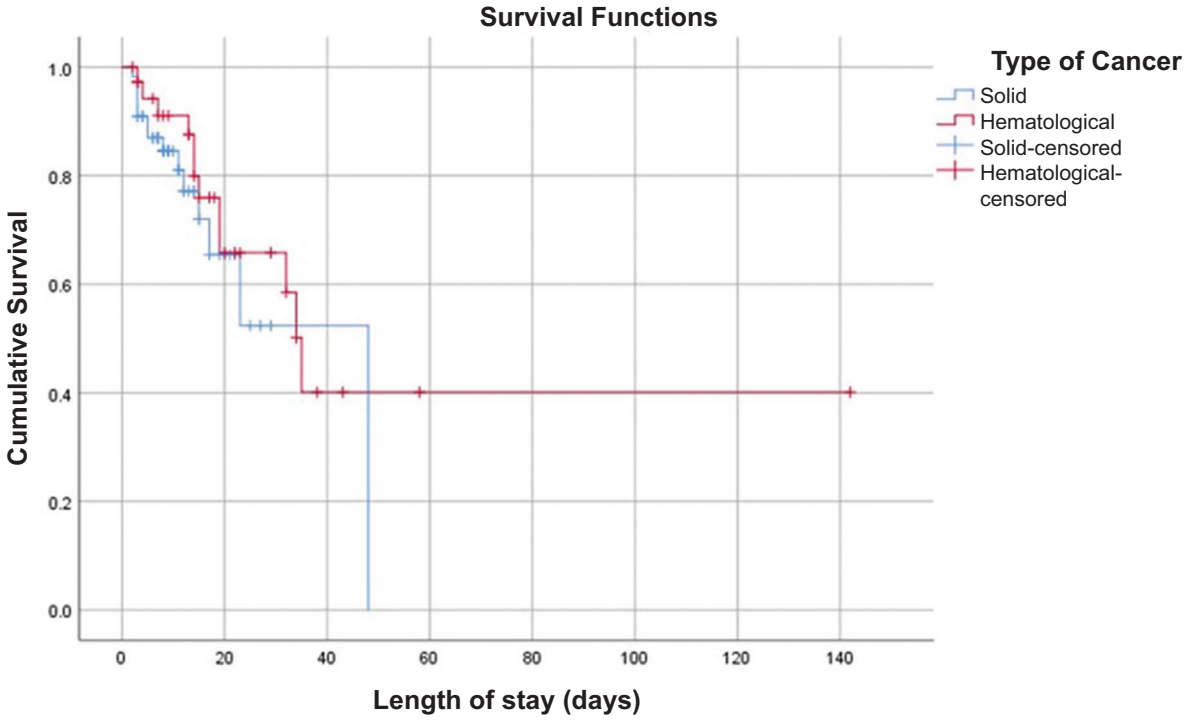

Figure 2. *Kaplan-Meier survival analysis of patients with SARS-CoV-2 infection and neoplasm, categorized by neoplasm type.*

Table 2. COVID-19 Symptoms in Patients With and Without Cancer

Symptom, n (%)	Total (n = 1752)	Without Cancer (n = 1664)	With Cancer (n = 88)	p
Cough	1075 (61.4)	1031 (62.2)	44 (47.3)	0.004[a]
Fever	1014 (57.9)	973 (58.7)	41 (44.1)	0.006[a]
Headache	628 (35.9)	606 (36.6)	22 (23.7)	0.400[a]
Myalgia/Arthralgia	866 (49.5)	833 (50.2)	33 (35.5)	0.006[a]
Dyspnea	1308 (74.7)	1253 (75.6)	55 (59.1)	< 0.001[a]
Sore Throat	371 (21.2)	367 (22.1)	4 (4.3)	< 0.001[b]
Rhinorrhea	157 (9.0)	152 (9.2)	5 (5.4)	0.213[a]
Chest Pain	233 (13.3)	227 (13.7)	6 (6.5)	0.045[a]
Gastrointestinal Symptoms	368 (21.0)	352 (21.2)	16 (17.2)	0.352[a]

[a]Chi-square test
[b]Fisher's exact test.

especially those with lung cancer or metastases. In our study, non-cancer patients more frequently exhibited symptoms such as dyspnea, cough, fever, myalgia/arthralgia, and had higher ICU admission rates. These findings may be related to the fact that non-cancer patients also had more comorbidities, such as diabetes mellitus and kidney disease, which conditioned a higher rate of hospital admissions, severe pneumonia, and mortality[15-17].

The overall mortality rate in our study was 28.8% [505 deaths] (28.8% [479] among non-cancer patients and 29.5% [26] among cancer patients). Analysis of COVID-19 patients revealed no statistically significant difference in mortality between those with and without neoplasm (OR, 1.2; 95% confidence interval [CI], 1.037-1.053; p = 0.97), which contrasts with a French cohort where hospital mortality rates were twice as high among cancer vs non-cancer patients[18]. However,

Table 3. Logistic Regression Model for Mortality from COVID-19

Variable	OR	95%CI	p
Age	1.045	1.037-1.053	< 0.001
Cancer			
No	1	-	-
Yes	1.2	0.725-1.963	0.488
Sex			
Female	1	-	-
Male	1.426	1.138-1.785	0.002
Clinical Severity			
Mild	1	-	-
Moderate	1.423	0.975-2.075	0.067
Severe	2.347	1.515-3.636	< 0.001
Critical	3.635	1.456-9.074	0.006

95%CI: 95% Confidence Interval; OR: Odds Ratio.

having cancer and COVID-19 was associated with greater clinical severity (OR, 2.347; 95%CI, 1.515-3.636; p = 0.012). The reduced mortality may be attributed to measures implemented by health care personnel, including a designated entry for cancer patients without respiratory symptoms to facilitate timely care and treatment, short lengths of stay, limited waiting room access to avoid overcrowding, and ongoing education for patients and families on preventive measures (handwashing, coughing protocol, social distancing, mask use) and recognition of COVID-19 symptoms[19].

The health care workforce underwent restructuring, with alternating schedules to prevent widespread absenteeism and service disruptions in case of infections. Precautionary and protective measures were established at the pandemic's onset. Unfortunately, according to data published by the Ministry of Health, 251,237 health care workers in Mexico were infected, 62% of whom were male with an average age of 37 years. Among them, 32% were nurses and 25.7% were doctors, resulting in 4,127 deaths.

Conclusions

Although cancer patients presented with greater clinical severity, there were no differences in mortality vs non-cancer patients. Additionally, cancer patients had lower ICU admission rates. The findings of this study provide only an approximation of the characteristics of COVID-19 patients with cancer in Mexico. Further studies are needed to identify factors worsening the prognosis for these patients. Part of the outcomes can be attributed to the diligent efforts of health care personnel, who consistently implemented appropriate sanitary measures. These results underscore the importance of organizing health care units to prevent infections, not only from SARS-CoV-2 but also from any nosocomial infections, in cancer patients undergoing treatment. Preventive measures, including physical protocols and vaccination, remain essential.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors obtained approval from the Ethics Committee for the analysis and publication of clinically obtained data. Informed consent from patients was not required as this is a retrospective observational study.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence in the drafting of this manuscript, nor for the creation of figures, graphics, tables, or their corresponding footnotes.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
2. Asociación Mexicana de Lucha Contra el Cáncer. El cáncer en México y el mundo. México: AMLCC; 2020. (Consultado el 28-02-2022.) Disponible en: https://www.amlcc.org/el-cancer-en-mexico-y-el-mundo/.
3. Xu C, Li L, Wang W. Challenges in advanced lung cancer diagnosis during the COVID-19 pandemic. Technol Cancer Res Treat. 2021;20:1-4.
4. Bardet A, Fraslin AM, Marghadi J, Borget I, Faron M, Honoré C, et al. Impact of COVID-19 on healthcare organisation and cancer outcomes. Eur J Cancer. 2021;153:123-32.
5. Heneghan C, Jefferson T. The effects of cancer delays during the COVID-19 pandemic. UK: Collateral Global, 2021. (Consultado el 28-02-2022.) Disponible en: https://collateralglobal.org/article/effects-of-cancer-delays-during-the-covid-19-pandemic/.
6. Sawyers A, Chou M, Johannet P, Gulati N, Qian Y, Zhong J, et al. Clinical outcomes in cancer patients with COVID-19. Cancer Rep (Hoboken). 2021;4:e1413.
7. Hijano DR, Maron G, Hayden RT. Respiratory viral infections in patients with cancer or undergoing hematopoietic cell transplant. Front Microbiol. 2018;9:3097.
8. Haineala B, Zgura A, Badiu DC, Iliescu L, Anghel RM, Bacinschi XE. Lung cancer, Covid-19 infections and chemotherapy. In Vivo. 2021;35:1877-80.
9. Mohanty A, Agnihotri S, Mehta A, Rawal S. COVID-19 and cancer: sailing through the tides. Pathol Res Pract. 2021;221:153417.

10. Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020;395: 1907-18.
11. Cadena-Estrada JC, Olvera-Arreola SS, López-Flores L, Pérez-Hernández E, Lira-Rodríguez G, Sánchez-Cisneros N, et al. [Nursing before COVID-19, a key point for the prevention, control and mitigation of the pandemic.] Arch Cardiol Mex. 2020;90(Supl):94-9.
12. Cruickshank S. Covid-19: el impacto en las personas afectadas por el cáncer, en las enfermeras oncológicas y en los servicios sanitarios. Enferm Clin. 2021;31:201-2.
13. Castañeda CA, Castillo M, Rojas-Vilca JL, Fuentes H, Gómez HL. COVID-19 en pacientes con cáncer: revisión sistemática. Revista Peruana de Medicina Experimental y Salud Publica. 2020;37:611-9.
14. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-COV-2: A MULTICENTER STUDY during the COVID-19 outbreak. Cancer Discov. 2020;10:1-9.
15. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020;31: 894-901.
16. Liu C, Zhao Y, Okwan-Duodu D, Basho R, Cui X. COVID-19 in cancer patients: risk, clinical features, and management. Cancer Biol Med. 2020; 17:519-27.
17. Lima-Martínez MM, Carrera Boada C, Madera-Silva MD, Marín W, Contreras M. COVID-19 and diabetes: a bidirectional relationship. Clin Investig Arterioscler. 2021;33:151-7.
18. Bernard A, Cottenet J, Bonniaud P, Piroth L, Arveux P, Tubert-Bitter P, et al. Comparison of cancer patients to non-cancer patients among COVID-19 inpatients at a national level. Cancers (Basel). 2021;13:1436.
19. Elizarrarás-Rivas J, Cruz-Ruiz NG, Elizarrarás-Cruz JD, Robles-Rodríguez PV, Vásquez-Garzón VR, Herrera-Lugo KG, et al. Medidas de protección para el personal de salud durante la pandemia por COVID-19. Rev Mex Anest. 2020;43:315-24.

ORIGINAL ARTICLE

Endoscopic submucosal dissection for the treatment of gastrointestinal neoplasia in a tertiary-care center in Mexico

Disección endoscópica submucosa para el tratamiento de neoplasias gastrointestinales en un centro de tercer nivel en México

Óscar V. Hernández-Mondragón and Luis F. García-Contreras*

Departamento de Endoscopia Gastrointestinal, Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Mexico City, Mexico

Abstract

Objective: *The aim of this study was to evaluate the experience of using endoscopic submucosal dissection (ESD), a techni- que considered as first-line of treatment, for the management of early neoplastic lesions (ENL), and subepithelial lesions (SEL) < 4 cms in size, in a tertiary-care, high-volume medical center in Mexico.* **Method:** *Patients > 18 years-old, candidates to ESD with ENL and SMT, between January 2008 and October 2022 were included.* **Results:** *ESD was performed in 246 patients (137 ENL and 109 SMT), 52.2% gastric, 23.1% colonic, 19.5% esophageal and 5.2% in duodenum. Benign/ premalignant were 74.4%, and 25.6% malignant, being the SMT the most frequent (44.3%) and gastrointestinal stromal tumor. En-bloc resection, R0, and curative resection rates were 97.2%, 94.5%, and 85.8%, respectively. The most common adverse event was trans- procedural bleeding (18.3%) followed by perforation (6.9%), both endoscopically treated without mortality. Recurrence was presented in 9.44% at 177 months of follow-up.* **Conclusions:** *ESD is a safe and effective endoscopic surgical option of treatment for ENL and SMT in Mexican population when performed in experienced centers.*

Keywords: *Endoscopic submucosal dissection. Early neoplastic lesions. Subepithelial tumors. Safety. Efficacy.*

Resumen

Objetivo: *El objetivo del presente trabajo fue evaluar la experiencia en el uso de la disección endoscópica submucosa (DES), la cual es considerada una técnica de primera línea, para el tratamiento de lesiones neoplásicas tempranas (LNT) y lesiones subepiteliales (LSE) menores a 4 cms de tamaño, en un centro de tercer nivel de atención y alto volumen en México.* **Método:** *Se incluyeron, entre enero de 2008 y octubre de 2022, pacientes mayores de 18 años candidatos a DES por LNT y LSE en el tubo digestivo.* **Resultados:** *Se realizaron 246 intervenciones (137 LNT y 109 LSE), el 52.2% gástricas, el 23.1% colónicas, el 19.5% esofágicas y el 5.2% duodenales. El 74.4% fueron lesiones benignas/premalignas y el 25.6% fueron malignas, siendo las LSE las más frecuentes (44.3%) y dentro de estas el tumor del estroma gastrointestinal. La resección en bloque, R0 y curativas fueron el 97.2%, el 94.5% y el 85.8%, respectivamente. El evento adverso mas común fue la hemorragia transproce- dimiento (18.3%), seguida de la perforación (6.9%), ambas manejadas endoscópicamente, sin mortalidad. La recurrencia a 177 meses se presentó en el 9.44% de los pacientes.* **Conclusiones:** *La DES es una opción de tratamiento quirúrgico endoscópi- co segura y efectiva para LNT y LSE en nuestra población cuando se realiza en centros con alta experiencia.*

Palabras clave: *Disección endoscópica submucosa. Lesión neoplásica temprana. Lesión subepitelial. Eficacia. Seguridad.*

***Correspondence:**
Óscar V. Hernández-Mondragón
E-mail: mondragonmd@yahoo.co.uk

Date of reception: 05-02-2023
Date of acceptance: 26-09-2023
DOI: 10.24875/CIRUE.M23000775

Cir Cir (Eng). 2024:92(6):758-769
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Gastrointestinal cancer accounts for up to 35% of cancer-related deaths[1-4]. It has a high morbidity and mortality rate, primarily due to late detection, which is more pronounced in Latin America[5-9], despite best efforts for early detection[10-12].

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are key components in the management of premalignant or early GI malignancies and subepithelial lesions (SEL)[13,14]. EMR is used for lesions <1.5 cm[15], while ESD is used for larger lesions[16], with the latter showing higher complete resection rates compared to EMR (92-98% vs 78-81%; $p < 0.001$)[17,18], and lower morbidity and mortality compared to conventional surgical treatments[19,20].

ESD is a safe and effective technique[21], representing the reference method for treating early neoplastic lesions (ENL) and SELs ranging from 2 to 4 cm, specifically gastrointestinal stromal tumors (GISTs)[22,23]. The recurrence rate is lower with ESD vs EMR (1-2% vs 6-10%; $p < 0.05$)[1,2,12]. Its adoption in Mexico and Latin America is lower than in Asia[24,25], with contributing factors related to the procedure (difficulty, potentially severe adverse events, and prolonged procedure times) and to the physician (limited experience, extensive knowledge of the team and materials, lack of training centers, and low prevalence and incidence which limits the learning curve)[26-28]

Given the advantages of ESD in treating ENL and SEL, its incorporation into clinical practice is necessary in our country. Therefore, our objective is to describe our experience with ESD for treating ENL and SEL in a tertiary care center in Mexico.

Method

We conducted a retrospective study from January 2008 through October 2022. Patients older than 18 years with suspected ENL or SEL in the digestive tract were included. For ENL, patients with poorly differentiated histology, endoscopic findings suggestive of deep invasion or advanced lesions were excluded, while for SEL, patients with poor prognosis factors (necrosis, ulceration, lymph node metastasis) were excluded. Informed consent was obtained from all cases.

Demographic characteristics of the patients, procedures, and histological analyses were documented. The procedures were performed by the authors, both experienced endoscopists with previous experience in ESD (>200 procedures each).

Preoperative evaluation and equipment

Endoscopic evaluation for all cases was carried out with Olympus equipment models GIF-H-180 and GIF-H180 J (Olympus, Tokyo, Japan) or Fujinon models EG-450WR5 H, EG-590WR, EG-600 WR, and EG-760R (Fujinon, Tokyo, Japan), and for colonoscopy, Olympus models CF-Q180 and CF-H190L (Olympus, Tokyo, Japan) or Fujinon models EC-450WR5, EC-590WR, EC-600 WR, EC-760R, and EC-760R-VL (Fujinon, Tokyo, Japan).

ENL

Lesions were characterized using vital or digital chromoendoscopy with NBI (Narrow Band Imaging, Olympus, Tokyo, Japan) or BLI (Blue Light Imaging, Fujinon, Tokyo, Japan), depending on the equipment used. The classifications of the Japanese Esophageal Society, the international NBI group classification for Barrett's esophagus (BING), the simplified endoscopic algorithm for gastric cancer (MESDA-G), and the Kudo and NICE classifications for squamous esophageal cancer, early gastric cancer, and colon lesions, respectively, were used. To define the morphology of all gastrointestinal lesions found, the Paris classification was used[29-35] (Fig. 1).

SEL

Endoscopic ultrasound (EUS) was performed for characterization, and histological confirmation was obtained. The treatment algorithm is shown in Fig. 2.

Endoscopic Submucosal Dissection

ESD for ENL

CO_2 was used in all cases, with an ENDOstratus insufflation pump (Medivators, Minneapolis, Minnesota, USA), an ERBE electrosurgical unit (ERBE, VIO-200D, 300-D, or VIO-3, Tübingen, Germany), type I, O, or T knives coupled to the ERBEJET unit (ERBE, Tübingen, Germany), BT-knife 2.0 or 2.5 mm (Fujifilm, Tokyo, Japan), and Coagrasper (Olympus, Tokyo, Japan) for hemostasis of vessels. Submucosal

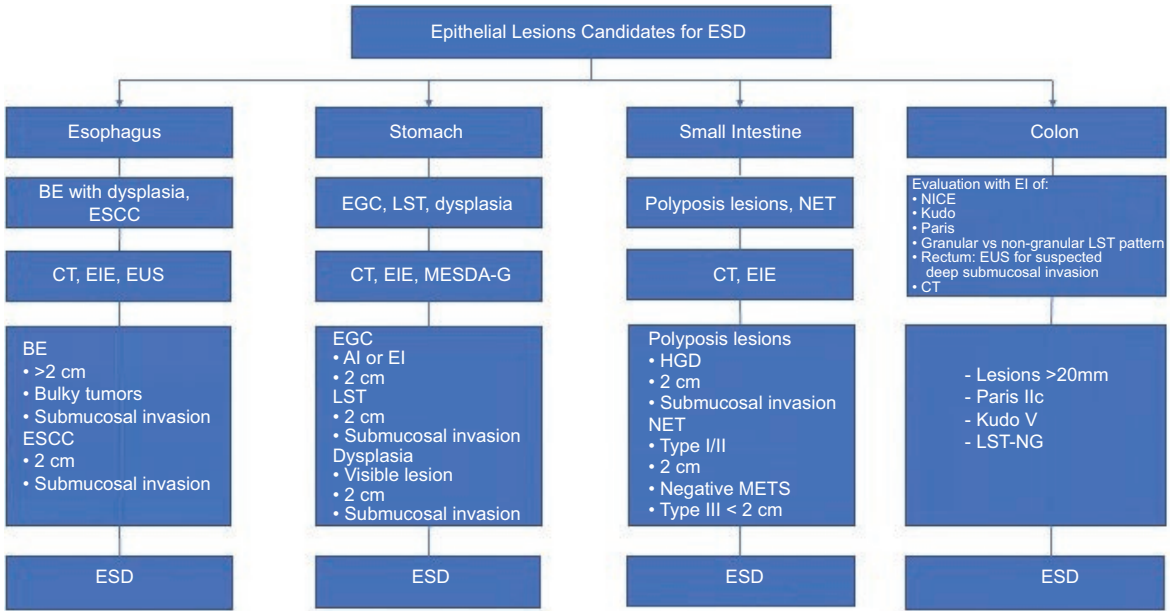

Figure 1. *Diagnostic algorithm for epithelial lesions eligible for endoscopic submucosal dissection.*
ESCC: Esophageal squamous cell carcinoma; EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; BE: Barrett's esophagus; HGD: High-grade dysplasia; EIE: Enhanced imaging endoscopy; NET: Neuroendocrine tumor; CT: Computed tomography; EUS: Endoscopic ultrasound; LST: lateral spreading tumor
+ Enhanced imaging endoscopy: use of digital chromoendoscopy and vital dye as well as magnification.
[a]EUS use is restricted to cases of suspected deep submucosal invasion despite a thorough endoscopic evaluation.
AI = Absolute indications; EI = Extended treatment indications for EGC: AI = Well/moderately differentiated cancer, non-ulcerated, ≤ 2 cm. EI = Well/moderately differentiated cancer > 2 cm, ulcerated lesions ≤ 3 cm, poorly differentiated cancer and non-ulcerated ≤ 2 cm, cancer with submucosal invasion < 500 microns, well-differentiated and ≤ 3 cm.

elevation was performed with 0.9% saline solution or hydroxypropyl methylcellulose (Lagricel, Laboratorios Sophia, Mexico), combined with 0.5% methylene blue or 0.1-0.3% indigo carmine. The 5 steps of the original technique were performed:

1. Marking: Points made with monopolar coagulation 5 mm outside the lesion (soft coagulation, effect 4 at 80 W).
2. Submucosal injection: Elevation with 0.5% methylene blue plus saline solution.
3. Circular incision: Dissection with endocut mode I (interval 3, duration 3, effect 3) 5 mm outside the marking.
4. Submucosal dissection: Complete resection of the lesion in the submucosal plane; in the case of hemostasis, soft coagulation was performed at 80 W, effect 4.
5. Specimen extraction: Fixation and review of the treated area in search of muscle injury, and if necessary, endoscopic management using hemoclips (Boston Scientific, Natick, Massachusetts, USA) or OTS clip (Over-The-Scope clip, Tübingen, Germany), at the physician's discretion (Fig. 3).

ESD for SEL

According to the size, location, and characteristics of the lesion, the same ESD technique as for epithelial lesions was used, or a modification combining tunneling or EMR was performed (Fig. 4).

HISTOLOGICAL ANALYSIS

Histological analysis of the specimens was performed on epithelial lesions (EL), confirming the presence of marking points, and on SEL to assess the integrity of the capsule. Fixation was performed with formalin, and cuts were made every 2 mm. The specimens were classified as R0 (complete resection with negative lateral and deep margins), R1 (positivity in one of the margins), R2 (macroscopic presence of residual tumor), and RX (unable to assess complete resection).

Adverse events

Both in EL and SEL, adverse events before, during, and after the procedure were documented, as well as

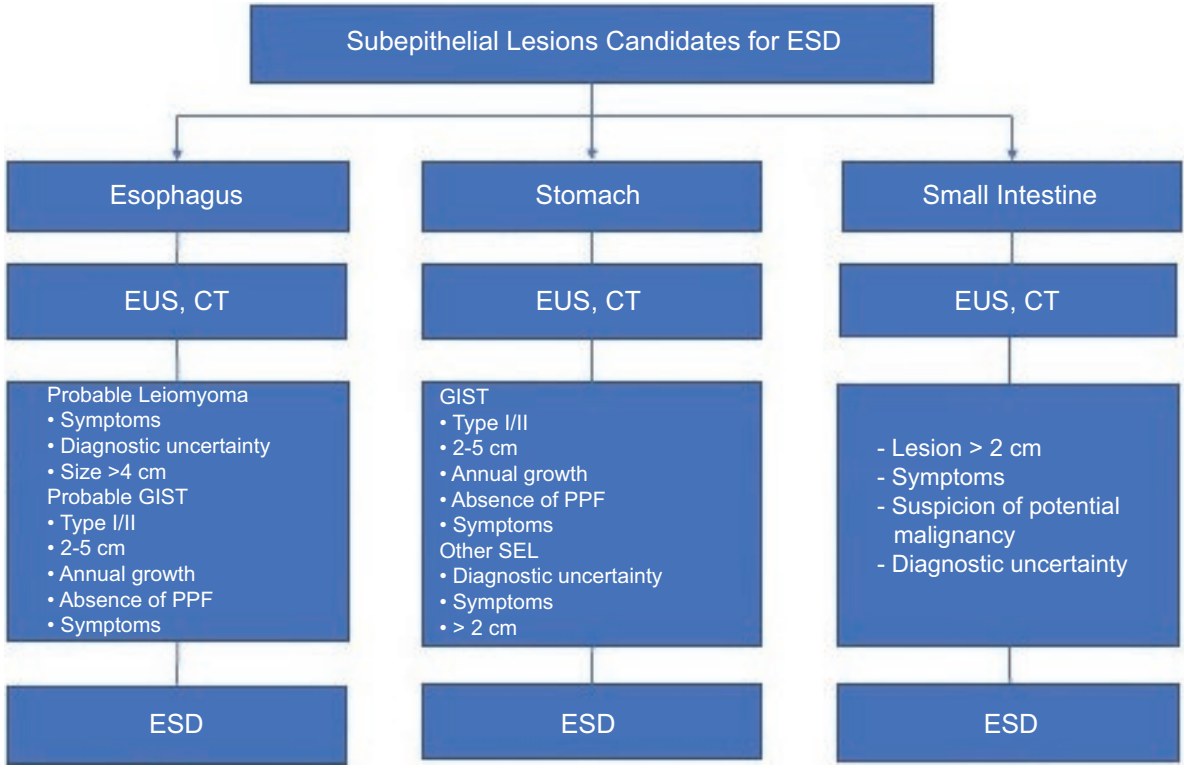

Figure 2. *Diagnostic algorithm for subepithelial lesions eligible for endoscopic submucosal dissection.*
GIST: Gastrointestinal stromal tumor; ESD: Endoscopic submucosal dissection; PPF: Poor prognosis factors: SEL: Subepithelial lesions; CT: Computed tomography; EUS: Endoscopic ultrasound.
PPF in GIST: Ulcerated lesions and/or presence of irregular borders, hypoechoic foci (necrosis), hyperechoic foci (bleeding), heterogeneous enhancement, presence of METS at distance or lymph nodes via EUS/CT.

the type of management (endoscopic, conservative, or surgical). In cases of clinically significant pneumoperitoneum (alteration in ventilatory or circulatory mechanics), abdominal or thoracic decompression was performed as needed, using a Veress needle. In the case of perforation or muscle damage, appropriate management was given at the discretion of the endoscopist.

Objectives

The objective of this study was to document the safety, efficacy, operative time, adverse events, clinical success, and tumor recurrence in patients undergoing ESD for the treatment of both neoplastic lesions (ENL) and subepithelial lesions (SEL) in the gastrointestinal tract.

Statistical analysis

The sample size calculation was based on the efficacy of ESD in the treatment of neoplastic lesions (ENL) and subepithelial lesions (SEL), which according to previous studies[12,16,23,25] is greater than 90%. With an alpha error of 5% and assuming a 95% confidence interval, a minimum of 138 patients was required, using a validated statistical program (Epi-Info, USA). The general characteristics of the patients and the procedures were documented. The results were expressed as mean and standard deviation, or as median and interquartile ranges, depending on their distribution, for quantitative variables, and as frequencies and percentages for qualitative variables. Bivariate comparison was performed with the Kruskal-Wallis test, and linear association with linear-by-linear association. A $p < 0.05$ was considered statistically significant. The SPSS 27 program (IBM, Chicago, IL, USA) was used.

Ethical considerations

Informed consent was obtained from each patient, and due to the retrospective nature of the study, approval from the ethics committee was not required.

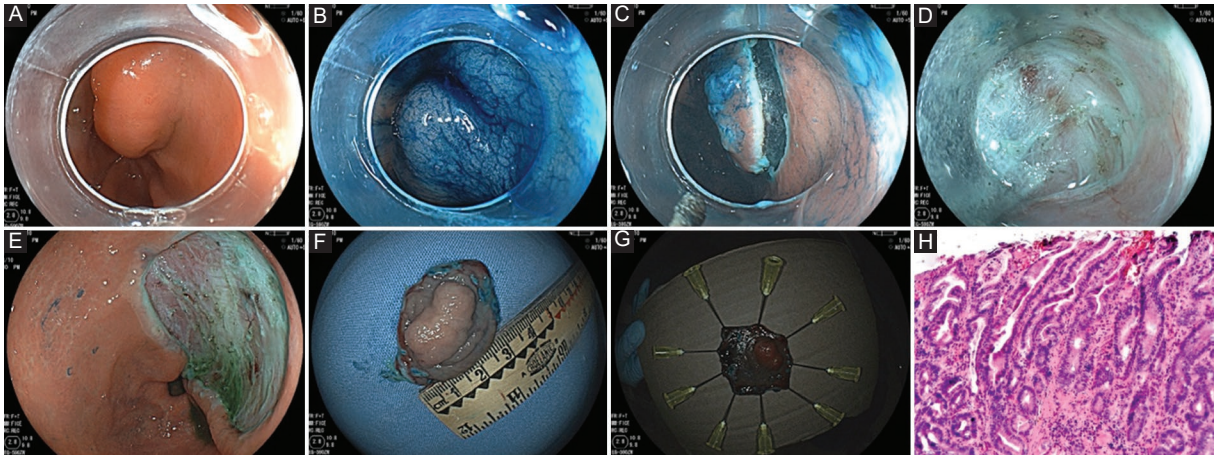

Figure 3. *Endoscopic submucosal dissection performed on a gastric adenoma.* **A:** *lesion located in the pre-pyloric region.* **B:** *chromoendoscopy with methylene blue.* **C:** *circumferential incision.* **D:** *submucosal dissection.* **E:** *post-dissection surgical bed.* **F** *and* **G:** *specimen obtained.* **H:** *histology showing low-grade dysplasia.*

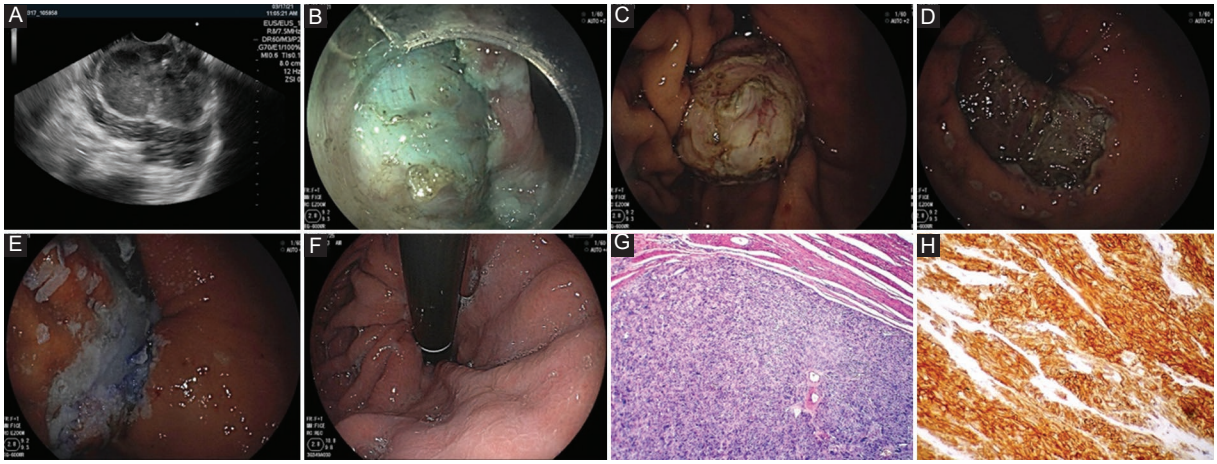

Figure 4. *Combined endoscopic dissection with tunneling for resection of a subepithelial tumor.* **A:** *subepithelial lesion dependent on the 4th echolayer with cystic degeneration and calcifications, measuring 65 × 43 mm in diameter.* **B:** *exposed submucosal lesion.* **C:** *dissected lesion.* **D:** *resection bed.* **E:** *closure of the surgical bed with OVESCO clips and cyanoacrylate.* **F:** *follow-up 5 months after endoscopic submucosal dissection.* **G:** *histology with hematoxylin and eosin staining.* **H:** *immunohistochemistry with CD-117 positive.*

Results

General characteristics of the patients and procedures

Between January 2008 and October 2022, 246 procedures were performed (137 ENL and 109 SEL). There were no differences in sex or age between the two groups. Insulin-independent diabetes was the most common comorbidity (ENL 54.7% and SEL 58.7%). A difference was found in the histology before ESD between the two groups due to the inherent nature of the epithelial or subepithelial pathology (p = 0.01). The stomach was the most common location for ESD, with 128 lesions (52%). The median size for ENL and SEL was 22.1 and 25.7 mm, respectively (p = 0.22). The classical technique was the most widely used in both groups, and en block resection was similar between ENL and SEL (97.1% vs 96.3%; p = 0.53). The length of stay was similar in both groups, with a median of 2 days (Table 1).

Adverse events

Pneumoperitoneum occurred in 74 patients (33 ENL and 41 SEL), 12 of whom (16.2%) required

Table 1. General Characteristics of Patients and Procedures According to the Type of Lesion

Characteristics	ENL (n = 137)	SEL (n = 109)	p
Male Sex, n (%)	74 (54)	61 (55.9)	0.21[a]
Age (years), Median, IQR	55 (16-93)	52 (22-78)	0.35[b]
Comorbidity, n (%)			
Diabetes	75 (54.7)	64 (58.7)	0.88[c]
Hypertension	64 (46.7)	55 (50.4)	
Chronic kidney disease	42 (30.6)	21 (19.2)	
Ischemic Heart Disease	31 (22.6)	32 (29.3)	
Autoimmune Disease	18 (13.3)	12 (11)	
Other	4 (2.9)	5 (4.6)	
Anticoagulation, n (%)	26 (18.9)	18 (16.5)	0.35[a]
ASA Use, n (%)	46 (33.5)	35 (32.1)	0.12[a]
Alcohol, n (%)	28 (20.4)	22 (20.1)	0.45[a]
Smoking, n (%)	65 (47.4)	33 (30.2)	0.51[a]
Pre-ESD Histology, n (%)			0.01[c]
IM with LGD	8 (3.3)	16 (14.6)	
IM with HGD	25 (10.2)	93 (85.4)	
GAC	16 (6.5)		
CA	12 (4.9)		
LST-G	29 (11.8)		
LST-NG	12 (4.9)		
Barrett with LGD	8 (3.3)		
Barrett with HGD	8 (3.3)		
EC	6 (2.4)		
NET	13 (5.3)		
Pb Leiomyoma	-		
Pb (GIST)	-		
Location, n (%)			0.02[c]
Esophagus	28 (20.4)	20 (18.4)	
Stomach	73 (53.4)	55 (50.4)	
Duodenum	8 (5.8)	5 (4.6)	
Colon	28 (20.4)	29 (26.6)	
Size (mm), Median (IQR)	22.1 (6.5-81.2)	25.7 (14.5-65.5)	0.22[b]
Technique, n (%)			0.37[c]
Classic ESD	82 (59.8)	55 (50.4)	
ESD + Tunneling	44 (32.1)	41 (37.6)	
ESD + EMR	11 (8.1)	13 (12)	
Operative Time (min), Median (IQR)	71.5 (27.8-348.1)	78.5 (35.5-188.9)	0.91[b]
EN Block Resection, n (%)	133 (97.1)	105 (96.3)	0.53[a]
Length of stay (days), Median (IQR)	2 (1-4)	2 (1-6)	0.15[b]

CA: Colon adenoma; GAC: Gastric adenocarcinoma; ASA: Aspirin; EC: Esophageal carcinoma; HGD: High-grade dysplasia; LGD: Low-grade dysplasia; ESD: Endoscopic submucosal dissection; GIST: Gastrointestinal stromal tumor; LNT: Early neoplastic lesion; SEL: Subepithelial lesion; LST-G: Lateral spreading tumor, granular variety; LST-NG: Lateral spreading tumor, non-granular variety; IM: Intestinal metaplasia; Pb: Probable; EMR: Endoscopic mucosal resection; IQR: Interquartile range; NET: Neuroendocrine tumor.
[a]Mann-Whitney U test.
[b]Chi-square test.
[c]Linear by linear association.

decompression with a Veress needle. Transoperative bleeding occurred in 45 cases (18.3%), being more frequent in SEL (23.8% vs 13.8%; p = 0.04); endoscopic management achieved control in all cases. In 17 patients (6.9%), bleeding occurred after 24 hours (10 ENL and 7 SEL; p = 0.55), and endoscopic review

Table 2. Adverse Events of Endoscopic Submucosal Dissection According to Lesion Type

Adverse Event	ENL (n = 137)	SEL (n = 109)	p
Post-polypectomy Syndrome, n (%)	2 (1.4)	2 (1.8)	0.21[a]
Pneumoperitoneum, n (%)	33 (24.1)	41 (37.6)	0.26[a]
None, n (%)	25 (18.2)	31 (28.4)	0.09[a]
Pneumomediastinum, n (%)	15 (10.9)	13 (11.9)	0.11[a]
Hemorrhage During Procedure, n (%)	19 (13.8)	26 (23.8)	0.04[a]
Perforation, n (%)	8 (5.8)	9 (8.3)	0.34[a]
Hemorrhage>24 hours, n (%)	10 (7.3)	7 (6.4)	0.55[a]
Abdominal Pain, n (%)	8 (5.8)	15 (13.7)	0.19[a]
Mortality, n (%)	0 (0)	0 (0)	0.08[a]
Need for Surgery, n (%)	3 (2.1)	2 (1.8)	0.71[a]

[a]Chi-square test.

was performed on all of them, with 7 patients requiring endoscopic management (3 hemoclips, 2 monopolar coagulation, and 2 combined treatment), achieving total control in all. Perforation occurred in 17 patients (6.9%) (8 ENL and 9 SEL; p = 0.34) and was treated endoscopically in 14 (6 hemoclips, 3 OTS clips, 2 cyanoacrylate, and 3 combined treatment) and surgically in 3. Five patients required surgical exploration 24 hours after ESD due to suggestive signs of perforation (1 in the duodenum, 2 in the colon, and 2 in the stomach), and perforation was confirmed in one case. There were no cases of mortality during or after the procedure (Table 2).

Histology

Benign/premalignant lesions were found in 74.4% and malignant lesions in 25.6%. Low-risk GIST was the most common lesion, with 60/183 (24.5%) patients, and well-differentiated gastric adenocarcinoma in malignant lesions, with 22 patients (8.8%). ENL occurred in 137/246 cases (55.7%), most of which were at SM1 level, in 120/137 (87.6%) patients. En block resection was performed in 239/246 (97.2%), with complete resection (R0) in 233/246 (94.7%; 130 ENL [94.8%] and 103 SEL [94.5%]), R1 in 12/246 (4.9%; 7 ENL and 5 SEL), and R2 in 1/246 (0.4%; 1 ENL). Finally, curative resection was achieved in 211/246 (85.8%; 117 ENL [85.4%] and 96 SEL [86.2%]). The correlation between pre- and post-ESD histology was found in 91% of cases (126 ENL [91.6%] and 99 SEL [90.8%]) (Table 3).

Table 3. Final Histological Findings

Characteristics	(n = 246)
Benign or Premalignant Lesions, n (%)	183 (74.4)
Barrett with LGD	5 (2)
Barrett with HGD	13 (5.3)
Intestinal Metaplasia with LGD	10 (4)
Intestinal Metaplasia with HGD	14 (5.7)
Tubulovillous Adenoma with LGD	15 (6.1)
Tubulovillous Adenoma with HGD	24 (9.7)
Villous Adenoma with LGD	4 (1.6)
Villous Adenoma with HGD	4 (1.6)
GI Stromal Tumor (GIST) Very Low, Low, or Intermediate Risk	60 (24.5)
Leiomyoma	30 (12.3)
Granular Cell Tumor	2 (0.8)
Lipoma	2 (0.8)
Malignant Lesions, n (%)	63 (25.6)
Well-Differentiated EC	2 (0.8)
Poorly Differentiated EC	2 (0.8)
Well-Differentiated GAC	22 (8.8)
Poorly Differentiated GAC	3 (1.2)
Well-Differentiated CA	4 (1.6)
Poorly Differentiated CA	2 (0.8)
GIST with High-Risk Features	16 (6.5)
NET	12 (4.9)
Depth of Invasion in ENL, n (%)	137 (100)
Mucosa and Superficial Submucosa (SM1)	120 (87.6)
Deep Submucosa (SM2)	17 (12.4)
Complete Resection (R0), n (%)	233 (94.7)
ENL	130/137 (94.8)
SEL	103/109 (94.5)
Final Curative Resection, n (%)	211 (85.8)
ENL	117/137 (85.4)
SEL	96/109 (86.2)
Histological Correlation Pre- vs Post-DES, n (%)	224/246 (91)
ENL	126/137 (91.6)
SEL	99/109 (90.8)

CA: Colorectal Adenoma; GAC: Gastric Adenocarcinoma; EC: Esophageal Carcinoma; HGD: High-Grade Dysplasia; LGD: Low-Grade Dysplasia; DES: Endoscopic Submucosal Dissection; GIST: Gastrointestinal Stromal Tumor; LNT: Early Neoplastic Lesion; SEL: Subepithelial Lesion; IM: Intestinal Metaplasia; SM1: Superficial Submucosa; SM2: Deep Submucosa.

Lesion distribution

The region with the highest frequency of procedures was the stomach (128/246; 52%). In the esophagus, leiomyoma was the most common lesion, with 21 cases (43.8%); in the stomach, low-grade GIST was the most frequent, with 52 cases (40.6%); in the colon, the lateral growth lesion of the non-granular variety with high-grade dysplasia, with 24 cases (42.1%); and in the duodenum, neuroendocrine tumors, with 8 cases (61.5%) (Fig. 5).

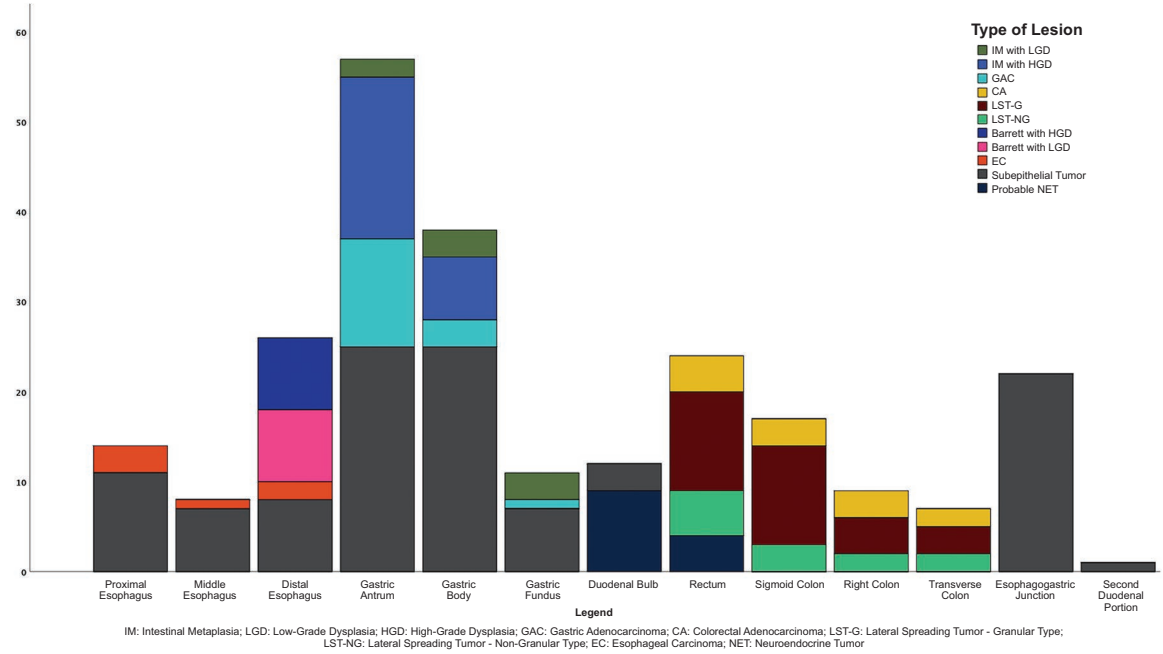

Figure 5. *Distribution of resected lesions based on their location.*

Table 4. Recurrence during Follow-up

Characteristics	Accumulated Recurrence (n = 233)
3 months, n (%)	1 (0.42) ENL 1/SEL 0
6 months, n (%)	2 (0.85) ENL 1/SEL 1
12 months, n (%)	3 (1.28) ENL 2/SEL 1
24 months, n (%)	6 (2.57) ENL 3/SEL 3
36 months, n (%)	9 (3.86) ENL 5/SEL 4
48 months, n (%)	12 (5.15) ENL 7/SEL 5
60 months, n (%)	17 (7.29) ENL 11/SEL 6
177 months (last cutoff), n (%)	22 (9.44) ENL 12/LSE 10

Recurrence at Follow-up

Of the 239/246 patients who underwent en block resection (97.2%), 233/246 (94.7%) had R0 resection. Most recurrences occurred within the first 5 years in 12 patients (7.29%), and by October 2022 (177 months post-ESD), a total of 22 (9.44%) recurrences were observed, 12 of which were ENL and 10, SEL. Treatment offered was endoscopic in 8 (successful in 6), while the other 14 recurrences required surgery and neoadjuvant therapy in all cases. Curative resection was achieved in 211/246 (85.8%; ENL 85.4% and SEL 86.2%; p = 0.45). No advanced lesions were found at follow-up, and mortality rate was 8.1% at 177 months, but without any association with tumor recurrence (Table 4 and Fig. 6).

Organ-related endoscopic submucosal dissection

The largest lesion sizes resected were in the colon vs the duodenum (26.5 vs 10.3 mm; p < 0.001), also showing the longest resection times (95.4 vs 55.6 min; p < 0.001). There were no differences in the length of hospital stay, en block resection rate, R0 rate, or type of lesion (ENL vs SEL). Bleeding was more common in the stomach, with 11 patients (8.6%), and perforation was more frequent in the colon, with 5 patients (8.8%) (Table 5).

Discussion

The aim of this study was to evaluate the experience of ESD for the treatment of ENL and SEL. We confirmed that it is a safe, effective, and reproducible technique in

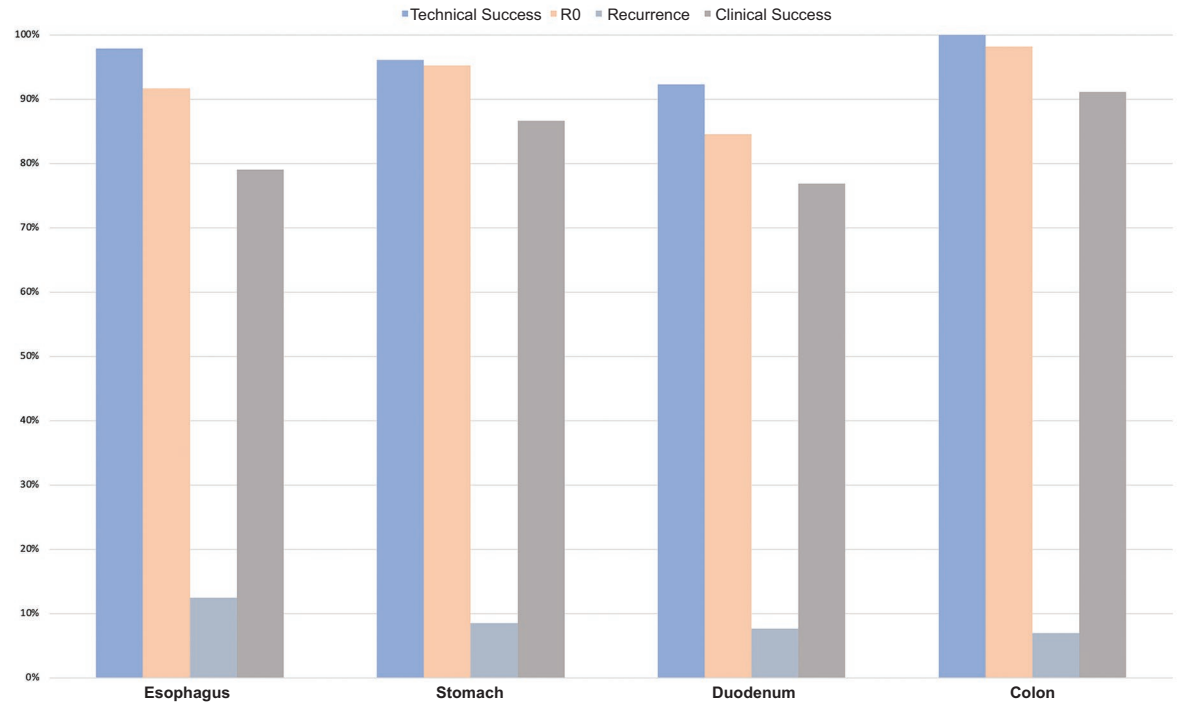

Figure 6. *Technical success, R0, recurrence, and clinical success of endoscopic submucosal dissection by region.*

Table 5. Characteristics of Endoscopic Submucosal Dissection by Regions of the Digestive Tract

Characteristics	Esophagus (n = 48)	Stomach (n = 128)	Duodenum (n = 13)	Colon (n = 57)	p
Size (mm), median, IQR	17.5 (8.1-40)	24.1 (10.1-65.1)	10.3 (6.5-15)	26.5 (8.4-81.2)	< 0.001[a]
Time (min), median, IQR	62 (34.5-96)	78.1 (33.1-278)	55.6 (27.8-88)	95.4 (28.1-348)	< 0.001[a]
Length of stay (days), median, IQR	1 (1-5)	3 (2-7)	3 (2-6)	2 (1-8)	0.22[a]
En block resection, n (%)	47 (97.9)	123 (96.1)	12 (92.3)	57 (100)	0.25[b]
Severe adverse events, n (%)					
Severe hemorrhage	3 (6.3)	11 (8.6)	1 (7.7)	2 (3.5)	0.04[b]
Perforation	1 (2.1)	10 (7.8)	1 (7.7)	5 (8.8)	0.04[b]
R0, n (%)	44 (91.7)	122 (95.3)	11 (84.6)	56 (98.2)	0.94[b]

[a]Kruskal-Wallis.
[b]Linear-by-linear association.

our setting. It has become established as a safe and effective technique[12,13,36-39], although its introduction in Latin America and Mexico has been slow[14,16,40]. Despite this, countries such as Brazil, Chile, Peru, and Colombia have published good results for ESD in the treatment of ENL and SEL, similar to those documented in the East[9,24,27,40-45]. In our country, the group of Carames et al.[46] reported the use of ESD in 32 patients with intestinal metaplasia, obtaining good results.

In the present study, we included 246 lesions (137 ENL and 109 SEL), with male sex being more predominant (54% and 55.9%, respectively) in both groups, similar to what has been reported by various Latin American authors (52-66%), such as Emura et al.[43] and others[27,41,44]. Age and other demographic factors were also similar to those reported by other authors, such as Medina et al.[47], who used this technique to treat ENL and SEL.

The largest lesions required longer ESD times and were more common in the colon (26.5 mm and 94.5 min), which is similar to what has been reported by other authors, such as Arantes et al.[9] and Palacios

et al.[27], and also similar to what was found in Eastern centers by Su et al.[48] and Jiao et al.[49]. These findings are clear for ENL, where the lesions are epithelial, and delays in dissection are associated with the presence of transoperative bleeding, location, and fibrosis, unlike SEL, where resection times are also highly variable but similar to other ESD studies in ENL and SEL[41,44,48,49].

Perforation occurred in 17 cases (ENL 5.8% and SEL 8.3%), and transoperative bleeding was slightly more frequent in SEL (23.8% vs 13.8% in ENL), probably related to the location and greater vascularization of SEL vs ENL. However, adverse events were controlled endoscopically, similar to what has been reported in other Asian and Latin American centers where endoscopic resolution demonstrated an efficacy higher than 80%[1,9,10,13,16,49,50], as observed in our cohort (82.5%).

Our case series represents the largest documented in Latin America, with an en block resection rate of 97.2% (97.1% for ENL vs 96.3% for SEL; p = 0.53), similar to results reported by other authors, such as Arantes et al.[9] and Palacios et al.[27], with R0 for gastric ENL at 96.3% and 99%, respectively. These findings are also consistent with those published by Saito et al.[50] in East Asia, who, in a multicenter study for the treatment of colorectal lesions, reported a lesion size of 34.2 mm, an operative time of 90 minutes, and a block resection rate of 95.4%, all comparable to our results (26.5 mm, 95.4 minutes, and 100%).

The main benefit of ESD is that it provides a mid- and long-term prognosis very similar to what is observed with conventional surgical treatments[36,42,48]. In gastric cancer, a reduction in mortality of up to 63% has been confirmed[50]. This is achieved with adequate en block resection and R0, which in our case was 94.7% overall, being lower in the duodenum, with 84.6%, but consistent with what Eastern experts recommend, suggesting it should be > 80% in this region[50], and variable depending on the region and histology of the resected lesions. Specifically, in the stomach, R0 has been documented in 94.7-95.1%, in the colon in 92-95.3%, and in the esophagus in 91.5-93.9%; results similar to those in our cohort (95.3, 98.2, and 91.7%, respectively) and higher than those reported by other authors in Latin America, such as Arantes et al.[9], with an en block resection rate of 95.5%, R0 of 88.8%, and a curative resection rate of 76.1%.

The overall recurrence in our cohort was 9.44% at 177 months, of which 12 cases were ENL and 10 were SEL, with a clinical success rate of 85.8% (ENL 85.4% and SEL 86.2%), which, although different from other centers, can be explained by the heterogeneity of the resected lesions. However, in the subgroup analysis by region, we found that ESD for gastric and colorectal ENL in our cohort was 1.4% and 2.1%, respectively, and the highest recurrence was in GIST-type lesions, similar to findings by other authors[27,37,39,42,44].

The weaknesses of our study stem from the inherent bias of its retrospective nature, being single-center, conducted by 2 physicians, and its limited applicability in other centers; the latter is due to the fact that, although our results are comparable to those from large Eastern centers, this is because, as a reference center, the number of cases and experience are greater compared to other Mexican centers where this advantage is not available, meaning the results could be different. However, our strengths include being the largest cohort reported in Latin America, the inclusion of ENL and SEL, long-term evaluation and follow-up of patients, and the clear and specific documentation of procedures, adverse events, and histology.

Conclusions

In patients with ENL or SEL who meet appropriate clinical indications, ESD represents the first-line therapy, with excellent short-, mid-, and long-term results, provided it is performed in centers with the appropriate infrastructure and experience.

Acknowledgments

The authors wish to thank the departments of gastroenterology, surgery, and pathology for their support in collecting patient data for this study.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors obtained approval from the Ethics Committee for the analysis and publication of clinically obtained data. Informed consent from patients was not required as this is a retrospective observational study.

References

1. Fleischmann C, Probst A, Ebigbo A, Faiss S, Schumacher B, Allgaier H-P, et al. Endoscopic submucosal dissection in Europe: results of 1000 neoplastic lesions from the German Endoscopic Submucosal Dissection Registry. Gastroenterology. 2021;161:1168-78.
2. Abdelfatah MM, Barakat M, Ahmad D, Ibrahim M, Ahmed Y, Kurdi Y, et al. Long-term out-comes of endoscopic submucosal dissection versus surgery in an early gastric cancer: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2019;31:418-24.
3. Lu L, Mullins C, Schafmayer C, Zeibig S, Linnebacher M. A global assessment of recent trends in gastrointestinal cancer and lifestyle-associated risk factors. Cancer Commun. 2021;41:1137-51.
4. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, et al. Global burden of 5 major types of gastrointestinal cancer. Gastroenterology. 2020;159:335-49.
5. Miller K, Ortiz A, Pinheiro PS, Bandi P, Minihan A, Fuchs HE, et al. Cancer statistics for the US Hispanic/Latino population, 2021. CA Cancer J Clin. 2021;71:466-87.
6. Pérez TE, Abdo FJM, Zavala SMR, Badillo VGY, Casillas GGB. Tratamiento quirúrgico del cáncer gástrico en el Servicio de Gastroenterología del Hospital General de México. Rev Med Hosp Gen Mex. 2010;73:9-15.
7. Sánchez JJ. Tendencias de mortalidad y años potenciales de vida perdidos por cáncer gástrico en México, 2000-2012. Rev Gastroenterol Mex. 2016;81:65-73.
8. Carioli G, Bertuccio P, Mazvezzi M, Boffetta P, Levi F, Negri E, et al. Cancer mortality predictions for 2021 in Latin America. Eur J Cancer Prev. 2021;31:217-27.
9. Arantes V, Aliaga R, Pedrosa M. Endoscopic submucosa dissection for superficial gastric neoplasias in two referral hospitals in Brazil: can the Japanese and South Korean results be equaled? Rev Gastroenterol Mex. 2021;86:244-52.
10. Villalobos JJ, Bourlon MT, Loaeza A, Torres G. Variaciones en la frecuencia de cáncer del aparato digestivo en el transcurso de 35 años en cuatro instituciones de la Ciudad de México de distinto nivel socioeconómico. Gac Med Mex. 2014;150:49-57.
11. Gómez H, Lamadrid H, Cahuana L, Silverman-Retana O, Montero P, González-Robledo M, et al. The burden of cancer in Mexico 1990-2013. Salud Publica Mex. 2016;58:118-31.
12. Icaza ME, Tanimoto MA, Huerta FM, Remes JM, Carmona R, Ángeles A, et al. El consenso mexicano sobre detección y tratamiento del cáncer gástrico temprano. Rev Gastroenterol Mex. 2020;85:69-85.
13. Akiho H, Esaki M, Ogino H, Hosokawa T, Mizutani T, Ihara E. Clinical outcome of endoscopic submucosal dissection for early gastric cancer in a post-operative stomach. Gastrointest Endosc. 2018;87:AB 244.
14. Takizawa K, Ono H, Muto M. Current indications of endoscopic submucosal dissection for early gastric cancer in Japan. Jpn J Clin Oncol. 2019;49:797-802.
15. Bausys R, Bausys A, Maneikis K, Belogorceva B, Stratilatocvcas E, Strupas K. Safety of expanded criteria for endoscopic resection of early gastric cancer in a Western cohort. BMC Surg. 2018;18:1-6.
16. Pimentel P, Dinis M, Ponchon T, Repici A, Vieth M, De Ceglie A. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015;47:829-54.
17. Strong AT, Rodríguez J, Kroh M, Posky JL. Intramural surgery: a new vista in minimally invasive therapy. J Am Coll Surg. 2017;225:339-42.
18. Yabuuchi Y, Kakushima N, Takizawa K, Tanaka M, Kawata N, Yoshida M, et al. Short-and long-term outcomes of endoscopic submucosal dissection for early gastric cancer in the remnant stomach after gastrectomy. J Gastroenterol. 2019;54:511-20.
19. Yang MJ, Shin SJ, Lee K, Myung K, Lim S, Kang J, et al. Non-neoplastic pathology results after endoscopic submucosal dissection for gastric epithelial dysplasia or early gastric cancer. Endoscopy. 2015;47:598-604.
20. Dohi O, Hatta W, Gotoda T, Naito Y, Oyama T, Kawata N, et al. Long-term outcomes afternoon-curative endoscopic submucosal dissection for early gastric cancer according to hospital volumes in Japan: a multicenter propensity-matched analysis. Surg Endosc. 2019;33:4078-88.
21. Tanoue K, Fukunaga S, Nagami Y, Sakai T, Maruyama H, Ominami M, et al.Long-term outcome of endoscopic submucosal dissection for early gastric cancer in patients with severe comorbidities: a comparative propensity score analysis. Gastric Cancer. 2019;22:558-66.
22. Yang D, Coman RM, Kahaleh M, Waxman I, Wang A, Sethi A, et al. Endoscopic submucosal dissection for Barrett's early neoplasia: a multicenter study in the United States. Gastrointest Endosc. 2017;86:600-7.
23. Jee YS, Hwang SH, Rao J, Park D, Kim H, Lee H-J, et al. Safety of extended endoscopic mucosal resection and endoscopic submucosal dissection following the Japanese Gastric Cancer Association treatment guidelines. Br J Surg. 2009;96:1157-61.
24. Mejía, R, Sáez J, Norero E, Briones P, Ceroni M, Martínez C, et al. Long-term results of endoscopic submucosal dissection (ESD) for the treatment of early gastric cancer (EGC) in a high-volume Latin American center. Surg Laparosc Endosc Percutan Tech. 2020;31:165-9.
25. Quiroz CD, Herrera JJ, Rojano M, Del Río Suárez, Morales J, Mucio M. Endoscopic gastric submucosal dissection in low-grade intraepithelial neoplasia. Rev Gastroenterol Mex. 2014;79:149-51.
26. Catalano F, Mengardo V, Trecca A, Tomezzoli A, Rodlla L, Cerofolini A, et al. The impact of experience on short and long-term outcomes on gastric ESD: a Western series. Updates Surg. 2019;71:359-65.
27. Palacios F, Benites H, Marin L, Bardalez P, Vasquez J, Alva E, et al. Short and mid-term results of endoscopic submucosal dissection in early gastric cancer: prospective study in Peru 2012-2018. Endoscopy. 2019;51:S249-50.
28. Donoso A, Sharp A, Parra-Blanco A, Roa J, Bacler J, Crovari F, et al. Disección submucosa endoscópica en cáncer gástrico incipiente: experiencia inicial en el Hospital Clínico de la Pontificia Universidad Católica de Chile. Rev Med Chile. 2015;143:1277-85.
29. Oyama T, Inoue H, Arima M, Momma K, Omori T, Ishihara R, et al. Prediction of the invasion depth of superficial squamous cell carcinoma based on microvessel morphology: magnifying endoscopic classification of the Japan Esophageal Society. Esophagus. 2017;14:105-12.
30. Goda K, Fujisaki J, Ishihara R, Takeuchi M, Takahashi A, Takaki Y, et al. Newly developed magnifying endoscopic classification of the Japan Esophageal Society to identify superficial Barrett's esophagus-related neoplasms. Esophagus. 2018;15:153-9.
31. Sharma P, Bergman JJ, Goda K, Kato M, Messman H, Alsop B, et al. Development and validation of a classification system to identify high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus using narrow-band imaging. Gastroenterology. 2016;150:591-8.
32. Yao K, Uedo N, Kamada T, Hirasawa T, Nagahama T, Yoshinaga S, et al. Guidelines for endoscopic diagnosis of early gastric cancer. Dig Endosc. 2020;32:663-98.
33. Hewett DG, Kaltenbach T, Sano Y, Tanaka S, Saunders B, Ponchon T, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology. 2012;143:599-607.
34. Kudo S, Tamura S, Nakajima T, Yamano H, Kusaka H, Watanabe H. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointest Endosc. 1996;44:8-14.
35. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3-43.
36. Probst A, Golger D, Arnholdt H, Messman H. Endoscopic submucosal dissection of early cancers, flat adenomas and submucosal tumors in the gastrointestinal tract. Clin Gastroenterol Hepatol. 2009;7:149-55.
37. Strong AT, Ponsky JL. Review: endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR). Ann Laparosc Endosc Surg. 2016;1:1-8.
38. Ko BM. History and development of accessories for endoscopic submucosal dissection. Clin Endosc. 2017;50:219-23.
39. Maple JT, Abu BK, Chauhan SS, Hwang J, Komanduri S, Manfredi M, et al. Endoscopic submucosal dissection. Gastrointest Endosc. 2015;81: 1311-25.
40. Draganov P, Wang A, Othman M, Fukami N. AGA Institute clinical practice update: endoscopic submucosal dissection in the United States. Clin Gastroenterol Hepatol. 2019;17:16-25.
41. Araújo M, Pimentel P, Libanio D, Canha M, Ribeiro M. How is endoscopic submucosal dissection for gastrointestinal lesions being implemented? Results from an international survey. GE Port J Gastroenterol. 2020;27:1-17.
42. Mejía R, Sáez J, Briones P, Norero E, Ceroni M, Díaz A, et al. Disección endoscópica submucosa para el tratamiento de neoplasias incipientes del tubo digestivo: experiencia en un centro universitario de alto volumen. Rev Med Chil. 2021;149:501-7.

43. Emura F, Mejía J, Donneys A, Ricaurte O, Sabbagh L, Cadavid L, et al. Therapeutic outcomes of endoscopic submucosal dissection of differentiated early gastric cancer in a Western endoscopy setting (with video). Gastrointest Endosc. 2015;82:804-11.
44. Chaves D, Moura E, Milhomem D, Arantes V, Yamazaki K, Maluf F, et al. Initial experience of endoscopic submucosal dissection in Brazil to treat early gastric and esophageal cancer: a multi-institutional analysis. Arq Gasteroenterol. 2013;50:148-52.
45. Global Cancer Observatory. Mexico. Disponible en: Globocanhttps://gco.iarc.fr/today/data/factsheets/populations/484-mexicofactsheets.pdf.
46. Carames J, Pioppo L, Carames M, Gaidhane M, Kahaleh M. ESD is an efficacious technique for cure of early gastric cancer in Northern Mexico. Gastrointest Endosc. 2019;89:Su 1351.
47. Medina J, Nava W, Barron J, Miranda A, López J. Incidencia de los tumores del estroma gastrointestinal en la población mexicana. Revisión sistemática. Gac Mex Oncol. 2018;17:40-7.
48. Su W, Ming W, Zhang D, Zhu Y, Lv M, Zhu L, et al. Predictors of the difficulty for endoscopic resection of gastrointestinal stromal tumor and follow up data. J Gastroenterol Hepatol. 2022;37:48-55.
49. Jiao R, Zhao S, Jiang W, Wei X, Huang G. Endoscopic submucosal dissection of gastrointestinal stromal tumours: a retrospective cohort study. Cancer Manag Res. 2020;12:4055-61.
50. Saito Y, Kawano H, Takeuchi Y, Ohata K, Oka S, Hotta K, et al. Current status of colorectal endoscopic submucosal dissection in Japan and other Asian countries: progressing towards technical standardization. Dig Endosc. 2012;24:67-72.

ORIGINAL ARTICLE

Comparison posterior lumbar stabilization with dynamic rod system and rigid rod system for lumbar degenerative disease

Comparación de la estabilización lumbar posterior con el sistema de barras dinámicas y el sistema de barras rígidas para la enfermedad degenerativa lumbar

Alp Karaaslan, Necat Biber, Burak Özdemir, Kadir Altaş, Ercan Kaya, Ece Sağlam Çifci, and Recep Başaran*
Department of Neurosurgery, Sancaktepe İlhan Varank Training and Research Hospital, Istanbul, Turkey

Abstract

Objective: *This research aims to assess the clinical and radiological outcomes of both dynamic rod system (PLSDR) and rigid rod system (PLSRR) when treating lumbar degenerative disease (LDD).* **Method:** *A retrospective review of 98 patients who underwent posterior stabilization surgery with a posterior approach in our clinic between 2018 and 2023 was conducted. The patients were divided into two groups based on the type of implant used: Those with PLSRR (Group 1) and those with PLSDR (Group 2).* **Results:** *In a comparative study, Group 1 had a higher prevalence of discopathy (49% vs. 24.5%, p = 0.012). Differences in surgical operation levels existed, and notably, only Group 1 had five-level surgeries (8.2%, p = 0.033). Pfirrmann disk degeneration grades differed significantly (p < 0.001), with Group 2 mainly in Grade I (77.6% vs. 36.7% in Group 1). Stenosis (57.1% vs. 28.6%, p = 0.004) and facet hypertrophy (71.4% vs. 47%, p = 0.014) were higher in Group 1. Group 1 also showed a greater adjacent segment degeneration (ASD) incidence (81.6% vs. 51%, p = 0.001). Both groups had primarily proximal ASD degeneration (p = 0.202). Compression fractures were absent. Follow-up durations were similar (p = 0.183).* **Conclusions:** *In treating LDD, the PLSDR shows potential advantages over PLSRR, including preservation of degeneration in adjacent segments.*

Keywords: *Lumbar degenerative disease. Dynamic system. Rigid rod system.*

Resumen

Objetivo: *Evaluar los resultados clínicos y radiológicos de los sistemas de varilla dinámica y de varilla rígida en el tratamiento de la enfermedad degenerativa lumbar.* **Método:** *Se realizó una revisión retrospectiva de 98 pacientes que se sometieron a cirugía de estabilización posterior con un abordaje posterior en nuestra clínica entre 2018 y 2023. Los pacientes se dividieron en dos grupos según el tipo de implante utilizado: varilla rígida (grupo 1) o varilla dinámica (grupo 2).* **Resultados:** *En el estudio comparativo, el grupo 1 tuvo una mayor prevalencia de discopatía (49 vs. 24.5%; p = 0.012). Hubo diferencias en los niveles de operación quirúrgica y, notablemente, solo el grupo 1 tuvo cirugías de cinco niveles (8.2%; p = 0.033). Los grados de degeneración del disco de Pfirrmann difirieron significativamente (p < 0.001) con el grupo 2, principalmente en el grado I (77.6 vs. 36.7% en el grupo 1). Las estenosis (57.1 vs. 28.6%; p = 0.004) y la hipertrofia facetaria (71.4 vs. 47%; p = 0.014) fueron mayores en el grupo 1. El grupo 1 también mostró una mayor incidencia de degeneración del segmento adyacente (81.6 vs. 51%; p = 0.001). Ambos grupos tuvieron principalmente degeneración del segmento adyacente proximal (p = 0.202). No hubo fracturas por compresión. Las duraciones de los seguimientos fueron similares (p = 0.183).* **Conclusiones:** *En el tratamiento de la enfermedad degenerativa lumbar, el sistema de varilla dinámica muestra ventajas potenciales sobre el de varilla rígida, incluida la preservación de la degeneración de segmentos adyacentes.*

Palabras clave: *Enfermedad degenerativa lumbar. Sistema dinámico. Sistema de varilla rígida.*

***Correspondence:**
Alp Karaaslan
E-mail: alpkaraaslan44@gmail.com

Date of reception: 16-12-2023
Date of acceptance: 26-12-2023
DOI: 10.24875/CIRUE.M23000798

Cir Cir (Eng). 2024;92(6):770-775
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Chronic low back pain is a prevalent issue leading to significant social and economic challenges. In industrialized nations, it is believed that between 70% and 85% of individuals will experience low back pain at some point in their lives[1-4]. The primary cause of this pain is lumbar degenerative disease (LDD), encompassing conditions like lumbar disc herniation, lumbar spinal stenosis, and lumbar spondylolisthesis. At present, LDD can be treated through non-invasive or surgical means. While non-invasive therapies can reduce symptoms for many, surgery remains the primary solution for advanced LDD cases[4,5].

One common method employed is the PLSRR[6]. Spinal fusion is often deemed the primary treatment for LDD. Some techniques boast a fusion success rate of 100%, though clinical outcomes typically range between 60% and 80%. Even with the positive results from this surgery, there are potential complications, such as issues with the instruments used, non-union, infections, and donor site discomfort. Crucially, spinal fusion might boost the range of motion (ROM) in neighboring segments, possibly causing adjacent segment degeneration (ASD)[6-8].

Due to the limitations of fusion, experts have investigated surgeries that maintain motion, such as artificial lumbar disk replacement and dynamic stabilization. The PLSDR serves as a substitute for traditional rigid tools and fusion in treating LDD. In principle, it provides the benefit of conserving motion in the neighboring segments and reducing strain on the adjacent discs and facet joints[7,8].

To the best of our knowledge, there are limited studies that compare the clinical results of the PLSDR and PLSRR. Therefore, this research aims to assess the clinical and radiological outcomes of both PLSDR and PLSRR when treating LDD.

Method

Study design and groups

A retrospective review of 98 patients who underwent posterior stabilization surgery with a posterior approach in our clinic between 2018 and 2023 was conducted. The patients were divided into two groups based on the type of implant used: Those with PLSRR (Group 1, Fig. 1) and those with PLSDR (Group 2, Fig. 2).

Patient data including age, gender, presence of comorbid diseases, and follow-up durations were recorded. All patients underwent lumbar magnetic resonance imaging. Radiological evaluations focused on assessing degeneration in the proximity of the proximal and distal segments for both systems. Degeneration assessment considered the presence of discopathy, facet hypertrophy, stenosis, scoliosis, and listhesis. In addition, for the differentiation between discopathy and disk degeneration, staging was conducted based on the Pfirrmann grading system (Table 1)[9].

Eligibility criteria

Patients who had undergone posterior stabilization for traumatic lumbar spine injuries, lumbar interbody fusion, and posterior thoracic stabilization were excluded from this study. Patients who had posterior stabilization surgeries targeted at lumbar degenerative spine were included in this study.

Ethical approval and informed consents

The study was approved ethically by non-interventional ethics committee of Sancaktepe Training and Research hospital (date: October 11, 2023. No: 211). Written informed consents were obtained from all patients and/or their guardians.

Surgical procedures

All surgeries were performed by the same surgical team and similar techniques were used for both groups. After general anesthesia, patients were positioned in the prone position and an incision was made in the posterior midline. Muscles were dissected to reveal the bone structures. In Group 2, pedicle screws were placed first and the placements of the pedicle screws were checked under fluoroscopy. After placing the dynamic rod system, a laminectomy was performed to achieve decompression, and it was ensured that the medial facet joints were preserved as much as possible. For many patients, basic decompression was performed, but in cases of significant narrowing, extensive decompression was required. In cases with lumbar disk herniation, partial discectomy and foraminotomy were performed (Fig. 3)[10,11].

For Group 1, patients were first positioned in the prone position and a midline incision was made, passing through the skin and subcutaneous layers. Bone structures were exposed through blunt muscle dissection. Under fluoroscopy guidance, pedicle screws

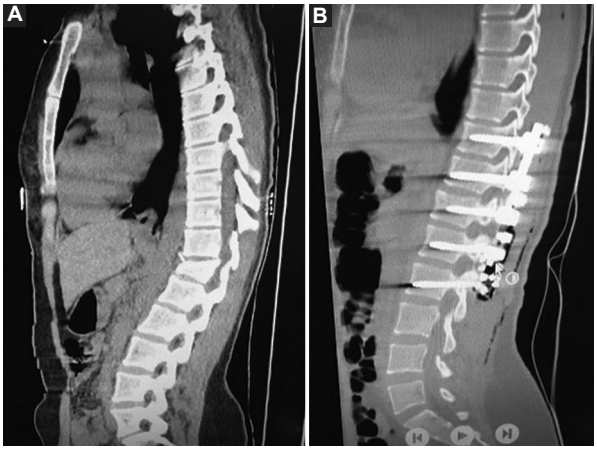

Figure 1. *Rigid rod system and bone fusion.* **A:** *pre-operative view* **B:** *post-operative view.*

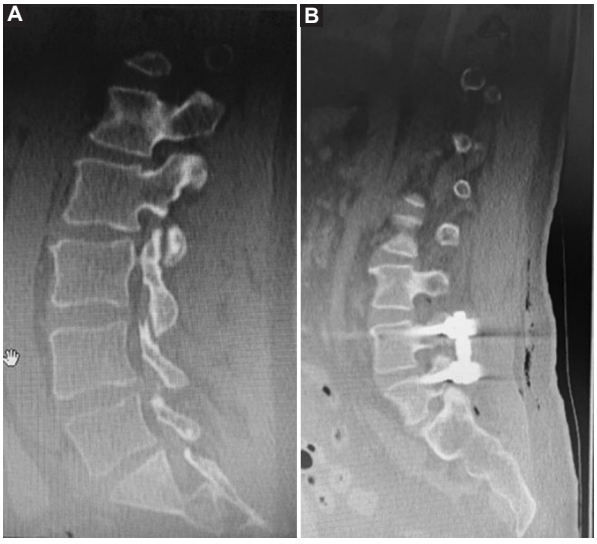

Figure 2. *Dynamic stabilization system.* **A:** *pre-operative view* **B:** *post-operative view.*

were appropriately placed. The rigid rod system was locked to the pedicle screws. Procedures such as laminectomy, hemilaminectomy, or facetectomy were performed for decompression. Discectomy was applied to some patients. Fusion was performed for patients using allogeneic and autologous bone grafts, 5 cc for each level. Decortication was applied to the bones to expand the fusion area (Fig. 4)[10,11].

Patients were allowed to walk on the 3rd day post-surgery. They were advised to wear a lumbar brace for 12-week post-surgery, after which they could resume their regular activities.

Table 1. Pfirrmann grading system[9]

Grade	Definitions
Grade I	A normal disc
Grade II	An inhomogeneous disc with normal disc height and a clear difference between the nucleus and annulus
Grade III	An inhomogeneous gray disc with a loss of the clear border between the nucleus and annulus and normal to slightly decreased disc height
Grade IV	An inhomogeneous hypointense dark gray disc with significant disc height loss
Grade V	A inhomogeneous black disc with disc space collapse

Statistical analysis

The patient information was evaluated using various statistical techniques, including the creation of descriptive statistics, the calculation of frequencies, and the analysis of other factors spanning all categories. Quantitative figures were represented as mean ± standard deviation. The distribution normality of continuous data was assessed through the Shapiro–Wilk and Kolmogorov–Smirnov tests. For continuous variables that followed a normal distribution, the Student's *t*-test was utilized. For data not adhering to a normal distribution, non-parametric tests were used. Categorical data were analyzed using the χ^2 test. The data analysis was conducted using SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). A two-tailed $p \leq 0.05$ was deemed to indicate statistical significance.

Results

A total of 98 patients were included in our study, with 49 patients from Group 1 and 49 patients from Group 2. Table 2 summarizes the comorbidities. The most prevalent comorbidities were diabetes (15.7%) and hypertension (13.9%). Gastrointestinal diseases and hyperlipidemia followed, with 9.3% and 8.3%, respectively. Anxiety/Depression affected 7.4% of participants. Notably, 18.5% had no comorbidities.

In our comparative analysis, both groups presented a closely matched age profile, with an average age of 53.3 ± 13.53 years in Group 1 and 52.5 ± 10.41 years in Group 2 (p = 0.744). Gender distribution revealed a marked contrast with males constituting 18.4% in Group 1 and rising to 43% in Group 2, a variation found

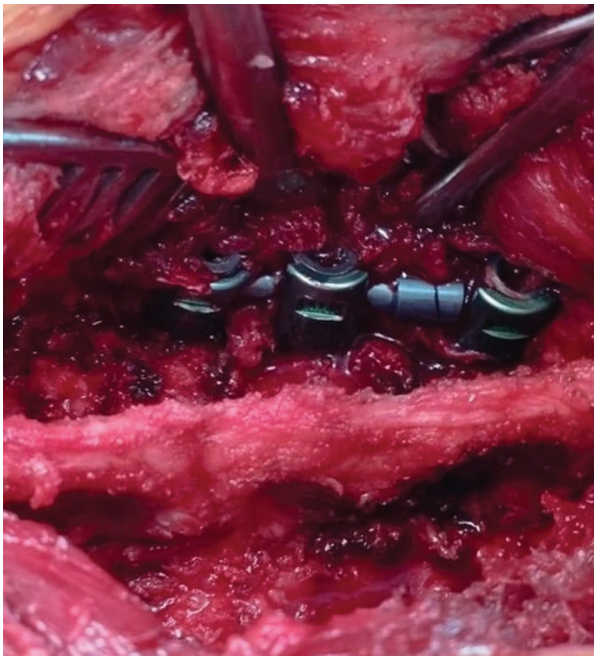

Figure 3. *Dynamic stabilization system intraoperative view.*

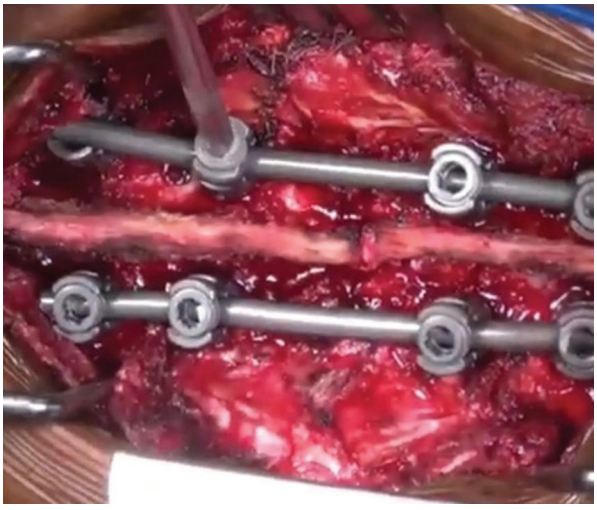

Figure 4. *Intraoperative view of posterior stabilization with rigid rod system and bone fusion.*

Table 2. Comorbidity of the individuals

Comorbidity	n	%
Diabetes	17	15.7
Hypertension	15	13.9
Gastrointestinal diseases	10	9.3
Hyperlipidemia	9	8.3
Anxiety/depression	8	7.4
Coronary artery disease	6	5.6
Gonarthrosis	5	4.6
Hypothyroidism	5	4.6
Urogenital diseases	4	3.7
Arthritis	4	3.7
Vertigo	2	1.9
Asthma	1	0.9
Anemia	1	0.9
Psoriasis	1	0.9
None	20	18.5
Total	108	100

to be significant (p = 0.009). Discopathy was more prevalent in Group 1 (49%) than in Group 2 (24.5%) (p = 0.012). Regarding surgical operating levels, Group 2 had a slight lead in single-level operations (4.1%) compared to Group 1 (0%). For two-level surgeries, Group 1 had 45% and Group 2 reported 51%. Three-level surgeries were conducted on 30.5% of Group 1 and 40.8% of Group 2. Four-level operations were more common in Group 1 (16.3%) than in Group 2 (4.1%). Interestingly, only Group 1 reported five-level surgeries, affecting 8.2% of its cohort (p = 0.033). In terms of the Pfirrmann disk degeneration grade, a glaring distinction was noted. Group 2 predominantly fell under Grade I (77.6%) compared to Group 1 (36.7%). While Group 1 had 26.5% individuals in Grade II, Group 2 had a slight reduction at 16.3%. Grade III was observed in 18.4% of Group 1 versus 6.1% of Group 2. Grade IV was unique to Group 1 with 16.3%, and only 2% of Group 1 was classified under Grade V. This gradient in disk degeneration grades across both groups was notably significant (p < 0.001). When examining stenosis, Group 1 showcased a higher prevalence (57.1%) in contrast to Group 2's 28.6% (p = 0.004). Facet hypertrophy was also more common in Group 1 (71.4%) than in Group 2 (47%) (p = 0.014). While Group 2 presented a 4.1% incidence of scoliosis, it was absent in Group 1 (p = 0.153). The prevalence of listhesis was minimal across groups, at 2% for Group 1 and 4.1% for Group 2 (p = 0.558). The incidence of ASD was markedly higher in Group 1 (81.6%) compared to Group 2 (51%) (p = 0.001). Concerning the ASD degeneration location, Group 2 had 4% at the

Table 3. Comparison of the groups

Variables	Group 1 (n = 49%)	Group 2 (n = 49%)	p
Age (year)*	53.3 ± 13.53	52.5 ± 10.41	0.744
Gender (M)	9 (18.4)	21 (43)	0.009
Discopathy	24 (49)	12 (24.5)	0.012
Operating levels			0.033
1 level	0 (0)	2 (4.1)	
2 levels	22 (45)	25 (51)	
3 levels	15 (30.5)	20 (40.8)	
4 levels	8 (16.3)	2 (4.1)	
5 levels	4 (8.2)	0 (0)	
Pfirrmann disc degeneration grade			< 0.001
Grade I	18 (36.7)	38 (77.6)	
Grade II	13 (26.5)	8 (16.3)	
Grade III	9 (18.4)	3 (6.1)	
Grade IV	8 (16.3)	0 (0)	
Grade V	1 (2)	0 (0)	
Stenosis	28 (57.1)	14 (28.6)	0.004
Facet hypertrophy	35 (71.4)	23 (47)	0.014
Scoliosis	0 (0)	2 (4.1)	0.153
Listhesis	1 (2)	2 (4.1)	0.558
ASD (yes)[&]	40 (81.6)	25 (51)	0.001
Location of the degeneration ASD[&]			0.202
Distal	0 (0)	1 (4)	
Proximal	40 (100)	24 (96)	
Compression fracture	0 (0)	0 (0)	N/A
Follow-up (month)*	41.7 ± 7.62	43.7 ± 6.98	0.183

*Mean ± standart deviation. [&]ASD: Adjacent segment degeneration; N/A: non-applicable.

distal end, whereas proximal degeneration was dominant in both groups: 100% in Group 1 and 96% in Group 2 (p = 0.202). Notably, compression fractures were absent in both groups. During the follow-up period, Group 1 participants averaged a duration of 41.7 ± 7.62 months, while Group 2's duration was slightly extended at 43.7 ± 6.98 months (p = 0.183) (Table 3).

Discussion

Spinal fusion surgery is recognized as an effective approach for addressing lumbar degenerative conditions. While this surgical intervention is commonly recommended for conditions like isolated disk degeneration, primary and secondary instabilities, recurrent disk herniation, and pseudarthrosis, existing studies have highlighted potential risks such as ASD, equipment malfunction, pseudoarthrosis, nonunion, infections, and pain at the donor site. To mitigate these challenges, dynamic semi-rigid stabilization was introduced in 1994[12,13]. This technique aims to maintain motion at the treated sections while preventing excessive movement and subsequent spondylosis at neighboring segments. Prior research indicates that Dynesys stabilization combined with decompression offers promising short- and long-term results for lumbar degenerative conditions. The method not only alleviates back and leg discomfort but also maintains the movement of stabilized segments, limits tissue damage, and eliminates the need for bone harvesting for fusion[12,13].

A systematic review previously conducted by Chou et al. indicated no notable differences between fusion and dynamic stabilization in terms of visual-analog scale (VAS), oswestry disability ındex (ODI), complications, and subsequent surgeries[7]. Existing research does not provide long-term evidence establishing whether dynamic stabilization reduces ASD rates. However, when assessing post-operative ASD and operated segment ROM, PLSDR has statistically lower outcomes compared to fusion. Our findings diverge from those reported by other researchers. In a meta-analysis led by Wang et al., both fusion and Dynesys were shown to be equally effective in treating degenerative lumbar diseases, as evidenced by no significant differences in the VAS scores for back and leg pain. Prior studies have also shown both methods, leading to marked improvements in VAS for back and leg pain as well as ODI[8]. Yet, no discernible differences between the two methods were identified at any evaluation period. In our study, ROM was not evaluated. In terms of ASD, the incidence of ASD was markedly higher in PLSRR group (81.6%) compared to PLSDR group (51%) (p = 0.001). Concerning the ASD degeneration location, Dynesys had 4% at the distal end, whereas proximal degeneration was dominant in both groups.

Dynamic stabilization primarily offers the benefit of maintaining motion at the treated segment, which could potentially minimize the risk of ASD. This anticipated decrease in ASD is chiefly due to preventing increased stress on adjacent segments. Data from our research indicate a significantly higher occurrence of ASD in the fusion group compared to the Dynesys group. Nonetheless, regarding the preventative aspect against ASD, earlier research has yielded mixed findings. Cakir et al. indicated that monosegmental posterior dynamic stabilization using Dynesys did not influence adjacent segment mobility when compared to monosegmental fusion[14]. Past researchers have posited that while the dynamic

system curtails instability at the treated segment, its efficacy in thwarting ASD remains ambiguous[15]. Conversely, Wu et al. demonstrated that, when compared to PLIF, Dynesys stabilization retains the movement of the stabilized segments, exerting minimal impact on the proximal adjacent segment, and may assist in deterring the onset of ASD[16]. Within our cohort, Group 1 exhibited a marked increase in the prevalence of stenosis at 57.1%, which is significantly higher than that observed in Group 2, which had a prevalence of 28.6% ($p = 0.004$). This stark contrast between the two groups in our study underscores the varying manifestations of post-operative stenosis in different surgical interventions.

This study has limitations: Firstly, the cohort size is comparatively limited, necessitating a more extensive patient group to corroborate our findings. Secondly, given that our research is retrospective, it has certain inherent constraints; there's a need for a future prospective study. Thirdly, there might be potential discrepancies due to individual variations between the surgeons conducting the procedures and those assessing the radiographic images, despite both having extensive experience at the same institution. Finally, the average observation period for this research is 41 month; a more extended period is essential to comprehensively evaluate both clinical and radiographic differences between the two groups.

Conclusion

In treating LDD, the Dynesys dynamic stabilization system shows potential advantages over PLIF, including preservation of degeneration in adjacent segments. However, both methods present unique challenges. Further long-term studies are crucial to establish definitive superiority.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Abi-Hanna D, Kerferd J, Phan K, Rao P, Mobbs R. Lumbar disk arthroplasty for degenerative disk disease: literature review. World Neurosurg. 2018;109:188-96.
2. Kuo CH, Huang WC, Wu JC, Tu TH, Fay LY, Wu CL, et al. Radiological adjacent-segment degeneration in L4-5 spondylolisthesis: comparison between dynamic stabilization and minimally invasive transforaminal lumbar interbody fusion. J Neurosurg Spine. 2018;29:250-8.
3. Lee CH, Jahng TA, Hyun SJ, Kim CH, Park SB, Kim KJ, et al. Dynamic stabilization using the Dynesys system versus posterior lumbar interbody fusion for the treatment of degenerative lumbar spinal disease: a clinical and radiological outcomes-based meta-analysis. Neurosurg Focus. 2016;40:E7.
4. Ciplak NM, Suzer T, Senturk S, Yaman O, Sasani M, Oktenoglu T, et al. Complications of 2-level dynamic stabilization: a correlative clinical and radiological analysis at two-year follow-up on 103 patients. Turk Neurosurg. 2018;28:756-62.
5. Zhang Y, Zhang ZC, Li F, Sun TS, Shan JL, Guan K, et al. Long-term outcome of dynesys dynamic stabilization for lumbar spinal stenosis. Chin Med J (Engl). 2018;131:2537-43.
6. Macki M, Bydon M, Weingart R, Sciubba D, Wolinsky JP, Gokaslan ZL, et al. Posterolateral fusion with interbody for lumbar spondylolisthesis is associated with less repeat surgery than posterolateral fusion alone. Clin Neurol Neurosurg. 2015;138:117-23.
7. Chou D, Lau D, Skelly A, Ecker E. Dynamic stabilization versus fusion for treatment of degenerative spine conditions. Evid Based Spine Care J. 2011;2:33-42.
8. Wang H, Peng J, Zeng Q, Zhong Y, Xiao C, Ye Y, et al. Dynesys system vs posterior decompression and fusion for the treatment of lumbar degenerative diseases. Medicine (Baltimore). 2020;99:e19784.
9. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine (Phila Pa 1976). 2001;26:1873-8.
10. Wang H, Lv B. Comparison of clinical and radiographic results between posterior pedicle-based dynamic stabilization and posterior lumbar intervertebral fusion for lumbar degenerative disease: a 2-year retrospective study. World Neurosurg. 2018;114:e403-11.
11. Guan J, Liu T, Yu X, Li W, Feng N, Jiang G, et al. Biomechanical and clinical research of Isobar semi-rigid stabilization devices for lumbar degenerative diseases: a systematic review. Biomed Eng Online. 2023;22:95.
12. Zhang Y, Shan JL, Liu XM, Li F, Guan K, Sun TS. Comparison of the dynesys dynamic stabilization system and posterior lumbar interbody fusion for lumbar degenerative disease. PLoS One. 2016;11:e0148071.
13. Peng BG, Gao CH. Is dynesys dynamic stabilization system superior to posterior lumbar fusion in the treatment of lumbar degenerative diseases? World J Clin Cases. 2020;8:5496-500.
14. Cakir B, Carazzo C, Schmidt R, Mattes T, Reichel H, Käfer W. Adjacent segment mobility after rigid and semirigid instrumentation of the lumbar spine. Spine (Phila Pa 1976). 2009;34:1287-91.
15. Li JX, Phan K, Mobbs R. Oblique lumbar interbody fusion: technical aspects, operative outcomes, and complications. World Neurosurg. 2017;98:113-23.
16. Wu H, Pang Q, Jiang G. Medium-term effects of dynesys dynamic stabilization versus posterior lumbar interbody fusion for treatment of multisegmental lumbar degenerative disease. J Int Med Res. 2017;45:1562-73.

ORIGINAL ARTICLE

Treatment effectiveness according to frequencies in patients with sudden sensorineural hearing loss

Eficacia del tratamiento según las frecuencias en pacientes con pérdida auditiva sensorioneural súbita

Ahmet Celik[1] and Ferit Akil [2]*

[1]Department of Otorhinolaryngology, Silopi State Hospital, Sirnak; [2]Department of Otorhinolaryngology, Memorial Diyarbakır Hospital, Diyarbakır. Turkey

Abstract

Objective: *The objective of the study is to evaluate combined hyperbaric oxygen therapy (HBOT) and steroids on hearing in sudden sensorineural hearing loss (SSNHL) patients.* **Method:** *A total of 50 patients with sudden hearing loss that started within 1 week and who received a combination of intravenous steroid therapy and HBOT in their medical treatment were assigned to the otolaryngology department for 1 week, followed by intravenous steroid therapy at 1 mg/kg/day and then reduced doses for 1 week. They were treated once in a hyperbaric chamber where they breathed 100% oxygen at 2.5 atm pressure for 60 min, for a total of 20 sessions.* **Results:** *Hearing loss was observed in 54% of participants in the right ear. Significant improvements were observed in hearing thresholds across all tested frequencies after treatment with a specific intervention ($p < 0.001$ for each comparison). Combined steroid and HBOT significantly improved hearing across low and high frequencies ($p < 0.001$). Improvement in hearing at low frequencies was significantly greater than at high frequencies ($p < 0.01$). Post hoc analysis showed greater hearing improvement at lower frequencies compared to higher ones.* **Conclusions:** *This study demonstrated that combined steroid and HBOT significantly improves hearing thresholds in patients with idiopathic SSNHL, especially at lower frequencies.*

Keywords: *Sudden sensorineural hearing loss. Hyperbaric oxygen therapy. Corticosteroids.*

Resumen

Objetivo: *Evaluar la terapia combinada de oxígeno hiperbárico y corticosteroides en pacientes con pérdida auditiva sensorioneural súbita.* **Método:** *Se incluyeron 50 pacientes con pérdida auditiva súbita iniciada dentro de 1 semana, quienes recibieron un tratamiento médico combinando corticosteroides intravenosos y terapia de oxígeno hiperbárico. Fueron asignados al departamento de otorrinolaringología por 1 semana, seguido de corticosteroides intravenosos a dosis de 1 mg/kg al día y luego dosis reducidas por 1 semana. Se trató a los pacientes en una cámara hiperbárica en la que respiraron oxígeno al 100% a una presión de 2.5 atm durante 60 minutos, para un total de 20 sesiones.* **Resultados:** *Se observó pérdida auditiva en el oído derecho en el 54% de los participantes. Se encontraron mejoras significativas en los umbrales auditivos en todas las frecuencias después del tratamiento con una intervención específica ($p < 0.001$ para cada comparación). La combinación de corticosteroides y terapia de oxígeno hiperbárico mejoró significativamente la audición en frecuencias bajas y altas ($p < 0.001$). La mejora en la audición en frecuencias bajas fue significativamente mayor que en altas ($p < 0.01$). Un análisis post hoc mostró una mayor mejora auditiva en las frecuencias bajas comparadas con las altas.* **Conclusiones:** *Este estudio demostró que la terapia combinada de corticosteroides y oxígeno hiperbárico mejora significativamente los umbrales auditivos en pacientes con pérdida auditiva sensorioneural súbita idiopática, en especial en frecuencias bajas.*

Palabras clave: *Pérdida auditiva sensorioneural súbita. Terapia de oxígeno hiperbárico. Corticosteroides.*

***Correspondence:**
Ahmet Celik
E-mail: ahmetcelikk1982@gmail.com

Date of reception: 09-04-2024
Date of acceptance: 13-05-2024
DOI: 10.24875/CIRUE.M24000799

Cir Cir (Eng). 2024;92(6):776-784
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Sudden sensorineural hearing loss (SSNHL) presents a significant clinical challenge within the field of otolaryngology, representing an acute onset of hearing impairment that necessitates immediate medical attention[1-4]. Characterized by a rapid reduction in hearing capacity, SSNHL is defined as a sensorineural hearing loss of 30 decibels (dB) or more across at least three contiguous audiometric frequencies occurring within a 72-h period[5,6]. This condition is a perplexing medical emergency, not only due to its abrupt manifestation but also because its etiopathogenesis remains largely enigmatic, complicating both diagnosis and treatment strategies[2,4,5].

The prevalence and incidence rates of SSNHL underscore its significance within the general population, with estimates suggesting that it accounts for approximately 1% of all sensorineural hearing loss cases[1-3,7]. Epidemiological studies report an incidence ranging from 5 to 20 cases/100,000 individuals annually, highlighting the condition's relatively uncommon yet impactful presence in clinical practice[2,8,9]. Despite its rarity, the potential for spontaneous recovery – reported in various studies to range between 32% and 65% – further complicates the clinical approach to management and underscores the urgency for efficacious treatment modalities[4,8,9].

The etiology of SSNHL is multifactorial, with numerous proposed mechanisms including viral infections, vascular occlusions, autoimmune diseases, and more[2,10]. However, a significant proportion of cases remains idiopathic, with no discernible cause, which has led to challenges in developing targeted treatment strategies. In the absence of clear etiological pathways, the management of SSNHL often adopts a broad-spectrum approach aimed at mitigating the effects of potential underlying causes[10].

Corticosteroids have long been the cornerstone of SSNHL treatment, favored for their anti-inflammatory and immunosuppressive properties[11-13]. Administered either systemically or locally (intratympanically), corticosteroids aim to reduce cochlear inflammation and edema, thereby potentially salvaging hearing. The choice between systemic and local administration often depends on the severity of hearing loss, patient comorbidities, and potential side effects, making treatment personalization a critical aspect of management[11,13].

Beyond corticosteroids, hyperbaric oxygen therapy (HBOT) has emerged as a supplementary treatment modality for SSNHL, especially in idiopathic cases[14]. First introduced in 1979, HBOT increases the amount of dissolved oxygen in the blood, enhancing oxygen delivery to the cochlea and potentially reducing hypoxia-induced damage[14,15]. While not universally accepted as a standard treatment due to variable efficacy across studies, HBOT has shown promise, particularly when used in conjunction with corticosteroids[16]. The synergistic effects of HBOT and corticosteroids have been documented in several clinical trials, suggesting improvements in both high and low-frequency hearing thresholds in patients with idiopathic SSNHL[17].

In this study, we investigated the impact of combined HBOT and intravenous steroid treatments on hearing recovery across high and low-frequency ranges in patients with idiopathic SSNHL.

Method

Patients and design

In this study, a meticulously selected cohort of 50 individuals presenting with SSNHL was examined. These participants were recruited from the patient population at the Department of Otorhinolaryngology, a leading institution renowned for its specialized care and innovative treatment approaches in the realm of ear, nose, and throat disorders.

The sample size, comprising 54 patients, was determined based on a 95% confidence level, utilizing the Jamovi J power software for calculations. To confidently (with a probability > 0.95) we identify an effect size of $\delta \geq 0.5$, required a sample size of 54, assuming a two-sided detection criterion. This criterion accommodates a maximum Type I error rate of $\alpha = 0.05$ (Fig. 1).

Eligibility criteria

The eligibility for participation was confined to patients who experienced the onset of sudden hearing loss within a 1-week timeframe. This criterion was essential to differentiate the acute phase of SSNHL from more prolonged or progressive hearing impairments, thereby focusing on those most likely to benefit from immediate intervention. In addition, only those who had commenced a combined treatment regimen consisting of intravenous steroid therapy and HBOT were considered for inclusion.

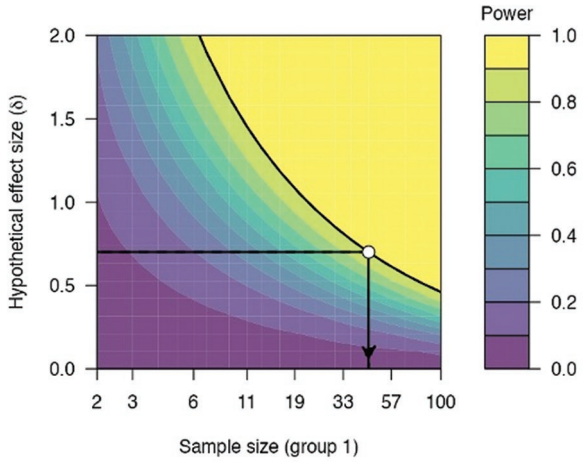

Figure 1. *Power contour.*

Ethical approval

The research protocol received formal approval from the local Ethical Committee. This endorsement, signified by approval number 121, was officially granted on May 22, 2017.

Treatment protocol

All participants in this study underwent a meticulously designed treatment regimen within a hyperbaric chamber, a specialized medical environment designed to significantly increase atmospheric pressure. Within this chamber, patients inhaled pure 100% oxygen at a pressure of 2.5 atmospheres (atm) for a duration of 60 min. This elevated pressure, significantly above sea-level atmospheric conditions, facilitates the dissolution of greater amounts of oxygen in the bloodstream, potentially enhancing the repair of damaged auditory cells and tissues. The HBOT was administered across a series of 20 sessions, conducted daily, to ensure a consistent and cumulative therapeutic effect aimed at optimizing hearing recovery outcomes. Concurrently, patients received a concomitant treatment regimen of intravenous steroid therapy, initiated at a dosage of 1 mg/kg/day.

Statistical analysis

IBM SPSS 25.0 for the Windows statistical package program was used for the statistical evaluation of the research data. Measured variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages (%). It was checked whether the data conformed to the normal distribution. Normally distributed dependent t-test was used to compare the previous and next groupings. The one-way analysis of variance (ANOVA) test technique was used to compare more than two independent groups. When a significant difference was observed in the ANOVA test, the *post hoc* LSD test was used to determine the source of the difference between the groups. Wilcoxon signed-rank test was used to compare before and after groupings that did not show normal distribution. χ^2 test was used to compare qualitative variables. The hypotheses were taken bilateral and $p \leq 0.05$ was accepted as a statistically significant result.

Results

A total of 50 patients were included in this study. The study presents a demographic breakdown with an average age of 51 ± 15.1 years, comprising 62% males and 38% females. Hearing loss was observed in 54% of participants in the right ear and 46% in the left. Upper respiratory tract infections were reported in 38% of the subjects, whereas 62% were unaffected. Smoking habits were noted, with 42% of participants being smokers and 58% non-smokers. Vertigo and vascular pathology were each reported in 22% of the subjects, significantly lower than those without these conditions (78%). Effort-related issues were rare, affecting only 2% of participants (Table 1).

Significant improvements were observed in hearing thresholds across all tested frequencies after treatment with a specific intervention. For the frequency of 250 Hz, the median hearing threshold improved from 65.00 dB before treatment to 22.50 dB after treatment, with a mean reduction from 62.00 ± 28.61 dB to 32.00 ± 27.79 dB ($p < 0.001$). At 500 Hz, the median threshold decreased from 72.50 dB to 27.50 dB, and the mean values improved from 66.60 ± 31.16 dB to 35.70 ± 29.15 dB ($p < 0.001$). For 1000 Hz, the median threshold went from 72.50 dB to 27.50 dB, with mean values changing from 68.00 ± 33.58 dB to 38.40 ± 31.29 dB ($p < 0.001$). At 2000 Hz, the median threshold improvement was from 72.50 dB to 37.50 dB, with mean values improving from 69.00 ± 32.13 dB to 43.40 ± 32.57 dB ($p < 0.001$). The 4000 Hz frequency showed a median threshold decrease from 72.50 dB to 55.00 dB, and mean values decreased from 73.90 ± 30.26 dB to 53.20 ± 33.12 dB ($p < 0.001$). At 8000 Hz, both median and mean thresholds showed improvement from

Table 1. Demographic data

Frequencies	Mean ± SD or n (%)
Age	51 ± 15.1
Gender	
Male	31 (62)
Female	19 (38)
Hearing loss	
Right ear	27 (54)
Left ear	23 (46)
Upper respiratory tract infection	
Yes	19 (38)
No	31 (62)
Smoking	
Yes	21 (42)
No	29 (58)
Vertigo	
Yes	11 (22)
No	39 (78)
Vascular pathology	
Yes	11 (22)
No	39 (78)
Related to efforts	
Yes	1 (2)
No	49 (98)

SD: standard deviation.

Table 2. Evaluation of the effects of combined steroid and hyperbaric oxygen therapy on (sudden) sensorineural hearing loss separately by each frequency pathway

Mean ± SD	Median (dB)	Mean ± SD (dB)	p
250 Hz			< 0.001
Before treatment	65.00	62.00 ± 28.61	
After treatment	22.50	32.00 ± 27.79	
500 Hz			< 0.001
Before treatment	72.50	66.60 ± 31.16	
After treatment	27.50	35.70 ± 29.15	
1000 Hz			< 0.001
Before treatment	72.50	68.00 ± 33.58	
After treatment	27.50	38.40 ± 31.29	
2000 Hz			< 0.001
Before treatment	72.50	69.00 ± 32.13	
After treatment	37.50	43.40 ± 32.57	
4000 Hz			< 0.001
Before treatment	72.50	73.90 ± 30.26	
After treatment	55.00	53.20 ± 33.12	
8000 Hz			< 0.001
Before treatment	75.00	71.90 ± 31.25	
After treatment	55.00	54.20 ± 33.63	

SD: standard deviation.

75.00 dB and 71.90 ± 31.25 dB before treatment to 55.00 dB and 54.20 ± 33.63 dB after treatment, respectively ($p < 0.001$). The data for each frequency and the statistical results are presented in table 2, and their graphical representation is displayed in figure 2.

The study also examined the impacts of combined steroids and HBOT on hearing loss, focusing on both low (250 Hz, 500 Hz, and 1000 Hz) and high (2000 Hz, 4000 Hz, and 8000 Hz) frequency ranges. The results indicated a significant enhancement in hearing thresholds across these frequencies. Notably, statistical analysis revealed that the improvements were highly significant ($p < 0.001$) across all comparisons, as visually represented in figure 3.

In the analysis conducted to identify the frequencies at which the treatment was most effective, it was found that the improvement in hearing at low frequencies was significantly greater than at high frequencies, with a t-value of 3.780 and a $p < 0.001$, as detailed in table 3. Furthermore, the calculated Cohen's d value of 0.53 for this difference indicates a medium effect size, suggesting a moderate but significant disparity in treatment effectiveness between low and high frequencies.

To ascertain at which frequency the combined steroid and HBOT yielded the most significant improvement, average hearing gains at frequencies 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz were analyzed using a one-way ANOVA. The ANOVA results revealed a significant variance in the average hearing gains across the measured frequencies, with an F value of 2.467 and a $p = 0.033$, as detailed in table 4.

The *post hoc* analysis, conducted to pinpoint the specific frequencies where these differences in hearing gain were observed, revealed that the improvement in hearing at 250 Hz was significantly greater than at 8000 Hz. Similarly, hearing gains at 500 Hz and 1000 Hz were also found to be significantly higher than those at 4000 Hz and 8000 Hz, indicating a notable variation in the effectiveness of the treatment across these frequencies (Table 5).

A Venn diagram involving gender, upper respiratory infection, smoking, and vertigo is given in figure 4.

Discussion

In this study involving 50 patients, we observed significant improvements in hearing thresholds across all frequencies after combined steroid and HBOT,

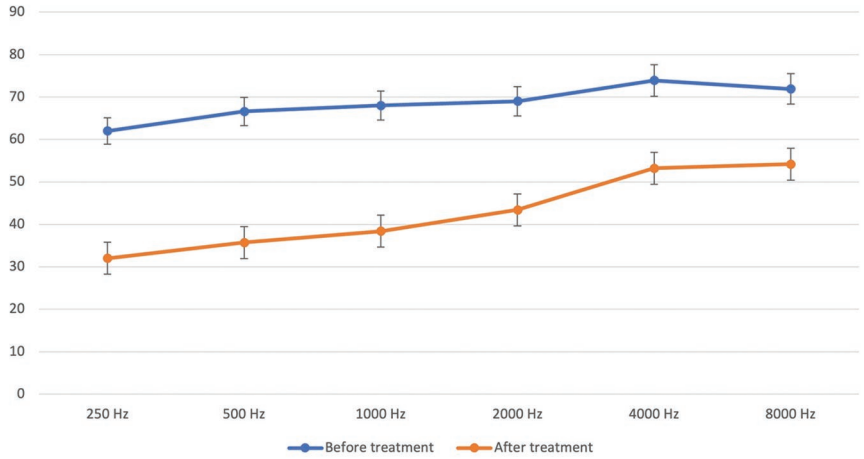

Figure 2. *Illustration of the effects of combined steroid and hyperbaric oxygen therapy on (sudden) sensorineural hearing loss separately by each frequency pathway.*

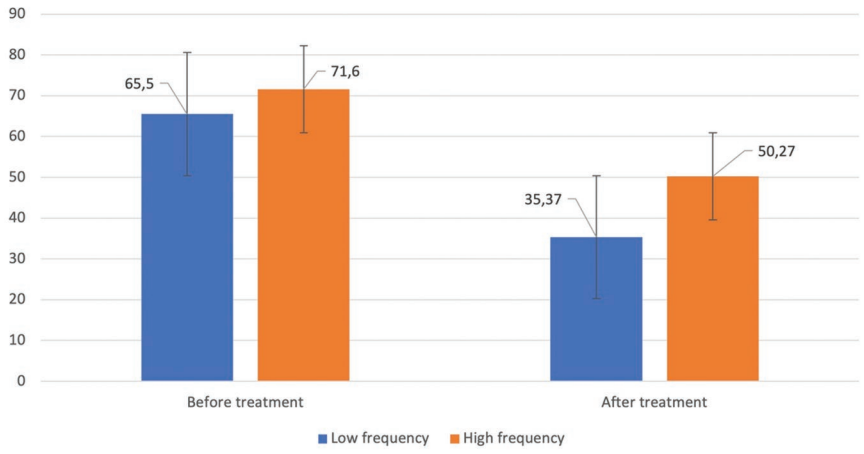

Figure 3. *Effect of hyperbaric oxygen and steroid therapy on low and high frequencies in patients with sudden hearing loss.*

Table 3. Evaluation of the efficacy of combined steroid and hyperbaric oxygen therapy in terms of average hearing gains at high and low frequencies

Frequencies	Mean ± SD (dB)	T	p
Hf_Lf	30.17 ± 25.5	3.780	< 0.001
Lf _Lf	21.33 ± 20.5		

Hf_Lf: improvement difference at high frequencies, Lf_Lf: improvement difference at low frequencies; N: number; $\bar{X}$ ± SD: mean ± standard deviation; t: dependent t-test value; p: dependent t-test statistical significance value; Effect size (Cohen d) value, d = 0.53.

particularly at lower frequencies. Analysis highlighted a notable enhancement in hearing at 250 Hz, 500 Hz, and 1000 Hz compared to higher frequencies, with statistical significance ($p < 0.001$). The effectiveness varied across frequencies, showing greater improvements at lower frequencies.

SSNHL is considered an urgent otologic condition with an unclear cause. It is characterized by a rapid hearing decline of more than 30 dB across three consecutive pure tone frequencies within 3 days[13,18,19]. While improvements in hearing can occur later, they are uncommon, with most recovery happening within the initial 2 weeks. Consequently, initiating corticosteroid treatment within the first 2-4 weeks following symptom onset is advised, as its effectiveness diminishes significantly after 4-6 weeks[11,14,17,19]. This study included cases of SSNHL diagnosed within the last week.

The recommended treatment approach is to administer oral prednisolone at a dosage of 1 mg/kg/day in

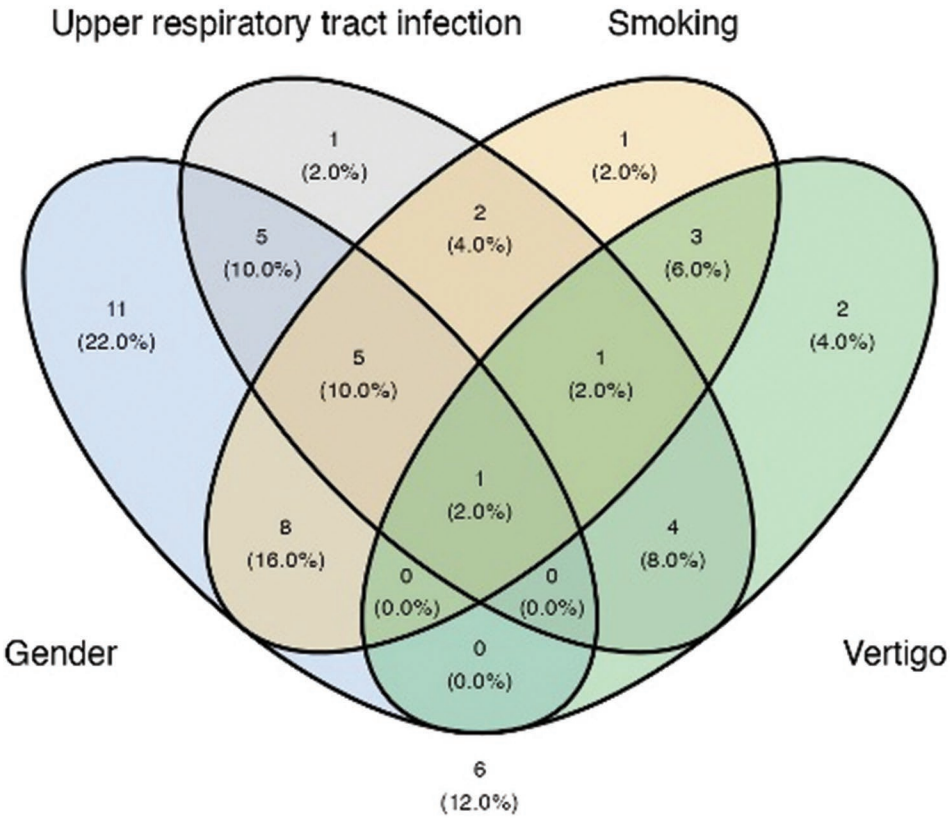

Figure 4. *Venn diagram of demographic data.*

Table 4. Evaluation of the efficacy of combined steroid and hyperbaric oxygen therapy with mean hearing gains at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz

Source of variance	Sum of squares	DF	Mean of squares	F	p
Between groups	7489.750	5	197.350	2.467	0.033
Within groups	178419.500	294	606.869		

DF: degrees of freedom, F: one-way analysis of variance (ANOVA) test value, p: one-way analysis of variance (ANOVA) test statistical significance value.

a single daily dose, continuing for 10-14 days. In this study, participants received a full dosage of 1 mg/kg/day for the 1st week, followed by tapered doses of prednisolone[20,21]. Steroids play a multifaceted role in the treatment of SSNHL, enhancing microvascular flow which is often reduced, dampening immune responses, lowering endolymphatic pressure, and exerting mineralocorticoid effects[14,17,18]. However, the precise mechanisms through which steroids aid in SSNHL treatment remain partially understood.

Systemic corticosteroids are typically the first line of treatment for SSNHL[22,23]. HBOT is suggested as either a primary treatment or a secondary option if the initial treatment does not lead to satisfactory recovery[14-16]. In this research, all participants underwent HBOT, breathing 100% oxygen at a pressure of 2.5 atmospheres for 60 min per session, across a total of 20 daily sessions, in conjunction with their prednisolone treatment.

HBOT as a treatment method for sudden hearing loss was first considered in the 1970s[15]. While the perilymphatic oxygen pressure decreases in SSNHL patients, the oxygen pressure in the perilymphatic fluid increases by 450% under hyperbaric conditions[24,25]. In today's conditions, oxygenation under hyperbaric conditions is the only known method of increasing the oxygen level in the endolymph. In the treatment of SSNHL, HBOT aims to increase the partial pressure of oxygen in the blood and then increase the partial pressure of oxygen in the endolymph, which feeds the sensory and neural elements of the cochlea through diffusion[17,26].

At present, HBOT is utilized either as a primary treatment or as a supplementary rescue therapy for SNHL. It is now advised to incorporate HBOT into the

Table 5. Evaluation of the efficacy of combined steroid and hyperbaric oxygen therapy for differences in mean hearing gains at 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz

Frequencies	Mean ± SD (dB)	8000 Hz	4000 Hz	2000 Hz	1000 Hz	500 Hz
250 Hz	26.59 ± 3.76	p = 0.013	p = 0.060	p = 0.373	p = 0.935	p = 0.855
500 Hz	26.92 ± 3.80	p = 0.008	p = 0.039	p = 0.283	p = 0.792	
1000 Hz	25.75 ± 3.64	p = 0.016	p = 0.418	p = 0.418		
2000 Hz	25.24 ± 3.57	p = 0.110	p = 0.321			
4000 Hz	21.82 ± 3.08	p = 0.543				
8000 Hz	20.78 ± 2.93					

N: number; Mean ± SD: mean ± standard deviation; p: statistical significance value of one-way analysis of variance (ANOVA) test.

treatment regimen for SSNHL unless there are clear reasons not to. In a study by Liu et al., 465 patients were categorized into three groups: the first group of 76 patients received only steroid treatment; the second group of 277 patients were treated with systemic steroids and dextran; and the third group, consisting of 112 patients, received a combination of steroids, dextran, and HBOT[27]. The findings indicated that adding HBOT to the treatment protocol resulted in an additional improvement of 10 dB in hearing gain compared to the other treatments[27]. Alimoglu et al. analyzed 58 patients (26.5%) who received only oral steroids (Group A), 61 patients (27.9%) who received oral steroids plus HBOT (Group B), 43 patients (19.6%) who were given intratympanic steroids (Group C), and 57 patients (26%) who underwent solely HBOT (Group D). The outcomes showed treatment success rates of 63%, 86%, 46%, and 43%, respectively, with the group receiving both steroids and HBOT showing the highest rates of complete recovery and response[28]. A 2007 study by Fujimura et al. found that combining steroids with HBOT had a more favorable impact on recovery in SSNHL compared to using steroids alone[29]. Similarly, Satar et al. found significant recovery in patients treated with medical therapy alone and those who received additional HBOT; however, no substantial difference was observed between the two groups[30]. Fattori et al. demonstrated that HBOT alone was less effective than a combined therapy of systemic steroids and HBOT[31]. In research conducted by Waldemar et al., when comparing patients who received a combination of high-dose steroids, betahistine, and HBOT (Group A) against those treated with steroids and betahistine alone (Group B), Group A exhibited superior hearing gain across all frequencies, with the differences being statistically significant[32]. Overall, when assessing the impact of combining steroid treatment with HBOT on hearing loss in patients with SSNHL, a significant improvement in the average hearing threshold post-treatment compared to before treatment was observed.

Research indicates that HBOT can be used not only as a primary form of treatment but also as a secondary, or salvage therapy, according to various studies[27,33,34]. Evidence from some studies suggests that HBOT significantly improves hearing thresholds when used as a rescue treatment[27,34]. In addition, it has been noted that HBOT tends to be more effective in cases of severe hearing loss[27]. In a 2017 retrospective study by Ajduk et al., on HBOT as a rescue treatment, findings indicated that patient age did not influence the effectiveness of the treatment. However, patients with hearing losses of 61 dB or greater showed a more significant response to HBOT compared to those with hearing losses under 60 dB[35]. Conversely, in a 2015 study conducted by Pezzoli et al. involving 135 patients undergoing HBOT as a rescue treatment, results demonstrated no significant difference in terms of initial hearing loss severity and recovery outcomes after HBOT[36]. In our study, all patients received both steroid therapy and HBOT within the 1st week of treatment.

Topuz et al. showed that the efficacy of HBOT is higher in younger patients (under 50 years of age) where it is significant to add HBOT to steroid treatment, especially at low frequencies (losses up to 60 dB)[37]. Hara et al. showed in their study that HBOT improves hearing, especially at low frequencies in the treatment of SSNHL[38]. In our study, when the effects of combined steroid and HBOT on hearing thresholds before and after treatment were examined separately for each frequency, it was observed that there was a significant improvement in the thresholds of each

frequency (250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz). It was observed that the hearing gain of the treatment, especially at low frequencies, was higher than at high frequencies. In our study, unlike other studies, the specific response of combined therapy on frequencies was evaluated for the 1st time. In our study, a significant difference was found between the average hearing gains of the frequencies. The hearing gain at 250 Hz was significantly higher than the hearing gain at 8000 Hz, the hearing gain at 500 Hz compared to the hearing gain at 4000 Hz and 8000 Hz, and the hearing gain at 1000 Hz compared to the hearing gain at 8000 Hz.

One limitation of this study is its relatively small sample size of 50 patients, which may affect the generalizability of the findings to the broader population with SSNHL. In addition, its retrospective design may introduce selection biases, impacting the robustness of the conclusions drawn. The research focuses exclusively on idiopathic SSNHL, potentially overlooking the nuances of hearing loss stemming from identifiable causes. Furthermore, the study's reliance on immediate post-treatment outcomes without long-term follow-up might not fully capture the durability of therapeutic effects. Future investigations should consider larger, more diverse populations and longitudinal designs to enhance the generalizability and depth of understanding of SSNHL treatment efficacy.

Conclusions

This study demonstrated that combined steroid and HBOT significantly improves hearing thresholds in patients with idiopathic SSNHL, especially at lower frequencies.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Kuhn M, Heman-Ackah SE, Shaikh JA, Roehm PC. Sudden sensorineural hearing loss: a review of diagnosis, treatment, and prognosis. Trends Amplif. 2011;15:91-105.
2. Young YH. Contemporary review of the causes and differential diagnosis of sudden sensorineural hearing loss. Int J Audiol. 2020;59:243-53.
3. Marx M, Younes E, Chandrasekhar SS, Ito J, Plontke S, O'Leary S, et al. International consensus (ICON) on treatment of sudden sensorineural hearing loss. Eur Ann Otorhinolaryngol Head Neck Dis. 2018;135:S23-8.
4. Prince AD, Stucken EZ. Sudden sensorineural hearing loss: a diagnostic and therapeutic emergency. J Am Board Fam Med. 2021;34:216-23.
5. Ntlhakana L, Hamid S. Exploring quality of life post sudden onset hearing loss: a convergent parallel approach. S Afr J Commun Disord. 2024;71:e1-7.
6. Aldajani NF, Aloufi AM, Binhudayb NA, Yahya BJ, Alkarni AF. Approach to sudden hearing loss among primary care physicians in Riyadh, Saudi Arabia. Cureus. 2024;16:e55849.
7. Kayahan Sirkeci B. Idiopathic sudden sensorineural hearing loss, but not compatible with the classical definition. Cureus. 2023;15:e47472.
8. Barron KA, Haimowitz SZ, Shah VP, Cowan P, Raia N, Ying YM. A review of bilateral sudden sensorineural hearing loss in pediatric patients. Int J Pediatr Otorhinolaryngol. 2023;165:111459.
9. Kim SH, Kim I, Kim H. Easing the burden of tinnitus: a narrative review for exploring effective pharmacological strategies. Cureus. 2024;16:e54861.
10. Yamada S, Kita J, Shinmura D, Nakamura Y, Sahara S, Misawa K, et al. Update on findings about sudden sensorineural hearing loss and insight into its pathogenesis. J Clin Med. 2022;11:6387.
11. Plontke SK, Meisner C, Agrawal S, Cayé-Thomasen P, Galbraith K, Mikulec AA, et al. Intratympanic corticosteroids for sudden sensorineural hearing loss. Cochrane Database Syst Rev. 2022;7:CD008080.
12. Herrera M, García Berrocal JR, García Arumí A, Lavilla MJ, Plaza G, Grupo de Trabajo de la Comisión de Audiología de la SEORL. Update on consensus on diagnosis and treatment of idiopathic sudden sensorineural hearing loss. Acta Otorrinolaringol Esp (Engl Ed). 2019;70:290-300.
13. Murray DH, Fagan PA, Ryugo DK. Idiopathic sudden sensorineural hearing loss: a critique on corticosteroid therapy. Hear Res. 2022;422:108565.
14. Wang HH, Chen YT, Chou SF, Lee LC, Wang JH, Lai YH, et al. Effect of the timing of hyperbaric oxygen therapy on the prognosis of patients with idiopathic sudden sensorineural hearing loss. Biomedicines. 2023;11:2670.
15. Goto F, Fujita T, Kitani Y, Kanno M, Kamei T, Ishii H. Hyperbaric oxygen and stellate ganglion blocks for idiopathic sudden hearing loss. Acta Otolaryngol. 1979;88:335-42.
16. Huang C, Tan G, Xiao J, Wang G. Efficacy of hyperbaric oxygen on idiopathic sudden sensorineural hearing loss and its correlation with treatment course: prospective clinical research. Audiol Neurootol. 2021;26:479-86.
17. Cho I, Lee HM, Choi SW, Kong SK, Lee IW, Goh EK, et al. Comparison of two different treatment protocols using systemic and intratympanic steroids with and without hyperbaric oxygen therapy in patients with severe to profound idiopathic sudden sensorineural hearing loss: a randomized controlled trial. Audiol Neurootol. 2018;23:199-207.
18. Cvorović L, Deric D, Probst R, Hegemann S. Prognostic model for predicting hearing recovery in idiopathic sudden sensorineural hearing loss. Otol Neurotol. 2008;29:464-9.

19. Slattery WH, Fisher LM, Iqbal Z, Friedman RA, Liu N. Intratympanic steroid injection for treatment of idiopathic sudden hearing loss. Otolaryngol Head Neck Surg. 2005;133:251-9.
20. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scand J Gastroenterol. 1978;13:833-7.
21. Lee HA, Chung JH. Contemporary review of idiopathic sudden sensorineural hearing loss: management and prognosis. J Audiol Otol. 2024;28:10-7.
22. Xie W, Karpeta N, Liu J, Peng H, Li C, Zhang Z, et al. Efficacy of intratympanic or postauricular subperiosteal corticosteroid injection combined with systemic corticosteroid in the treatment of sudden sensorineural hearing loss: a prospective randomized study. Front Neurol. 2023;14:1138354.
23. Yang W, Li X, Zhong J, Mei X, Liu H, Yang L, et al. Intratympanic versus intravenous corticosteroid treatment for sudden sensorineural hearing loss in diabetic patients: proposed study protocol for a prospective, randomized superiority trial. Trials. 2020;21:135.
24. Ohno K, Noguchi Y, Kawashima Y, Yagishita K, Kitamura K. Secondary hyperbaric oxygen therapy for idiopathic sudden sensorineural hearing loss in the subacute and chronic phases. J Med Dent Sci. 2010;57:127-32.
25. Keseroğlu K, Toptaş G, Uluat A, Bayir Ö, Çadalli Tatar E, Saylam G, et al. Addition of intratympanic steroid or hyperbaric oxygen treatment to systemic steroid treatment in sudden idiopathic sensorineural hearing loss treatment, and long-term results of salvage treatment. Turk J Med Sci. 2020;50:177-83.
26. Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. Expert Rev Neurother. 2014;14:233-6.
27. Liu SC, Kang BH, Lee JC, Lin YS, Huang KL, Liu DW, et al. Comparison of therapeutic results in sudden sensorineural hearing loss with/without additional hyperbaric oxygen therapy: a retrospective review of 465 audiologically controlled cases. Clin Otolaryngol. 2011;36:121-8.
28. Alimoglu Y, Inci E, Edizer DT, Ozdilek A, Aslan M. Efficacy comparison of oral steroid, intratympanic steroid, hyperbaric oxygen and oral steroid + hyperbaric oxygen treatments in idiopathic sudden sensorineural hearing loss cases. Eur Arch Otorhinolaryngol. 2011;268:1735-41.
29. Fujimura T, Suzuki H, Shiomori T, Udaka T, Mori T. Hyperbaric oxygen and steroid therapy for idiopathic sudden sensorineural hearing loss. Eur Arch Otorhinolaryngol. 2007;264:861-6.
30. Satar B, Hidir Y, Yetiser S. Effectiveness of hyperbaric oxygen therapy in idiopathic sudden hearing loss. J Laryngol Otol. 2006;120:665-9.
31. Fattori B, Berrettini S, Casani A, Nacci A, De Vito A, De Iaco G. Sudden hypoacusis treated with hyperbaric oxygen therapy: a controlled study. Ear Nose Throat J. 2001;80:655-60.
32. Narozny W, Sicko Z, Przewozny T, Stankiewicz C, Kot J, Kuczkowski J. Usefulness of high doses of glucocorticoids and hyperbaric oxygen therapy in sudden sensorineural hearing loss treatment. Otol Neurotol. 2004;25:916-23.
33. Murphy-Lavoie H, Piper S, Moon RE, Legros T. Hyperbaric oxygen therapy for idiopathic sudden sensorineural hearing loss. Undersea Hyperb Med. 2012;39:777-92.
34. Živaljević Z, Živić L, Mihailović N, Živković M, Vorkapić B, Baletić N. Treatment of sudden sensorineural hearing loss with hyperbaric oxygenation: our experience. Vojnosanit Pregl. 2017;74:156-60.
35. Ajduk J, Ries M, Trotic R, Marinac I, Vlatka K, Bedekovic V. Hyperbaric oxygen therapy as salvage therapy for sudden sensorineural hearing loss. J Int Adv Otol. 2017;13:61-4.
36. Pezzoli M, Magnano M, Maffi L, Pezzoli L, Marcato P, Orione M, et al. Hyperbaric oxygen therapy as salvage treatment for sudden sensorineural hearing loss: a prospective controlled study. Eur Arch Otorhinolaryngol. 2015;272:1659-66.
37. Topuz E, Yigit O, Cinar U, Seven H. Should hyperbaric oxygen be added to treatment in idiopathic sudden sensorineural hearing loss? Eur Arch Otorhinolaryngol. 2004;261:393-6.
38. Hara S, Kusunoki T, Honma H, Kidokoro Y, Ikeda K. Efficacy of the additional effect of hyperbaric oxygen therapy in combination of systemic steroid and prostaglandin E(1) for idiopathic sudden sensorineural hearing loss. Am J Otolaryngol. 2020;41:102363.

ORIGINAL ARTICLE

Usefulness of pelvic lymphadenectomy in staging of ovarian dysgerminoma

Utilidad de la linfadenectomía pélvica en la etapificación del disgerminoma de ovario

Moisés Zeferino-Toquero[1], Luz M. Rivas-Corchado[2], Germán Maytorena-Córdova[2], Horacio Reyna-Amaya[2], and Joel Bañuelos-Flores[2]*

[1]Servicio Oncología Quirúrgica, Unidad Médica de Alta Especialidad HGO 3, Centro Médico Nacional La Raza; [2]Servicio de Oncología Ginecológica, Unidad Médica de Alta Especialidad HGO 4 Luis Castelazo Ayala. Instituto Mexicano del Seguro Social, Ciudad de México, Mexico

Abstract

Objective: *To determine the usefulness of pelvic lymphadenectomy in the staging of ovarian dysgerminoma.* **Method:** *Patients with a histopathological diagnosis of ovarian dysgerminoma who were staged between January 1995 and December 2013 were retrospectively studied.* **Results:** *We found 39 cases, the mean age was 23.5 years. Histologically, 34 were pure dysgerminomas and 5 were mixed associated with endodermal sinus tumors. According to FIGO, we found stage IA in 15 patients, stage IB in 1 patient, stage IC in 8 patients, stage IIB in 1 patient, stage IIIA in 1 patient, and stage IIIC in 13 patients. Pelvic nodes with metastases were not documented in any of the patients studied.* **Conclusions:** *The lymphatic spread pattern in ovarian dysgerminomas is always towards the retroperitoneal nodes, both paracaval and paraaortic, but there is no spread towards the pelvic lymph nodes. Therefore, we recommend not performing pelvic lymphadenectomy in surgical staging in these patients.*

Keywords: *Dysgerminoma. Germinal ovarian cancer. Lymphadenectomy. Lymph node metastases.*

Resumen

Objetivo: *Determinar la utilidad de la linfadenectomía pélvica en la etapificación del disgerminoma de ovario.* **Método:** *Estudio retrospectivo de pacientes con disgerminoma de ovario etapificado entre enero de 1995 y diciembre de 2013.* **Resultados:** *Encontramos 39 casos, con una edad promedio de 23.5 años. Histológicamente, 34 fueron disgerminomas puros y 5 fueron mixtos asociados a tumor de senos endodérmicos. Encontramos etapa IA de la FIGO en 15 pacientes, etapa IB en 1 paciente, etapa IC en 8 pacientes, etapa IIB en 1 paciente, etapa IIIA en 1 paciente y etapa IIIC en 13 pacientes. En ninguna de las pacientes se documentaron ganglios pélvicos metastásicos.* **Conclusiones:** *El patrón de diseminación lin- fática en los disgerminomas de ovario fue hacia los ganglios retroperitoneales, tanto paracavales como paraaórticos, pero no hacia los ganglios linfáticos pélvicos. Recomendamos no realizar linfadenectomía pélvica en la etapificación quirúrgica en estas pacientes.*

Palabras clave: *Disgerminoma. Cáncer de ovario germinal. Linfadenectomía. Metástasis ganglionares.*

***Correspondence:**
Moisés Zeferino-Toquero
E-mail: moiseszz@hotmail.com

Date of reception: 22-06-2021
Date of acceptance: 26-09-2023
DOI: 10.24875/CIRUE.M23000776

Cir Cir (Eng). 2024;92(6):785-788
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Germ cell ovarian cancer is the second most common histological type among malignant ovarian neoplasms, accounting for 5% of all cases[1]. These neoplasms include a heterogeneous group of tumors with different histological types derived from the germ cells of the ovary, and they exhibit different molecular abnormalities, clinical presentations, and tumor biology[2]. Although dysgerminoma is rare, it is the most common malignant germ cell tumor of the ovary. It is often found in stage IA of FIGO, with bilaterality in 10% up to 15% of cases, and lymphatic metastases being more common than widespread intraperitoneal dissemination[3].

Treatment of dysgerminoma, as with other germ cell cancers, is based on staging and surgical cytoreduction similar to that used for epithelial ovarian cancer, preserving fertility in selected cases[4-8]. Undoubtedly, lymph node metastases in dysgerminoma are a predictor of poor prognosis[3,7,9,10]. However, the risk of lymph node metastases based on histological type has not been well studied in a large series of patients, and literature does not address whether these metastases occur in pelvic or retroperitoneal lymph nodes, as there are no studies on the lymphatic dissemination pathways of dysgerminoma that determine the incidence of involvement of both pelvic and paraaortic nodes.

Current literature is insufficient to determine whether the lymphatic spread of dysgerminomas follows the same pattern as epithelial cancers or, unlike these, has a preference for retroperitoneal paraaortic nodes rather than pelvic nodes.

The aim of this study is to determine the utility of pelvic lymphadenectomy in the staging of ovarian dysgerminoma.

Method

We conducted a retrospective observational study reviewing the health records of patients diagnosed histopathologically with ovarian dysgerminoma who underwent surgery in the gynecological oncology service at Hospital Luis Castelazo Ayala, Instituro Mexicano del Seguro Social (IMSS), Mexico City, between January 1995 and December 2013. Patients of any age who underwent surgery for ovarian tumors, whose intraoperative histopathological study reported dysgerminoma, and who had undergone complete surgical staging with systematic lymphadenectomy were included.

For this study, systematic lymphadenectomy included both pelvic and retroperitoneal lymphadenectomy, involving the removal of the common iliac, external iliac, internal iliac, and obturator fossa lymphatic chains in the pelvis, and the excision of intercavoaortic, paraaortic, and infrarenal paracaval lymph nodes in the retroperitoneum.

Patients with a prior diagnosis of ovarian cancer before surgery and those who had received preoperative chemotherapy were excluded. The following data were analyzed: demographic data, gynecological and obstetric history, preoperative serum cancer antigen 125 (Ca-125) and lactate dehydrogenase (LDH) levels, definitive histological type, disease stage according to the International Federation of Gynecology and Obstetrics (FIGO), number of lymph nodes resected, and presence or absence of lymph node metastases.

Results

During the study period, 677 cases of ovarian cancer were identified, 72 of which were germ cell tumors, and 43 dysgerminomas (59.7%). However, 4 cases were excluded where no systematic surgical staging was performed; the remaining 39 cases, which met the inclusion criteria, make up our study population.

The mean age of the group was 23.5 years (range: 13-47). The mean number of pregnancies was 2 (range, 0-5). Preoperative levels of Ca-125 and LDH were obtained in only 16 patients, with a mean of 118 U/L (range, 1.46-496) and 2113 U/L (range, 114-11,137), respectively. Conservative fertility-preserving staging surgery was performed in 28 patients (71.8%) and conventional radical surgery in 11 patients (28.2%).

Regarding histology, of the total dysgerminomas, 34 (87.17%) were pure, and 5 (12.82%) were mixed; all the mixed cases were associated with endodermal sinus tumor. The distribution by stages according to FIGO was as follows: 15 patients (38.46%) in stage IA, 1 patient (2.56%) in stage IB, 8 patients in stage IC, 1 patient (2.56%) in stage IIB, 1 patient (2.56%) in stage IIIA, and 13 patients (33.33%) in stage IIIC. None of the patients had pelvic lymph node metastasis. All patients with stage IIIC had retroperitoneal metastatic lymph nodes; of these, 11 also had disease limited to the pelvis, and 2 had widespread abdominal disease. The mean tumor size was 18.5 cm (range, 9-30).

Optimal cytoreduction was achieved in 32 patients (82%) and residual tumor was left in 7 patients (8%), all with tumor localized in the retroperitoneum due to conglomerates infiltrating the vessels.

The mean number of lymph nodes dissected per patient was 21.9 (range, 3-89). When differentiated into pelvic and paraaortic, on average, 17.6 pelvic nodes (range, 4-48) and 9.82 paraaortic nodes (range, 1-41) were dissected.

A total of 23 patients (58.97%) received adjuvant chemotherapy. The mean follow-up time was 83 months (range, 8-240). One patient had peritoneal recurrence that was non-resectable, and after receiving chemotherapy with a good response, the patient remains alive with no tumor activity. Another patient with retroperitoneal metastases and disseminated peritoneal disease continued with disease persistence and progression and died from tumor activity 8 months after surgical treatment.

Discussion

Although dysgerminoma is the most common germ cell cancer of the ovary, its incidence is low, and the small number of cases accumulated in the literature does not support long-term randomized clinical trials with a large sample of patients. The results of this study indicate that, in our population, 59% of germ cell tumors are dysgerminomas, a frequency similar to that reported by other authors in our country[11,12], but higher than the 27-38% reported in international literature[13-15]. Our service does not treat pediatric patients, only adult women, and yet the highest frequency of cases occurs in younger ages, with an average of 23.5 years, which is also similar to what has been reported in the literature.

Most patients in our population present in stage I of FIGO (61.5%), similar to what has been reported in other studies[10,13,15].

The prognostic impact of lymph node metastases in dysgerminoma has already been determined by several authors[3,9,10,14], as well as the influence they have on the recurrence pattern, so the role of lymphadenectomy is undisputed as part of surgical staging in this type of neoplasm. However, the existence of metastases in pelvic lymph nodes has not been previously documented.

Markovits et al.[16] performed lymphangiography on 36 women with dysgerminoma and found that, in these patients, the main lymphatic drainage pathway of the right ovary is toward the lateral side of the inferior vena cava, and the left ovary drains anterolaterally to the aorta; only a few accessory lymphatics on each side drain to the external iliac node group. This finding may support the results of our study, in which no pelvic lymph node metastases were found in any patient, despite some presenting with disseminated peritoneal disease or retroperitoneal lymph node metastases. On the other hand, the pattern of failure in our patients did not involve the pelvic lymphatic territory. Therefore, we can conclude that the removal of pelvic lymph nodes during surgical staging in the patients studied did not influence their prognosis.

Conclusions

Our results demonstrate that the lymphatic dissemination pattern in ovarian dysgerminomas is always toward the retroperitoneal lymph nodes, both paracaval and paraaortic, but there is no dissemination toward pelvic lymph nodes. Therefore, due to the absence of lymph node involvement in the patients studied, we do not recommend performing pelvic lymphadenectomy as part of the surgical staging in these patients.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors declare that this article does not contain patient data.

References

1. Ferlay J, Shin HR, Bray F. GLOBOCAN, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10. Lyon, France: International Agency for Research on Cancer; 2018. Disponible en: http://gco.iarc.fr/today

2. Prat J, Cao D, Carinelli S, and Mutter L. Teratoma (Chapter 1: Tumours of the ovary). En: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editores. WHO Classification of Tumours of Female Reproductive Organs. 4th ed. Lyon: IARC; 2014. p. 57-62.
3. Kumar S, Shah JP, Bryant CS, Imudia AN, Cote ML, Ali-Fehmi R, et al. The prevalence and prognostic impact of lymph node metastasis in malignant germ cell tumors of the ovary. Gynecol Oncol. 2008; 110:125-32.
4. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Ovarian cancer. Version 1.2021. Disponible en: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
5. Coquard R, Morice P, Lorusso D, Prat J, Oaknin A, Pautieet P, et al. Non-epithelial ovarian cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv1-18.
6. González-Lira G, Escudero-De Los Ríos P, Salazar-Martínez and Lazcano-Ponce EG. Conservative surgery for ovarian cancer and effect on fertility. Int J Gynaecol Obstet. 1997;56:155-62.
7. Karaloka A, Kimyon GC, Kilica C, Osman Turkmen O, Kilic F, Basaran D, et al. Cytoreductive surgery in advanced stage malignant ovarian germ cell tumors. J Gynecol Obstet Hum Reprod. 2019;48: 461-6.
8. Wang J, Chen R, Li J, Lu X. The individualized significance of lymphadenectomy across all age groups and histologies in malignant ovarian germ cell tumors. Arch Gynecol Obstet. 2020;302:1441-50.
9. Kasenda B, Harter P, Hirsch T, Ast A, Buhrmann C, Glaser F, et al. Para-aortic lymph node metastasis in malignant dysgerminoma of the ovary. Acta Obstet Gynecol. 2009;88:1288-90.
10. Vicus D, Beiner ME, Klachook S, Le LW, Laframboise S, Mackayet H. Pure dysgerminona of the ovary 35 years on: a single institutional experience. Gynecol Oncol. 2010;117:23-6.
11. Torres-Lobaton A, Pol-Kippes G, Roman-Bassaure E, Oliva Posada JC, Palomares MA, Quintero-Beulo G, et al. [Malignant ovarian germ cell tumors. Incidence at the Hospital General de México Oncology department]. Gamo. 2007;6:38-41.
12. Escudero-De los Ríos P, Bañuelos-Flores J, Quijano-Castro F, Labastida-Alméndaro S, López-Hernández D, Álvarez Blanco M, et al. [Clinical report of 90 cases with ovarian germ cell tumors]. Gamo. 2005;4:97-101.
13. Pectasides D, Pectasides E, Kassanos D. Anti tumour treatment. Germ cell tumors of the ovary. Cancer Treat Rev. 2008;34:427-41.
14. Chyong-Huey L, Ting-Chang C, Swei H, Wu TI, Chao A, Chou HH, et al. Outcome and prognostic factors in ovarian germ cell malignancies. Gynecol Oncol. 2005;96:784-91.
15. Lee KH, Lee HI, Kim BG, Nam JH, Kim WK, Kang SB, et al. Clinicopathologic characteristics of malignant germ cell tumors in the ovaries of Korean women. Int J Gynecol Cancer. 2009;19:84-7.
16. Markovits P, Bergiron C, Chauvel C, Castellino RA. Lymphography in the stating, treatment planning and surveillance of ovarian dysgerminomas. Am J Roentgenol. 1977;128:835-8.

ORIGINAL ARTICLE

Investigation of the effect of ABO blood types on the prognosis of endometrioid-type endometrial cancer

Investigación del efecto de los grupos sanguíneos ABO en el pronóstico del cáncer de endometrio de tipo endometrioide

Havva H. Keser-Şahin[1], Fazıl Avcı[2], Mehmet Kulhan[2], Abdul Hamid-Güler[2], Mete Can-Ateş[2], Çetin Çelik[2], and Ahmet Bilgi[2]*

[1]Department of Pathology, Hitit University Faculty of Medicine, Çorum; [2]Department of Obstetric and Gynecology, Selcuk University Faculty of Medicine, Konya. Turkey

Abstract

Objective: *The aim of this study was to examine how the ABO blood type affects endometrioid-type, EC prognosis.* **Method:** *A total of 522 patients diagnosed with EC between February 2010 and December 2021 were assessed, retrospectively. ABO blood types were used to divide the patients into four groups as A, B, O, and AB. Demographic data, menopause, prognostic variables, FIGO stage, and survival were evaluated. A in 217 patients, B in 84 patients, O in 181 patients, and AB blood type in 40 patients were analyzed.* **Results:** *Age, gravida, parity, body mass index, menopause, comorbidity, prognostic variables, FIGO stage, and survival according to the groups were similar (p > 0.012). Group A differed from other groups statistically in peritoneal fluid cytology (p = 0.004). B blood type had the best chance of cumulative overall survival, followed by AB, A, and O blood types, in that order (p = 0.170).* **Conclusion:** *In light of blood types sensitivity to endometrioid-type EC, O blood type has been identified as blood type with the highest risk of endometrioid EC.*

Keywords: *ABO blood-type system. Endometrial cancer. Prognosis.*

Resumen

Objetivo: *Examinar cómo los tipos de sangre ABO afectan el pronóstico del cáncer de endometrio de tipo endometrioide.* **Método:** *Se evaluaron retrospectivamente 522 pacientes diagnosticadas con CE entre 2010 y 2021. Se utilizaron los tipos de sangre ABO para dividir a las pacientes cuatro grupos: A, B, O, y AB. Se evaluaron la edad, la menopausia, las variables pronósticas, la etapa FIGO y la supervivencia. Se determinó el tipo de sangre A en 217 pacientes, el B en 84 pacientes, el O en 181 pacientes y el AB en 40 pacientes.* **Resultados:** *La edad, la menopausia, las variables pronósticas, la etapa FIGO y la supervivencia según grupos fueron similares (p > 0.012). El grupo A difirió estadísticamente de los otros grupos en la citología del líquido peritoneal (p = 0.004). El tipo de sangre B tuvo mejor probabilidad de una supervivencia global acumulativa, seguido por los tipos AB, A, y 0, en este orden (p = 0.170).* **Conclusión:** *A la luz de la sensibilidad de los tipos de sangre al cáncer de endometrio tipo endometrioide, el O ha sido identificado como el de mayor riesgo de cáncer endometrial tipo endometrioide.*

Palabras clave: *Sistema de tipo sanguíneo ABO. Cáncer endometrial. Pronóstico.*

***Correspondence:**
Havva Hande Keser-Şahin
E-mail: hndksr@hotmail.com

Date of reception: 28-01-2024
Date of acceptance: 14-03-2024
DOI: 10.24875/CIRUE.M24000800

Cir Cir (Eng). 2024;92(6):789-794
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

In developed countries, endometrial cancer (EC) is the fourth most common cancer in females and the most common gynecological cancer[1]. EC has 1.1% lifetime rate, 0.4% fatality rate, and good prognosis with early diagnosis[2]. Post-menopausal women account for more than 80% of patients with EC[3]. Type 1 and type 2 ECs are the categories of EC. Grade 1 and 2 endometrioid tumors associated with persistent estrogen stimulation are included in type 1 EC. They have typically a good prognosis because of early diagnosis. Type 2 EC encompasses grade 3 endometrioid and non-endometrioid tumors that develop from the atrophic endometrium and have a worse prognosis[4]. The most typical kind of EC is endometrioid-type EC[5]. Therefore, early detection of EC ensures an excellent survival rate[6] and this is associated with a reduction in cancer-related mortality. The ABO blood type has an important role in human blood systems. The ABO gene localization is on chromosome 9q34 and contains two specific glycosyltransferase alleles, A and B[6]. First, Landsteiner defined ABO antigens as surface components of erythrocytes[7]. The relationship between blood types and cancers has been investigated for a long time. Since the association between gastric cancer and A blood type was reported in 1953[8], many reports about other types of cancer have been published[9-12]. In addition, the relationship between gynecological cancers and the ABO blood type system was also investigated. Studies by Tryggvadottir et al. and Ravn et al. reported high levels of estradiol in association with the presence of A-B transferase proteins in human endometrial cells[12,13]. However, A and AB blood types were reported more frequently in recurrent miscarriages[14]. Some studies showed a positive relationship between the ABO blood type and the risk of EC[13] or other types of cancer[6,15]. The exact mechanisms underlying the effect of ABO blood types on cancer pathogenesis are unknown. However, a number of theories have been proposed. It is likely that specific blood type antigens help cancer cells to behave biologically more aggressively[16]. It was demonstrated, in particular, that the presence of the A antigen can increase cellular motility and gradually accelerate cell-to-cell contact between malignant cells[17]. In addition, it was suggested that ABO blood type antigens may contribute to the immune system generally and confer aggressive resistance to programmed cell death (apoptosis) specifically[18]. In addition, Wolpin et al. discovered relationships between the ABO blood types and various concentrations of chemicals related to cell adhesion, immunological defense, inflammation, and cellular signaling[10]. At present, studies showing that there is a relationship between ABO blood types and EC were carried out[19-22]. In addition, studies researching the effect of ABO blood types on the prognosis of EC were carried out[17,23-25].

The aim of the present study was to examine how the ABO blood type affects endometrioid-type, EC prognosis.

Method

Approval for this study was obtained from the Selçuk University Faculty of Medicine Ethics Committee with decision 2022/306 in accordance with the principles of the Declaration of Helsinki. In this retrospective study, a total of 522 patients were included from the Selçuk University Faculty of Medicine, Department of Gynecological Oncology between February 2010 and December 2021. The inclusion criteria were endometrioid-type EC diagnosed and followed up in the present clinic. Cases diagnosed with non-endometrioid type EC, cases diagnosed with concomitant cancer, and cases that were not operated on in the present clinic and could not be followed up were accepted as exclusion criteria. The patients were analyzed according to blood type (A, B, AB, and 0), age, menopause status (pre-menopause and post-menopause), prognostic factors (tumor size, myometrial invasion, grade degree, cervical involvement, lymphovascular invasion, and lymph node involvement), FIGO stage, overall survival (OS), and disease-free survival (DFS). Tumors were divided into three categories according to their grade: grade 1 or weak, grade 2 or moderate, and grade 3 or severe, and were named according to the FIGO grading system[26]. The blood types of the patients were recorded. FIGO stages 1 and 2 were called early stages, and 3 and 4 were named advanced stages[21].

Statistical analysis

SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used for all statistical calculations. Descriptive features (mean, median, minimum, maximum, and standard deviation) in the study were evaluated with the help of descriptive statistical tests. The normal distribution of the variables was analyzed with the Kolmogorov–Smirnov test. Comparisons for categorical parameters were analyzed with the aid

Table 1. Comparison of demographic data of patients diagnosed with endometrioid type endometrial cancer according to blood groups

Variables	A (n = 217)	B (n = 84)	O (n = 181)	AB (n = 40)	p
Age, year	64.1 ± 10.4	64.0 ± 8.5	64.5 ± 9.9	62.1 ± 11.2	0.566
Gravida, n (%)	4 (1-9)	4 (1-12)	4 (1-11)	4 (2-7)	0.208
Parity, n	3 (0-8)	3 (0-11)	3 (0-8)	3 (1-6)	0.464
Body mass index (kg/m^2)	32.8 ± 2.8	32.4 ± 2.4	32.1 ± 2.8	32.2 ± 2.0	0.073
Menopause, n (%)					0.236
Premenopause	21 (9.7)	3 (3.6)	11 (6.1)	4 (10.0)	
Post-menopause	196 (90.3)	81 (96.4)	170 (93.9)	36 (90.0)	
Co-morbidity, n (%)					0.983
None	122 (56.2)	53 (63.1)	108 (59.7)	24 (60.0)	
DM	8 (3.7)	3 (3.5)	7 (3.9)	1 (2.5)	
Hypertension	26 (12.0)	10 (12.0)	20 (11.0)	6 (15.0)	
Other	61 (28.1)	18 (21.4)	46 (25.4)	9 (22.5)	

n: number of patients; DM: diabetes mellitus.

of Spearman X^2 and Fisher's exact test. Tests for parametric values used the one-way analysis of variance test, and Tukey test as *post hoc* test. Non-parametric values were analyzed with the Kruskal–Wallis test and differences between groups were examined with Bonferroni correction and Mann–Whitney U test. DFS was the time from the end of cure to the presence of local recurrence or metastasis. OS was the time from the end of cure to the date of death or last follow-up. Outcome data were investigated with the Kaplan–Meier analysis and survival curves were evaluated using the log-rank test. Cox regression analysis was used for the outcome data. A $p < 0.05$ was considered significant.

Results

Of the 522 patients included in this study, A blood type was present in 217 patients, B blood type in 84 patients, 0 type in 181 patients, and AB blood type in 40 patients. The mean ages of the patients were similar in terms of the A, B, 0, and, AB blood types ($p = 0.566$). While there was no significance in terms of parity, gravida, body mass index, menopausal status, co-morbidity, grade of tumor, degree of myometrial invasion, tumor size, presence of LVIS, cervical involvement, type of surgery, pelvic and paraaortic lymph node positivity, presence of recurrence, and surgical stage, there was statistical significance in terms of peritoneal fluid among the blood types ($p = 0.004$). In the peritoneal fluid pathology, group A was statistically significant compared to the other groups ($p = 0.004$), and in the surgical stage, only O blood type was found to be significant ($p = 0.006$) (Tables 1 and 2). Group B had the best prognosis for cumulative DFS and OS, followed by AB, A, and O blood types, respectively (Figs. 1 and 2). In Cox regression analysis between blood types, – 2 log-likelihood (222.298) was calculated as $p = 0.171$.

Discussion

In this study in which endometrioid type EC cases were evaluated according to blood groups, when demographic and prognostic factors were compared between the cases, only peritoneal mayi positivity was found to be significantly different in blood group A. The best prognosis was found in blood group B, whereas the most risky blood group was found in blood group 0.

It was shown that blood types can affect different neoplastic and non-neoplastic processes in the body. Neoplastic cells can cause biologically aggressive behavior in specific blood types of antigens[26]. There are a number of studies that investigated the relationship between ABO blood type and EC[16,20,22,23,27]. In this study, blood type A (40.3%) was the most commonly detected blood type[23,24] and this was consistent with other studies about ECs in Iran[23], Siberia[16], China[20], and Italy[22,28]. In addition, contrary to this study, O blood type was most common among EC patients in Georgia and Saudi Arabia, whereas AB blood type was more common in an Armenian study and Le Pendu et al. detected that B blood type was the most common[17,21,29]. The distribution of blood types may differ between societies due to ethnic and regional differences.

Table 2. Clinicopathological features of endometrioid endometrial cancer cases according to blood types

Variables	A (n = 217%)	B (n = 84%)	O (n = 181%)	AB (n = 40%)	p
Surgery method, n (%)					0.233
Laparoscopic	23 (10.6)	12 (14.3)	30 (16.6)	8 (20.0)	
Laparatomic	194 (89.4)	72 (85.7)	151 (83.4)	32 (80.0)	
Surgery stage, n (%)					0.063
Early	192 (88.5)	71 (84.5)	150 (82.9)	32 (80.0)	
Advanced	25 (11.5)	13 (15.5)	31 (17.1)	8 (20.0)	
Peritoneal fluid					0.004*
Benign	214 (98.6)	78 (93.0)	167 (92.3)	35 (87.5)	
Malign	3 (1.4)	6 (7.0)	14 (7.7)	5 (12.5)	
Grade					0.660
1	152 (70.1)	55 (65.5)	120 (66.2)	30 (75.0)	
2	48 (22.1)	26 (31.0)	45 (25.0)	8 (20.0)	
3	17 (7.8)	3 (3.5)	16 (8.8)	2 (5.0)	
Degree of myometrial invasion, n (%)					0.192
< 50%	183 (84.3)	64 (76.2)	151 (83.4)	28 (70.0)	
> 50%	34 (15.7)	20 (23.8)	30 (16.6)	12 (30.0)	
Tumor size, cm	3.8 ± 2.2	4.5 ± 2.2	4.1 ± 2.4	3.9 ± 2.2	0.138
Lymphovascular invasion					0.493
Yes	20 (9.2)	12 (14.3)	24 (13.3)	4 (10.0)	
No	197 (90.8)	72 (85.7)	157 (86.7)	36 (90.0)	
Cervical involvement					0.436
Yes	26 (12.0)	16 (19.0)	28 (15.5)	5 (12.5)	
No	191 (88.0)	68 (81.0)	153 (84.5)	35 (87.5)	
Pelvic lymph node metastasis, n					0.399
Yes	16 (7.9)	9 (11.2)	20 (12.3)	6 (15.8)	
No	187 (92.1)	71 (88.8)	143 (87.7)	32 (84.2)	
Paraaortic lymph node metastasis, n					0.270
Yes	9 (4.4)	5 (6.3)	15 (9.3)	4 (10.5)	
No	194 (95.6)	75 (93.7)	147 (90.7)	34 (89.5)	
Recurrence, n					0.997
Yes	15 (6.9)	6 (7.1)	12 (6.6)	3 (7.5)	
No	202 (93.1)	78 (92.9)	169 (93.4)	37 (92.5)	
Ex status, n					0.175
Yes	8	1	12	1	
No	209	83	169	39	
OS, month	137.3 ± 7.0	149.6 ± 5.2	205.5 ± 16.0	141.2 ± 4.7	0.170
DFS, month	137.2 ± 7.0	151.4 ± 3.6	203.1 ± 16.5	141.2 ± 4.7	0.149

n: number of patient; OS: overall survival; DFS: disease-free survival.
*p-value is significant statistically.

EC is usually seen at advanced age and endometrioid-type is often detected in the early stage. Therefore, it has a good prognosis. However, Type 2 EC is estrogen-independent and has a poor prognosis. In the studies by Gitas et al.[24], and Mandato et al.[22], there were no significant associations between blood types according to age and death. Similarly, there was no difference between blood types in this study. In terms of menopause status, no difference was found in the studies by Gitas et al.[24], Xu et al.[20], and Abu-Zaid et al.[21] in accordance with this study. In addition, Mohammadian et al.[23] and Mandato et al.[22] also found a low risk of Grade 3 EC occurring in patients with A blood type. Consistent with these studies, the risk of developing Grade 3 EC was found to be less in the A blood type. Contrarily, there was no difference in terms of grade in the studies by Abu-Zaid et al.[21], and Gitas et al[24].

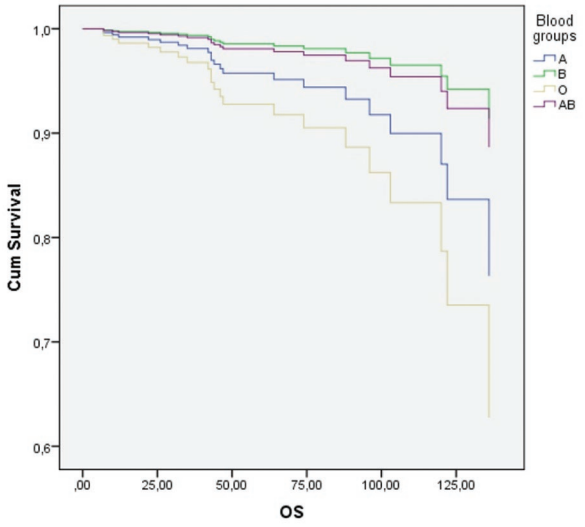

Figure 1. *Cox regression analysis of the relationship between the ABO blood types and overall survival.*

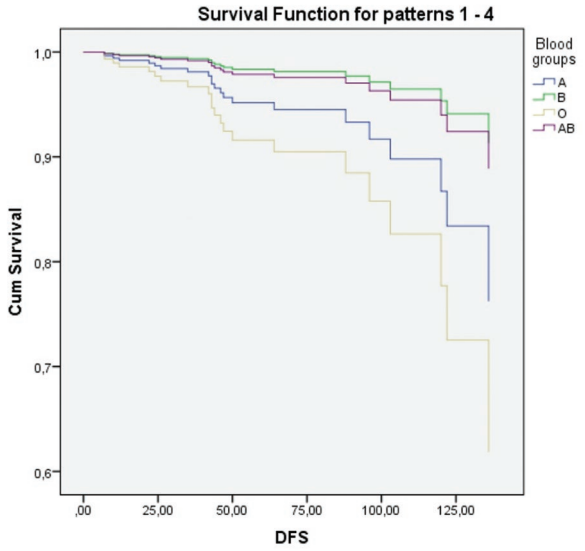

Figure 2. *Cox regression analysis of the relationship between the ABO blood types and disease-free survival.*

The presence or degree of myometrial invasion is one of the most important risk factors in EC. According to Mohammadian et al.[23], no significant difference was found in terms of myometrial invasion, which is one of the prognostic factors for EC. Mohammadian et al.[23] showed that there was no significant relationship between ABO blood type and cervical involvement. Similar to this study, no significant difference was found in terms of findings in this study either. In the studies by Mandato et al.[22], Abu-Zaid et al.[21], Gitas et al.[24], and Mohammadian et al.[23], there was no correlation between surgical stage and blood type. It was reported that there was no relationship[21,22]. In this study, there was no statistical significance in terms of blood types and surgical stage. Gitas et al.[24], Mandato et al.[22], and Mohammadian et al.[23] did not find any difference in terms of lymph node metastasis. Similarly, there was no difference in this study.

EC follow-ups frequently involve check-ups every 3-4 months for the first 2 years. Recurrences are usually detected within the first 2 years. No difference was found in terms of recurrence in the studies by Gitas et al.[24], Mandato et al.[22], and Abu Zaid et al.[21] Consistent with these studies, no difference was found in this study. Likewise, Mandato et al. reported that there was no significant association between ABO blood types, OS, and DFS times in patients diagnosed with EC[22]. Consistent with these studies, no difference was found in this study in terms of lymphovascular space invasion and OS. In terms of histological type, this study only included endometrioid-type. Contrary to these studies, a statistically significant difference was found between blood types in terms of peritoneal fluid ($p = 0.004$). There was no significant association among patients according to parity, tumor size, and surgical mode of operation (laparoscopy and laparotomy). No significant difference was found in the Cox regression analysis for DFS and OS by blood type. However, the cumulative survival time was maximum for B blood types followed by AB, A, and O blood types with decreasing frequency.

Limitations of the study

While the limitations of this study were that it was a single-center and retrospective study, the strengths of the study were that only endometrioid-type EC patients were included in the study, the high number of patients, and the evaluation of prognostic factors.

Conclusion

Blood types can be evaluated as an easily accessible and useful indicator in terms of sensitivity to endometrioid-type EC. O blood type is the riskiest blood type for endometrioid-type EC.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the approval of the Ethics Committee for the analysis and publication of clinical data obtained routinely. The informed consent of the patients was not required because it was a retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. ACOG Committee Opinion No. 734: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. Obstet Gynecol. 2018;131:e124-9.
3. Zhang C, Sung CJ, Quddus MR, Simon RA, Jazaerly T, Lawrence WD. Association of ovarian hyperthecosis with endometrial polyp, endometrial hyperplasia, and endometrioid adenocarcinoma in postmenopausal women: a clinicopathological study of 238 cases. Hum Pathol. 2017;59:120-4.
4. Piulats JM, Guerra E, Gil-Martín M, Roman-Canal B, Gatius S, Sanz-Pamplona R, et al. Molecular approaches for classifying endometrial carcinoma. Gynecol Oncol. 2017;145:200-7.
5. Hedrick-Ellenson L, Ronnett BM, Soslow RA, Lastra RR, Kurman RJ. Endometrial carcinoma. In: Kurman RJ, Hedrick Ellenson L, Ronnett BM, editors. Blaustein's Pathology of the Female Genital Tract. Cham: Springer International Publishing; 2019. p. 473-533.
6. Franchini M, Liumbruno GM, Lippi G. The prognostic value of ABO blood group in cancer patients. Blood Transfus. 2016;14:434-40.
7. Watkins WM. Biochemistry and genetics of the ABO, lewis, and P blood group systems. Adv Hum Genet. 1980;10:1-136, 379-85.
8. Aird I, Bentall HH, Roberts JA. A relationship between cancer of stomach and the ABO blood groups. Br Med J. 1953;1:799-801.
9. Annese V, Minervini M, Gabbrielli A, Gambassi G, Manna R. ABO blood groups and cancer of the pancreas. Int J Pancreatol. 1990;6:81-8.
10. Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, et al. ABO blood group and the risk of pancreatic cancer. J Natl Cancer Inst. 2009;101:424-31.
11. Pandey M, Gautam A, Shukla VK. ABO and Rh blood groups in patients with cholelithiasis and carcinoma of the gall bladder. BMJ. 1995;310:1639.
12. Tryggvadottir L, Tulinius H, Robertson JM. Familial and sporadic breast cancer cases in Iceland: a comparison related to ABO blood groups and risk of bilateral breast cancer. Int J Cancer. 1988;42:499-501.
13. Ravn V, Teglbjaerg CS, Mandel U, Dabelsteen E. The distribution of type 1 chain ABH and related histo-blood group antigens in normal cycling human endometrium. Int J Gynecol Pathol. 1993;12:70-9.
14. Malekasgar AM. ABO blood group prevalence in spontaneously repeated abortion. Turk J Haematol. 2004;21:181-7.
15. Liumbruno GM, Franchini M. Hemostasis, cancer, and ABO blood group: the most recent evidence of association. J Thromb Thrombolysis. 2014;38:160-6.
16. Yuzhalin AE, Kutikhin AG. ABO and Rh blood groups in relation to ovarian, endometrial and cervical cancer risk among the population of South-East Siberia. Asian Pac J Cancer Prev. 2012;13:5091-6.
17. Le Pendu J, Marionneau S, Cailleau-Thomas A, Rocher J, Le Moullac-Vaidye B, Clément M. ABH and Lewis histo-blood group antigens in cancer. APMIS. 2001;109:9-31.
18. Melzer D, Perry JR, Hernandez D, Corsi AM, Stevens K, Rafferty I, et al. A genome-wide association study identifies protein quantitative trait loci (pQTLs). PLoS Genet. 2008;4:e1000072.
19. Arab M, Noghabaei G. Comparison of age- standard incidence rate trends of gynecologic and breast cancer in Iran and other countries. Iran J Public Health. 2014;43:1372-9.
20. Xu WH, Zheng W, Xiang YB, Shu XO. ABO blood type is associated with endometrial cancer risk in Chinese women. Chin J Cancer. 2011;30:766-71.
21. Abu-Zaid A, Alsabban M, Abuzaid M, Alomar O, Al-Badawi IA, Salem H. ABO blood group and endometrial carcinoma: a preliminary single-center experience from Saudi Arabia. Cureus. 2017;9:e1959.
22. Mandato VD, Torricelli F, Mastrofilippo V, Ciarlini G, Pirillo D, Farnetti E, et al. Prognostic impact of ABO blood group on type I endometrial cancer patients-results from our own and other studies. J Cancer. 2017;8:2828-35.
23. Mohammadian S, Pouresmaeili F, Mohammadian A. Prognostic impact of ABO blood group on type I endometrial cancer in a population of Iranian patients. Hum Antibodies. 2020;28:313-7.
24. Gitas G, Proppe L, Alkatout I, Tsolakidis D, Rody A, Kotanidis C, et al. Is ABO blood group a risk or prognostic factor for patients with endometrioid endometrial cancer? A retrospective analysis in Germany. Blood Transfus. 2020;18:465-70.
25. Abu-Rustum NR, Zhou Q, Iasonos A, Alektiar KM, Leitao MM Jr., Chi DS, et al. The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered? Int J Gynecol Cancer. 2011;21:511-6.
26. Duan YF, Zhu F, Li XD, An Y, Zhang H, Zhou Y, et al. Association between ABO gene polymorphism (rs505922) and cancer risk: a meta-analysis. Tumour Biol. 2015;36:5081-7.
27. Adamian RT. Blood-type and rhesus distribution in Armenian women with endometrial carcinoma. Vopr Onkol. 2005;51:575-6.
28. Marinaccio M, Traversa A, Carioggia E, Valentino L, Coviello M, Salamanna S, et al. Blood groups of the ABO system and survival rate in gynecologic tumors. Minerva Ginecol. 1995;47:69-76.
29. Nakashidze I, Diasamidze A, Baratashvili D, Nagervadze M, Alibegashvili M, Ramishvili L, et al. Alteration of sex and non-sex hormones and distribution features of blood ABO system groups among the women with uterine body tumors. J Cancer Ther. 2014;5:411-9.

CASE REPORT

Gastric perforation due to mucormycosis infection in a kidney-pancreas transplant patient. A fatal complication

Perforación gástrica secundaria a infección por mucormicosis en un paciente con trasplante reno-pancreático. Una complicación fatal

Franco R. Pascual, Rodrigo Figueroa, Julieta Zanatta-Scattolini, Maximiliano Yance, Carlos Valenzuela, Rogelio Traverso, and Octavio Gil*

Servicio de Trasplante Hepático y Renopancreático, Sanatorio Allende, Córdoba, Argentina

Abstract

Mucormycosis is a rare deep fungal infection that develops mainly in immunosuppressed patients, being unusual the gastro- intestinal presentation. The adequate treatment consists in rapid and aggressive surgical debridement, along with initial adju- vant treatment with liposomal amphotericin B. Despite recent advances in the management of this disease, the prognosis is poor, with a high mortality rate. We will present a case of a 37-year-old male patient, who underwent a combined pancreas and kidney transplant, with gastric perforation secondary to deep mucormycosis.

Keywords: *Mucormycosis. Pancreas Transplantation. Kidney Transplantation. Gastrectomy.*

Resumen

La mucormicosis es una infección micótica profunda poco común que se desarrolla principalmente en pacientes inmunode- primidos, siendo la presentación gastrointestinal inusual. El tratamiento adecuado consiste en el desbridamiento quirúrgico rápido y agresivo, junto con el tratamiento coadyuvante inicial con anfotericina B liposomal. A pesar de los avances, el pro- nóstico es malo, con una alta tasa de mortalidad. Presentamos el caso de un paciente de 37 años sometido a un trasplante combinado de páncreas y riñón, que se presenta con perforación gástrica secundaria a infección por mucormicosis.

Palabras clave: *Mucormicosis. Trasplante de páncreas. Trasplante de riñón. Gastrectomía.*

***Correspondence:**
Franco R. Pascual
E-mail: francopascual23@gmail.com

Date of reception: 11-02-2022
Date of acceptance: 04-03-2022
DOI: 10.24875/CIRUE.M22000777

Cir Cir (Eng). 2024;92(6):795-798
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Mucormycosis is a deep fungal infection (DFI) that develops in immunocompromised patients. Its incidence has increased in recent years[1], especially in patients with diabetes mellitus, hematologic malignancy, solid organ transplants (SOT), and corticoid therapy[1,2]. The most common sites of infection are the paranasal sinuses, brain, lungs, and skin[3]. GI locations are rare.

Given that the most common fungal infections in SOT recipients are candidiasis, aspergillosis, and cryptococcosis[4], mucormycosis is a rare complication in this subset of patients, representing around 2% of all DFIs[5].

Despite adequate antifungal treatment and aggressive surgical intervention, mortality is high vs other common infectious diseases such as candidiasis and aspergillosis, ranging from 50% up to 90%, depending on the location[6].

A complicated case of gastric mucormycosis is described in an immunocompromised patient who presented with acute gastric perforation.

Case report

A 37-year-old male with a past medical history of diabetes mellitus since childhood and terminal chronic kidney disease on thrice-weekly dialysis underwent a combined pancreas and kidney transplant at the age of 32. Four years after the transplant, he lost the pancreatic graft due to multiple complications. The kidney graft was currently functioning normally, and the patient was on a standard immunosuppressive regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone.

The patient presented to the emergency department with diarrhea and fever. On physical examination, his temperature was 38°C, and the rest of his vital signs were within normal parameters. His abdomen was moderately distended, with absence of bowel sounds, and no signs of peritonitis.

Lab test results showed a normal white blood cell count, metabolic acidosis, and acute renal failure. Due to his immunocompromised condition, he was initially admitted to the intensive care unit and treated with fluid resuscitation and broad-spectrum IV antibiotics, including piperacillin-tazobactam 2.25 mg 3 times/day. Two days after admission, the patient experienced a sudden deterioration in his clinical condition, with the onset of severe abdominal pain.

Given the symptoms and findings on physical examination, an abdominal CT with oral and IV contrast was ordered, which showed an edematous gastric wall with the presence of air in the posterior wall, pneumoperitoneum, and free contrast material, indicating a perforation of a hollow viscera (Fig. 1).

The patient was quickly subjected to an exploratory laparotomy, during which a small amount of seropurulent fluid was found, along with a full-thickness gastric perforation on the anterior surface of the stomach, associated with transmural gastric necrosis (Fig. 2).

The rest of the intestine appeared normal. A total gastrectomy was performed without restoration of the tract, and a feeding tube was inserted into the distal end of the esophagus, which was exteriorized, forming an esophagostomy. The abdomen was left open and packed, due to the presence of purulent material and to allow for subsequent exploration of the abdominal cavity to assess the progression of necrosis. Two days after the initial surgery, a revision surgery was performed, during which no evidence of perforation, necrosis, or purulent material was found at any level; consequently, a Witzel-type jejunostomy was performed, and the abdominal wall was closed.

Histological examination of the stomach showed extensive necrosis of the gastric wall. Numerous fungal microorganisms were present, with angulated budding hyphae and angioinvasion found in the ulcer bed. The histological findings were consistent with gastric mucormycosis (Fig. 3).

The early postoperative course was satisfactory. The patient was treated with broad-spectrum antibiotics, including meropenem 500 mg once daily, tigecycline 50 mg twice daily, and fluconazole 200 mg once daily. However, the patient began to show progressive clinical deterioration. On postoperative day 15, as the pathological report confirmed the diagnosis of mucormycosis, liposomal amphotericin B 150 mg once daily was added to the treatment regimen. Despite timely surgical intervention and specific antifungal medication, the patient died on postoperative day 19 due to sepsis and multiple organ failure.

Discussion

We report the case of an immunocompromised patient who presented with an acute gastric perforation due to mucormycosis. What is unusual in our case is not only the location and presentation of this infection but also the time elapsed since the transplant (5 years).

Mucormycosis is caused by fungi belonging to the order Mucorales. Humans predominantly acquire the

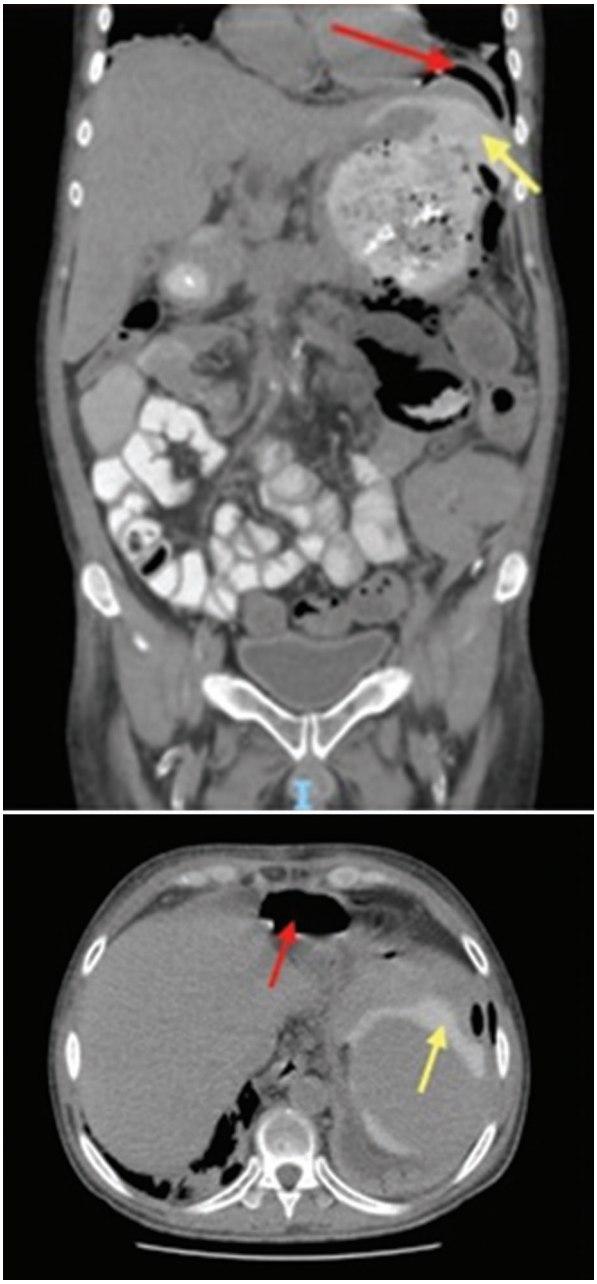

Figure 1. *Abdominal CT showing free air (red arrows) and free contrast material (yellow arrows) in the abdominal cavity, indicating a hollow viscera perforation.*

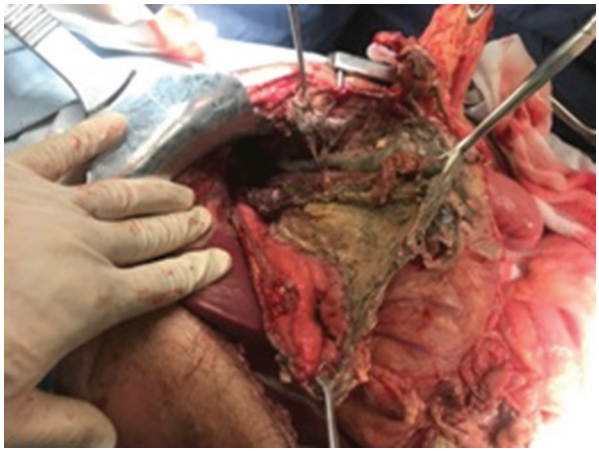

Figure 2. *Macroscopic appearance of the anterior gastric wall showing extensive transmural necrosis.*

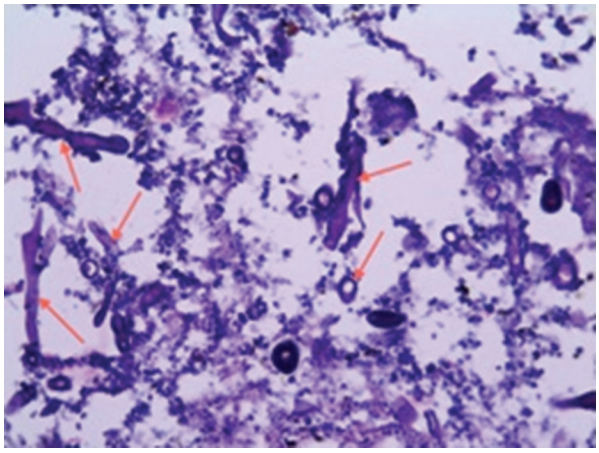

Figure 3. *Histological appearance of mucormycosis (×10). PAS stain showing the characteristic hyphae in clusters (arrows).*

infection through the inhalation of sporangiospores, occasionally by ingestion of contaminated food, or through traumatic inoculation[7]. Regardless of the route of infection (inhalation of spores from the air, ingestion, or direct inoculation to the skin), the spores germinate into hyphae and develop rapidly, invading blood vessels and causing thrombosis, infarction, and necrosis[8].

The clinical presentation varies greatly and can involve a specific organ or be disseminated. In a review of 851 cases, Jeong et al.[9] found that the rhino-orbital-cerebral region was the most common site of fungal infection (34%), followed by the skin (22%) and the lungs (20%).

As for GI involvement, the most common form is intestinal mucormycosis (52%), followed by gastric disease (42%)[10]. Gastric mucormycosis is commonly associated with SOT10. However, this infection can also be observed in immunocompetent hosts[11].

Regarding the clinical presentation, abdominal pain is the most frequent symptom (68%) of GI mucormycosis in this patient population, followed by GI bleeding (48%) and abdominal distension[10]. Diarrhea, one of the initial symptoms in our patient, represents < 10% of the clinical signs[1]. Gastric perforation is a very unusual presentation. To date, we have found 11 case reports

of patients who presented with gastric perforation due to mucormycosis. In this particular presentation, the mechanism could be a perforated ulcer (with or without bleeding) or gastric necrosis, as in our case. Reviewing the literature, the latter form of presentation is associated with a higher mortality rate (66% vs 33%).

The optimal management of DFI includes surgical debridement and effective antifungal treatment, as well as control of underlying risk factors, such as neutropenia, reduction or cessation of steroids, and reduction of immunosuppression when possible. Current treatment guidelines for DFI recommend combination therapy with an IV formulation of amphotericin B and surgery[12], as observed in our case and in most of the reports reviewed. Modern antifungal agents, such as posaconazole, have a good safety profile and in vitro activity vs mucormycosis. In one study[3], the results for patients on posaconazole were favorable, making it an alternative treatment option.

Early diagnosis or suspicion is of utmost importance, as early initiation of antifungal therapy is strongly associated with better patient survival[13].

However, our patient presented to the emergency department with fever and diarrhea, and initially, no severe abdominal complication was suspected. The sudden gastric perforation later and the histological examination were what ultimately led to the diagnosis of gastric mucormycosis. The delay in appropriate antifungal therapy in this case, on postoperative day 15, could explain the fatal outcome despite adequate surgical debridement.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patient referenced in the article. This document is held by the corresponding author.

References

1. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel). 2019;5:26.
2. Ambrosioni J, Bouchuiguir-Wafa K, Garbino J. Emerging invasive zygomycosis in a tertiary care center: epidemiology and associated risk factors. Int J Infect Dis. 2010;14(Suppl 3):e100-3.
3. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Chen SC-A, et al. Contemporary management and clinical outcomes of mucormycosis: a systematic review and meta-analysis of case reports. Int J Antimicrob Agents. 2019;53:589-97.
4. Neofytos D, Fishman JA, Horn D, Anaissie E, Chang C-H, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients: invasive fungal infections in SOT. Transpl Infect Dis. 2010;12:220-9.
5. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50:1101-11.
6. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634-53.
7. Richardson M. The ecology of the Zygomycetes and its impact on environmental exposure. Clin Microbiol Infect. 2009;15(Suppl 5):2-9.
8. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18:556-69.
9. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect. 2019;25:26-34.
10. Dioverti MV, Cawcutt KA, Abidi M, Sohail MR, Walker RC, Osmon DR. Gastrointestinal mucormycosis in immunocompromised hosts. Mycoses. 2015;58:714-8.
11. Kaur H, Ghosh A, Rudramurthy SM, Chakrabarti A. Gastrointestinal mucormycosis in apparently immunocompetent hosts — a review. Mycoses. 2018;61:898-908.
12. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect. 2014;20(Suppl 3):5-26.
13. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis. 2008;47:503-9.

CASE REPORT

Pneumopericardium caused by gastric ulcer perforation into the pericardium. An inusual complication

Neumopericardio secundario a perforación de una úlcera gástrica al pericardio. Una complicación inusual

Luis J. García-Vega[1], Guillermo I. Rivas-Santana[1], and Raymundo García-González[2]*

[1]Departamento de Cirugía General; [2]Departamento de Cirugía Cardiotorácica. Hospital General Regional 1, Instituto Mexicano del Seguro Social, Chihuahua, Chihuahua, Mexico

Abstract

Pneumopericardium is an unusual condition defined by the presence of gas into the pericardial sac. Gastric perforation into pericardium is a complication of gastric ulcer with high mortality. In this clinical case, we describe the condition of a male with a silent gastric ulcer, which penetrated into the pericardium, developing pneumopericardium and purulent pericarditis as a complication.

Keywords: *Pneumopericardium. Pericarditis. Gastric ulcer.*

Resumen

El neumopericardio es una condición inusual que se define por la presencia de gas dentro del saco pericárdico. La perforación gástrica al pericardio es una complicación de la úlcera gástrica con alta mortalidad. En este caso clínico describimos el pa- decimiento de un varón con una úlcera gástrica silente, la cual penetraba al pericardio, desarrollando neumopericardio y pericarditis purulenta como complicación.

Palabras clave: *Neumopericardio. Pericarditis. Úlcera gástrica.*

***Correspondence:**
Luis J. García-Vega
E-mail: luisjgvega@gmail.com

Date of reception: 02-05-2022
Date of acceptance: 02-06-2022
DOI: 10.24875/CIRUE.M22000778

Cir Cir (Eng). 2024;92(6):799-802
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Pneumopericardium is a rare condition defined by the presence of gaseous content in the pericardial cavity, caused by the establishment of a communication between the pericardium and neighboring structures containing air, and less frequently due to infections by gas-producing microorganisms[1]. Other notable factors include thoracic trauma, barotrauma, and iatrogenic factors related to surgical procedures[2].

Gastric perforation into the pericardium is an extremely rare and lethal complication of a benign gastric ulcer. Only a few cases of pneumopericardium due to the perforation of an intestinal organ into the pericardium have been described[3].

We present the case of a 71-year-old patient with pneumopericardium secondary to a gastric ulcer penetrating into the pericardium.

Case Report

A 71-year-old male with a history of type 2 diabetes mellitus treated with metformin 850 mg/24 h denied chronic use of nonsteroidal anti-inflammatory drugs. He had a left paraumbilical hernia containing peritoneal fat. His surgical history included trauma from a car accident, with open reduction of a left hip fracture and a pedicled skin flap from the left hemiabdomen for a right hand injury.

Ten days prior to admission, he experienced progressively intense epigastric pain, non-radiating, worsened by food intake, along with moderate-effort dyspnea. He presented to the emergency department with 24 hours of melena, approximately 1500 mL. Upon admission, he reported transfictive precordial pain.

The patient presented with a blood pressure of 90/60 mmHg, a heart rate of 80 beats per minute, a low-grade fever of 37.4 °C, and an oxygen saturation of 95%. He was in a semi-Fowler's position, appeared restless, and exhibited mild pallor of the skin. His mucous membranes were semi-hydrated, heart sounds were diminished in tone, and his abdomen was distended and tender upon palpation of the epigastrium, without signs of peritoneal irritation. Bowel sounds were reduced, and a rectal exam was positive for melena.

Laboratory results: hemoglobin: 10 g/dL; mean corpuscular volume: 77.2 fL; mean hemoglobin per red blood cell: 25.3 pg; leukocytes: 36,600 cells/mm^3 (94.1% neutrophils); creatinine: 3.2 mg/dL; blood urea nitrogen: 139.77 mg/dL. Normal cardiac enzymes. An electrocardiogram showed no acute or chronic abnormalities.

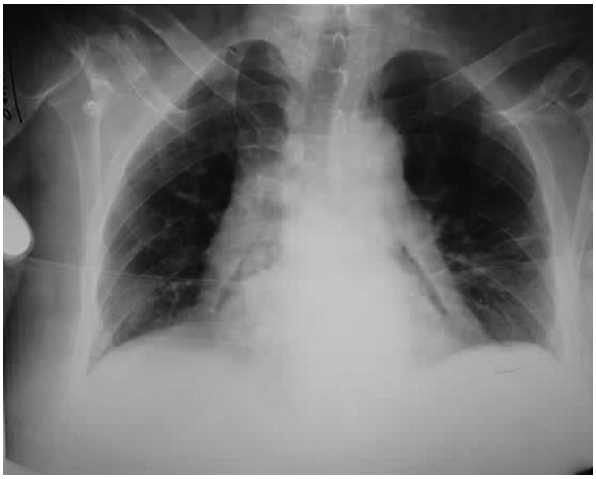

Figure 1. *Chest X-ray showing mediastinal widening and a radiolucent band encircling the pericardium.*

Within the imaging studies, a chest X-ray revealed pneumopericardium (Fig. 1), and thoracoabdominal computed tomography (CT) demonstrated a fistulous communication from the lesser curvature of the stomach to the pericardium, with pneumopericardium but no free abdominal air (Fig. 2). A gastroduodenal endoscopy was performed, revealing a gastric ulcer on the anterior gastric body penetrating the mediastinum, with cardiac motion visible through the pericardium and no evidence of active bleeding (Fig. 3). Subsequently, an echocardiogram showed no evidence of compromised cardiac output.

An emergency exploratory laparotomy was conducted using a supra- and midumbilical incision. The stomach lesser curvature was found to have fibrotic tissue adhered to the diaphragm, corresponding to a fistulous tract caused by a gastric ulcer penetrating the pericardium. A gastric defect approximately 3 × 2 cm in size was identified (Fig. 4). The ulcer margins were resected, and the defect was repaired in 2 layers, followed by the application of a Graham patch. A diaphragmatic plasty was also performed with primary closure using Vicryl 1-0. In a second surgical act, the incision was extended to the sternum for xiphoid resection and anterior pericardial fat dissection. A pericardiotomy measuring 3 × 3 cm was performed, revealing purulent exudate, which was sampled for culture.

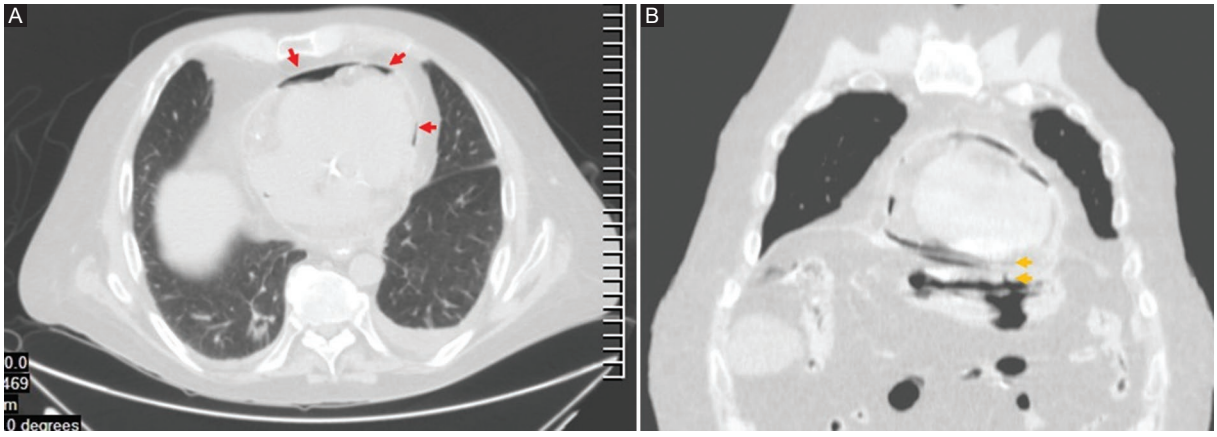

Figure 2. *Non-contrast thoracoabdominal CT in lung window.* **(A)** *axial view showing pneumopericardium (arrows).* **(B)** *coronal view showing the fistulous tract connecting the gastric chamber with the pericardium (arrows).*

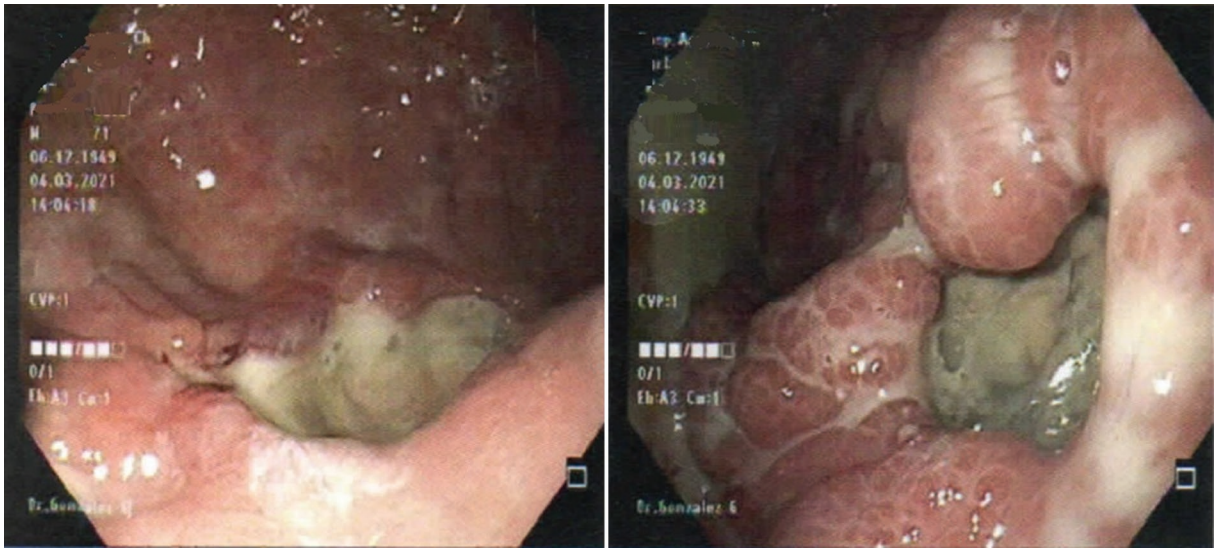

Figure 3. *Gastric endoscopy showing an ulcer on the gastric body near the lesser curvature, penetrating the mediastinum with visible pericardium.*

The pericardial cavity was irrigated with saline, and a 36-Fr drainage tube was placed in such cavity under direct visualization. Bilateral endopleural drains (36-Fr) were inserted, along with Penrose drains at the gastric fundus and a nasogastric tube for postoperative decompression. The abdominal wall was closed, and pleural seals were secured.

The patient was admitted to the intensive care unit, where mediastinal drainage continued to produce turbid fluid. The clinical course became complicated by multiple organ dysfunction due to sepsis, and the patient died 72 hours after the surgical procedure. Culture results identified *Candida albicans*, and the biopsy revealed a benign gastric ulcer.

Discussion

Gastric perforation into the pericardium is an extremely rare complication with high mortality rates ranging from 50% to 80%[4]. Its high fatality is linked to massive internal hemorrhage, bacterial peritonitis, or multiple organ failure due to hypovolemic, cardiogenic, or septic shock[2]. Pericarditis resulting from perforation of intestinal organs also has severe septic repercussions[5]. Gastric mucosa is often a site of fungal colonization by *C. albicans*, observed in 54.2% of gastric ulcers and 10.3% of chronic gastritis cases[6].

In the review of pneumopericardium cases due to fistulas secondary to surgical procedures such as

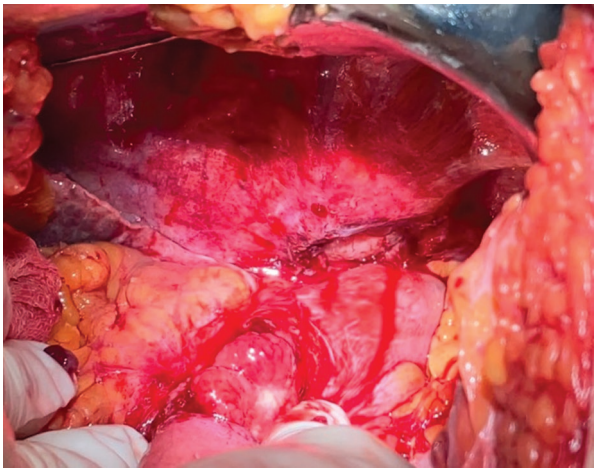

Figure 4. *Intraoperative image showing resection of the fistulous tract connecting the gastric ulcer to the pericardium.*

gastric fundoplications, esophagectomies, bariatric surgery, or partial gastrectomies, only a minority of cases were attributed to gastric ulcers[7].

Pneumopericardium poses a diagnostic challenge during initial evaluation due to its nonspecific symptoms, such as chest pain and dry cough[7]. Other signs can include dyspnea, epigastric pain, dysphagia, cardiac tamponade, hematemesis, and melena. A chest X-ray is the typical initial diagnostic study, revealing pneumopericardium. Oral contrast-enhanced abdominal CT can identify the disruption site, the fistulous tract, and the presence of air. Endoscopy is not recommended in some unstable patients due to the risk of hemodynamic instability caused by cardiac tamponade, which could worsen with increased air pressure in the stomach[8]. Therefore, thoracic and abdominal CT with oral contrast is suggested to prevent acute circulatory complications[9]. In this case, the patient underwent endoscopy without subsequent hemodynamic complications.

Given the high mortality rate, effective management requires a multidisciplinary approach and prompt surgical procedure. Currently, no guidelines or protocols have been published for managing such complications[9]. Early diagnosis, pericardial drainage, and tailored GI surgery are the best strategies to improve patient survival[1].

Conclusions

We report an extremely rare case of a gastric ulcer perforating into the pericardium. In cases of clinical suspicion, we emphasize the importance of early diagnostic imaging, particularly CT. Gastroduodenal endoscopy has relatively high sensitivity and should be employed when CT findings are equivocal and in hemodynamically stable patients. However, it is not advisable due to the risk of increased gastric air passage through the fistulous tract into the pericardium. Surgery is the only feasible curative therapy, despite its inherent risks. The type of procedure should be selected based on the individual criteria of each patient.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patient referenced in the article. This document is held by the corresponding author.

References

1. Poblador AR, Fernández AG, Martínez MG, Raposo LG, Chimeno IM, Iglesias RC, et al. Pneumopericardium caused by gastropericardial fistula. Rev Esp Enferm Dig. 2007;99:168-71.
2. Gołota JJ, Orłowski T, Iwanowicz K, Snarska J. Air tamponade of the heart. Kardiochir Torakochirurgia Pol. 2016;13:150-3.
3. Ufuk F. Gastric perforation into the pericardium. Am J Emerg Med. 2017; 35:1986.e1-2.
4. Kim WJ, Choi EJ, Oh YW, Kim KT, Kim CW. Gastropericardial fistula-induced pyopneumopericardium after esophagectomy with esophagogastrectomy. Ann Thorac Surg. 2011;91:e10-1.
5. Gabor S, Woltsche M, Maier A, Smolle-Jüttner FM. Pneumopericardium due to intrapericardial perforation of a gastric ulcer. Eur J Cardiothorac Surg. 2003;23:131-3.
6. Zwolinska-Wcisto M, Budak A, Bogdat J, Trojanowska D, Stachura J. Fungal colonization of gastric mucosa and its clinical relevance. Med Sci Monit. 2001;7:982-8.
7. Schulte-Hermes M, Klein-Wiele O, Vorpahl M, Seyfarth M. Acute tension pneumopericardium due to perforated gastric ulcer without diagnostic radiographic findings 72 h before perforation. J Cardiol Cases. 2018;18:201-3.
8. Reicher JJ, Mindelzun R. Case report: benign gastric ulcer erosion leading to a gastropericardial fistula in a patient with no known risk factors. Clin Imaging. 2014;38:547-9.
9. Łaski D, Łukiański M, Dubowik M, Pawlaczyk R, Żurek W, Marjański T, et al. Perforation of benign peptic ulcer in hiatal hernia into the pericardium, resulting in pneumopericardium. Endoscopy. 2014;46 (Suppl 1 UCTN):E423.

Solitary fibrous tumor of the abdominal wall: a new case with literature review

Tumor fibroso solitario de la pared abdominal: un nuevo caso con revisión de la literatura

María L. Ruiz-Juliá[1], Virgilio Ruiz-Luque[1], Macarena Ariza-Estepa[2], Jorge Díaz-Roldán[1], and Pablo Parra-Membrives[1]*

[1]Department of General and Digestive Surgery; [2]Department of Pathology. Valme University Hospital, Seville, Spain

Abstract

Objective: *We present a solitary fibrous tumor (SFT) of the abdominal wall treated laparoscopically.* **Method:** *We will discuss the clinicopathologic characteristics and will present a review of the literature.* **Results:** *SFTs are rare neoplasms of mesenchymal origin. Its location in the abdominal wall is extremely rare. To the best of our knowledge, only 20 cases have currently been described in the literature.* **Conclusions:** *Complete surgical resection is the main therapy for all cases. A laparoscopic approach is safe. Clinical-radiological follow-up must be carried out due to its uncertain behavior, and perioperative treatment may be necessary in high-risk patients.*

Keywords: *Extrapleural solitary fibrous tumor. Solitary fibrous tumor. Mesenchymal neoplasm.*

Resumen

Objetivo: *Presentamos un caso de tumor fibroso solitario de pared abdominal tratado por vía laparoscópica.* **Método:** *Se discuten las características clinicopatológicas y se presenta una revisión de la literatura.* **Resultados:** *Los tumores fibrosos solitarios son neoplasias raras de origen mesenquimatoso. Su localización en la pared abdominal es extremadamente rara. Hasta donde sabemos, solo se han descrito 20 casos en la literatura.* **Conclusiones:** *La resección quirúrgica completa es la terapia principal para todos los casos. El abordaje laparoscópico es seguro. Debe realizarse un seguimiento clínico-radiológico debido a su comportamiento incierto, pudiendo ser necesario un tratamiento perioperatorio en pacientes de alto riesgo.*

Palabras clave: *Tumor fibroso solitario extrapleural. Tumor fibroso solitario. Neoplasia mesenquimatosa.*

***Correspondence:**
María L. Ruiz-Juliá
E-mail: mlrj84@gmail.com

Date of reception: 13-04-2022
Date of acceptance: 03-06-2022
DOI: 10.24875/CIRUE.M22000801

Cir Cir (Eng). 2024;92(6):803-808
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Solitary fibrous tumor (SFT) is a rare neoplasm of mesenchymal origin. They are usually located at the intrathoracic level[1]. Other locations have been described[2], although, there are very few cases described based on the abdominal wall[1-15]. We present the case of an SFT of the abdominal wall (SFT-AW). We review its clinicopathologic characteristics based on current literature.

Case report

A 54-year-old woman suffering from renal lithiasis, that was referred to us due to an incidental finding on a computed tomography scan of a solid lesion in contact or arising from the major gastric curvature of 57 mm highly, suggestive of gastrointestinal stromal tumor (Fig. 1A). Physical examination was normal. No abdominal mass was palpable. The study was completed with endoscopic ultrasound. Endoscopic ultrasound revealed a 6 × 5 cm hypoechoic lesion with cystic areas. It was seemed to be dependent on the fourth layer of the gastric wall with extraluminal growth. A multidisciplinary team meeting was taken for surgical resection.

During surgery, a 6 cm diameter extraperitoneal tumor coming from the transverse muscle was found in the anterior abdominal wall. The aponeurosis was not affected. The tumor was removed by laparoscopy (Fig. 1B). A combination of two 5 and two 12 mm ports were placed in a semilithotomy position. Neither ascites fluid nor intra-abdominal lesions were visualized. The dissection headed through healthy tissue by electrocoagulation and the excision of tumor was completed by vessel sealer. The specimen was exteriorized through a 6-7 cm transverse incision by extending the 5 mm port on the left flank. The fascial defect was closed by primary repair using a continuous loop PDS suture. The patient was discharged after 24 h without any complications and is currently under disease-free follow-up.

The surgical specimen was fixed in 4% buffered formaldehyde and processed by standard techniques. The immunohistochemistry analysis was performed on the BenchMark ULTRA system (Ventana Medical Systems, Tucson, AZ) and using the following Ventana's antibodies: CD34 (clone QBEnd/10; primary antibody), CD99 (clone O13; mouse monoclonal primary antibody), bcl-2 (clone SP66; rabbit monoclonal primary antibody), S100 (polyclonal, primary antibody), beta-catenin (mouse monoclonal antibody), pan keratin (clone AE1/AE3/PCK26), CD10 (clone SP67; rabbit monoclonal primary antibody), actin smooth muscle (clone 1A4; mouse monoclonal antibody), desmin (clone DE-R-11; primary antibody), Ki-67 (clone 30-9; rabbit monoclonal primary antibody), and CD117/c-KIT (clone 9.7; primary antibody).

The external surface of the nodular surgical specimen was smooth with well-defined contours and marked vascularization. It measured 6 × 5 × 5 cm and showed mostly homogeneous solid whitish areas, of elastic consistency, with a microgranular surface. Multiple cystic formations with serous content were described, the largest one measuring 2 cm in maximum axis. A 2.5 cm solid pole of greater consistency was also identified. It presented a fine intact capsule.

The anatomopathological examination showed a markedly cellular formation with mild pleomorphism without necrosis, and also a hemangiopericytoma pattern with isolated outbreaks of hemorrhage (Fig. 2). The mitotic index was 2-3 mitotic/10 HPF. Immunohistochemistry revealed Ki-67 of ~7% (Fig. 3), strong positivity for CD34 (Fig. 4) and bcl-2, and weak for CD99. It was negative for CKAE1/AE3, smooth muscle actin, CD117, CD10, desmin, S-100, and beta-catenin. With these data, it was reported as SFT-AW.

Discussion

SFTs are rare neoplasms of spindle cell with fibroblastic or myofibroblastic characteristics, so any organ composed of mesenchymal cells has the potential to develop this type of neoplasm[11,13]. The most frequent extrathoracic location is in the abdomen (intraperitoneal, retroperitoneal, and pelvis). SFTs-AW represents < 2% of all soft-tissue tumors[2] and, to the best of our knowledge, 20 cases have currently been described in the literature (Table 1). SFTs have similar incidence in men and women, although SFTs-AW predominates in women[2]. Huang et al.[11] proposed a possible role of sex steroid hormones in the initiation or maintenance of these tumors. The most commonly diagnosis age is in the 50s and 60s[1]. In our review, we observed a wide age range of 21-79 years.

SFTs-AW usually appears as slow-growing and often asymptomatic masses, found as incidental discovery, as happened in our case. Therefore, they are

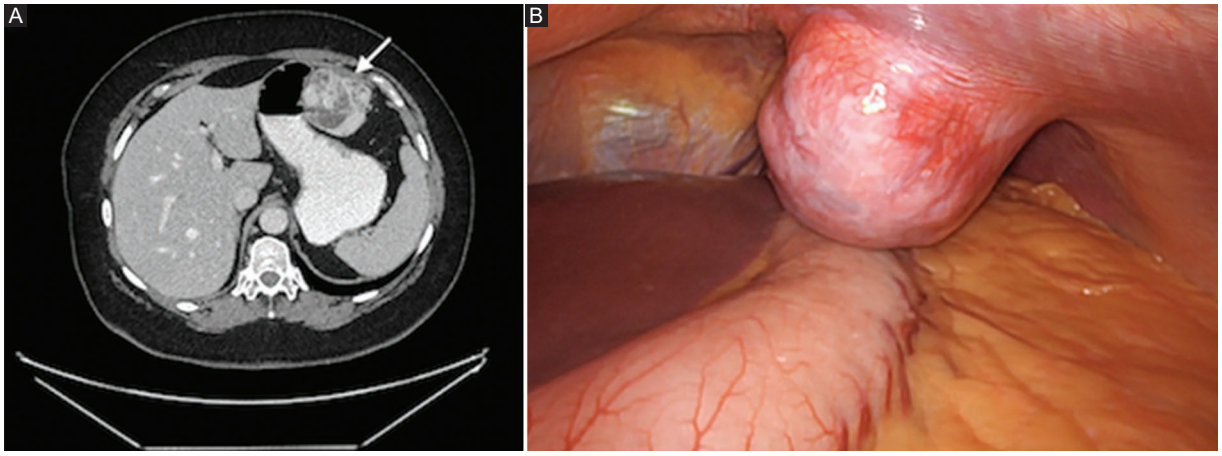

Figure 1. A: *computerized tomography: mass in intimate contact with the greater gastric curvature with dimensions of 6.1 × 6.3 × 5.4 cm in its transverse, anteroposterior, and craniocaudal axes, respectively. This lesion shows well-defined contours as well as a significant enhancement, delimiting hypodense areas inside it, probably due to necrosis.* **B:** *laparoscopic view of the tumor arising from the anterior abdominal wall.*

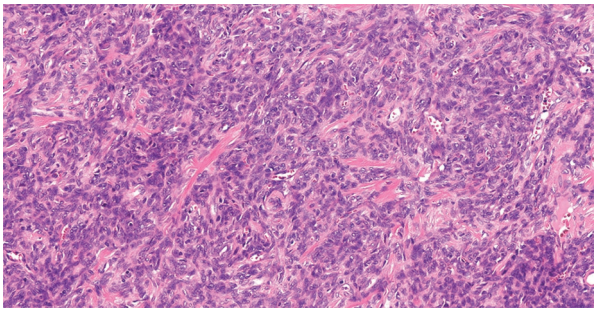

Figure 2. *Hematoxylin-eosin, ×20. Spindle cells with a patternless architecture, interspersed with collagen bundles with cracking artifact, and a characteristic hemangioperycitoid vascular pattern with staghorn vessels. This neoplasia is predominantly hypercellular with hypocellular areas, well-circumscribed, and with hemorrhagic areas with no evidence of necrosis.*

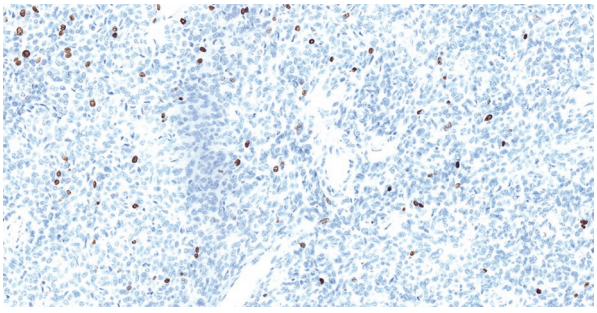

Figure 3. *Ki67 proliferative index of 7%.*

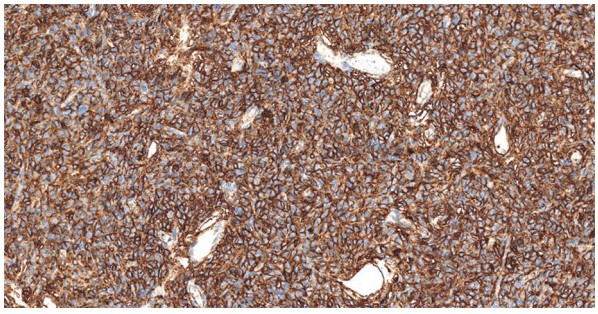

Figure 4. *Strong and diffuse positive immunostaining for CD34.*

difficult to diagnose and can simulate other mesenchymal neoplasms, both benign and malignant[2,13,16]. Both show radiological characteristics similar to other soft-tissue tumors and there are no specific pathognomonic findings for SFTs[1]. Neither fine-needle aspiration nor core-needle biopsy usually achieve a definitive diagnosis[1,14], requiring histological confirmation of the surgical specimen[1,16,17].

For an appropriate surgical resection, it must be considered that these neoplasms are encapsulated by a thin membrane that often contains small satellite lesions. If this capsule is not completely removed, residual satellite lesions can develop into deposits of micrometastases. Positive surgical resection margins are responsible for up to 40% of local recurrences and 75% of metastatic disease[16]. In our case, the resection was carried out safely and efficiently by laparoscopy, observing in the macroscopic study a fine whitish intact capsule and negative surgical margins.

Immunohistochemistry allows us to distinguish SFTs from other tumors. They are positive for CD34 in 90-95% of cases and for bcl-2 in 96% of cases. Other

Table 1. Reported cases of SFTs-AW

Case nº	Author	Age (years)/ Sex	Symptoms	Size (cm)	Treatment	Follow-up (months)	Recurrence	Metastases	IHQ CD34/ bcl-2	Malignancy
1	Mentzel et al.[5] (1997)	51/M†	Abdominal mass	4,8	Laparotomic surgical resection	NA§	NA	NA	+/NA	NA
2	Nielsen et al.[7] (1997)	NA	NA	NA	Laparotomic surgical resection	NA	-	-	+/NA	+
3	Vallat-Decouvelaere et al.[3] (1998)	50/F‡	Abdominal mass	1,9	Laparotomic surgical resection	13	-	-	+/NA	+
4	de Saint Aubain Somerhausen et al.[6] (1999)	45/F	Abdominal mass	14	Laparotomic surgical resection	ND	-	-	+/NA	-
5	de Saint Aubain Somerhausen et al.[6] (1999)	35/F	Painful abdominal mass	11,5	Laparotomic surgical resection	recent case	-	-	+/NA	-
6	Hasegawa et al.[9] (1999)	50/F	Abdominal mass	3	Laparotomic surgical resection	38	-	-	+/+	-
7	Hasegawa et al.[9] (1999)	60/F	Abdominal mass	5,5	Laparotomic surgical resection	156	-	-	+/+	-
8	Lee et al.[4] (2001)	67/M	Tumor in left inguinal hernia sac	1	Laparotomic surgical resection and hernia repair	39	-	-	-/NA	-
9	Lee et al.[4] (2001)	44/F	Tumor in ventral hernia sac	4,5	Laparotomic surgical resection and hernia repair	6	-	-	-/NA	-
10	Huang et al.[11] (2002)	50/F	Abdominal mass	4	Laparotomic surgical resection	14	-	-	+/+	-
11	Huang et al.[11] (2002)	38/F	Abdominal mass	7,5	Laparotomic surgical resection	12	-	-	+/+	-
12	Sawada et al.[8] (2002)	45/F	NA	3	Laparotomic surgical resection	NA	NA	NA	+/NA	NA
13	Ouazzani et al.[15] (2008)	66/M	Painless Abdominal mass	16	Laparotomic surgical resection	6	-	-	+/+	+
14	Migita et al.[13] (2009)	74/F	Abdominal mass	12	Laparotomic surgical resection	10	-	-	+/+	-
15	Mosquera et al.[10] (2009)	50/F	Abdominal mass	6,4	Laparotomic surgical resection	12	-	-	+/NA	-
16	Bi et al.[2] (2017)	79/F	Abdominal mass	15	Laparotomic surgical resection	48	-	+	NA	+
17	Testa et al.[12] (2019)	64/M	Abdominal mass	4,8	Laparotomic surgical resection	6	-	-	+/+	-
18	Fernández-Sanmillán et al.[14] (2018)	62/H	AUR‖	20	Laparotomic surgical resection	6	-	-	+/+	-
19	Ros et al.[1] (2020)	43/H	Micturition disorders	6	Laparotomic surgical resection	24	-	-	+/+	-
20	Ros et al.[1] (2020)	21/H	Supraumbilical lump	4	Laparotomic surgical resection	12	-	-	+/+	-

M: male; F: female; NA: not available; AUR‖: acute urinary retention.

common markers include vimentin and CD99 (70%). They usually show negative staining for cytokeratin, smooth muscle actin, desmin, S-100 protein, early membrane antigen, and c-kit[1,13].

The behavior of SFTs is usually benign, although local recurrence and even the appearance of metastasis are possible in 5-10% of patients, even 10 years after initial surgery, histologically benign SFTs included[12,18]. The mortality rate reported is 1%[16]. Histological characteristics related to malignancy include tumor size > 10 cm, high cellularity, and pleomorphism, more than 4 mitoses/10 HPF, presence of hemorrhage and necrosis, and incomplete resection[13,14]. Demicco et al.[19] developed a risk stratification model based on age, tumor size, and mitotic index, stratifying the study population into three groups: low risk, intermediate risk, and high risk. Distant metastases or deaths were not reported in the low-risk group. Disease-free survival at 5 years in the moderate and high-risk groups was 77% and 15%, respectively. Overall survival at 5 years in the moderate and high-risk groups was 93 and 60%, and 93 and 0% at 10 years, respectively.

The follow-up of these patients should be carried out with imaging tests every 3-6 months for the first 2-3 years and subsequently every 6-12 months up to 5 years, depending on the characteristics of tumor malignancy determined by histology and surgical resection margins[1]. Local recurrences can be controlled by new resection. However, the disseminated disease of SFTs does not usually respond to adjuvant treatments[20].

Conclusion

SFTs-AW is extremely rare mesenchymal tumors. Complete surgical resection is the main therapy for all cases, either through an open or laparoscopic approach. Clinical-radiological follow-up must be carried out due to its uncertain behavior, and perioperative treatment may be necessary in high-risk patients.

Funding

The authors declare that no funding was received.

Conflicts of interest

The authors have no related conflicts of interest to declare.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

References

1. Ros A, Cortés J, Belda T, Magan A, Illán-Gambín FJ, Aracil E, et al. Fibrous solitary tumor, a rare and ubiquitous neoplasy. J Surg Case Rep. 2020;6:rjaa156.
2. Bi X, Zhai J, Chun CD. Solitary fibrous tumor of the abdominal wall re-surfacing as unilateral pleural effusion and mass: a case report and review of the literature. Respir Med Case Rep. 2017;23:4-7.
3. Vallat-Decouvelaere AV, Dry SM, Fletcher CD. Atypical and malignant solitary fibrous tumors in extrathoracic locations: evidence of their comparability to intra-thoracic tumors. Am J Surg Pathol. 1998;22: 1501-11.
4. Lee JR, Hancock SM, Martindale RG. Solitary fibrous tumors arising in abdominal wall hernia sacs. Am Surg. 2001;67:577-81.
5. Mentzel T, Bainbridge TC, Katenkamp D. Solitary fibrous tumour: clinicopathological, immunohistochemical, and ultrastructural analysis of 12 cases arising in soft tissues, nasal cavity and nasopharynx, urinary bladder and prostate. Virchows Arch. 1997;430:445-53.
6. De Saint Aubain Somerhausen N, Rubin BP, Fletcher CD. Myxoid solitary fibrous tumor: a study of seven cases with emphasis on differential diagnosis. Mod Pathol 1999;12:463-71.
7. Nielsen GP, O'Connell JX, Dickersin GR, Rosenberg AE. Solitary fibrous tumor of soft tissue: a report of 15 cases, including 5 malignant examples with light microscopic, immunohistochemical, and ultrastructural data. Mod Pathol. 1997;10:1028-37.
8. Sawada N, Ishiwata T, Naito Z, Maeda S, Sugisaki Y, Asano G. Immunohistochemical localization of endothelial cell markers in solitary fibrous tumor. Pathol Int. 2002;52:769-76.
9. Hasegawa T, Matsuno Y, Shimoda T, Hasegawa F, Sano T, Hirohashi S. Extrathoracic solitary fibrous tumors: their histological variability and potentially aggressive behavior. Hum Pathol. 1999;30:1464-73.
10. Mosquera JM, Fletcher CD. Expanding the spectrum of malignant progression in solitary fibrous tumors: a study of 8 cases with a discrete anaplastic component--is this dedifferentiated SFT? Am J Surg Pathol. 2009;33:1314-21.
11. Huang HY, Sung MT, Eng HL, Lee TY, Ko SF, Wang CC, et al. Solitary fibrous tumor of the abdominal wall: a report of two cases with immunohistochemical, flow cytometric, and ultrastructural studies and literature review. APMIS. 2002;110:253-62.
12. Testa DC, Selvaggi F, Andreano T, Mazzola L, Cortellese R. Solitary fibrous tumor of the anterior abdominal wall. A case report and review of the literature. Ann Ital Chir. 2019;8:13;8:1-5.
13. Migita K, Watanabe A, Nakagawa K, Ohyama T, Sekigawa S. Solitary fibrous tumor of the abdominal wall. Int J Clin Oncol. 2009;14:555-9.
14. Fernández-Sanmillán D, De Melo Santos DM, Fernandez EL, Hernandez JR. Acute urinary retention due to solitary fibrous tumor of the abdominal wall. Turk J Urol. 2018;45:471-3.

15. Ouazzani A, Delrée P, De Saint Aubain N, Ceuterick M, Boudaka W. Malignant solitary fibrous tumor of the abdominal wall in a man. Ann Chir Plast Esthet. 2008;53:517-20.
16. Kayani B, Sharma A, Sewell MD, Platinum J, Olivier A, Briggs TW, et al. A review of the surgical management of extrathoracic solitary fibrous tumors. Am J Clin Oncol. 2018;41:687-94.
17. Orue-Echebarria MI, Garciafília L, Rodriguez-Bachiller L, Díaz-Zorita B, Velasco E, Ramón E, et al. Solitary extrapleural fibrous tumor with hepatic bilobar metastases: multimodal approach treatment. Clin Sarcoma Res. 2020;10:23.
18. Ronchi A, Cozzolino I, Marino FZ, Accardo M, Montella M, Panarese I, et al. Extrapleural solitary fibrous tumor: a distinct entity from pleural solitary fibrous tumor. An update on clinical, molecular and diagnostic features. Ann Diagn Pathol. 2018;34:142-50.
19. Demicco EG, Park MS, Araujo DM, Fox PS, Bassett RL, Pollock RE, et al. Solitary fibrous tumor: a clinicopathological study of 110 cases and proposed risk assessment model. Mod Pathol. 2012;25:1298-306.
20. Wilky BA, Montgomery EA, Guzzetta AA, Ahuja N, Meyer CF. Extrathoracic location and "borderline" histology are associated with recurrence of solitary fibrous tumors after surgical resection. Ann Surg oncol. 2013;20:4080-9.

CLINICAL CASE

Littoral cell angioma of the spleen in a 70-year-old male patient with myelodysplastic syndrome: a case report

Angioma de células litorales del bazo en un paciente varón de 70 años con síndrome mielodisplásico: reporte de un caso

Ioannidis Orestis[1], Symeonidis Savvas[1], Aggeliki Koltsida[1], Papadopoulou Stauroula[2], Malliora Anastasia[1], Christidis Panagiotis[1], Ouzounidis Nikolaos[1], Kotidis Efstathios[1], Pramateftakis Manousos George[1], Mantzoros Ioannis[1], and Angelopoulos Stamatios[1]*

[1]Department of Surgery, School of Medicine, Aristotle University of Thessaloniki; [2]Department of Pathology, General Hospital of Thessaloniki "G. Papanikolaou". Thessaloniki, Greece

Abstract

Introduction: *Littoral cell angioma (LCA) is a new subtype of vascular tumor, which has been reported infrequently worldwide. It is associated with visceral malignancies and other immunologic conditions.* **Clinical case:** *We present a case of a 70-year-old Caucasian male with a 6-year history of myelodysplastic syndrome, which was investigated for splenomegaly and pancytopenia. Radiological and histopathological examinations revealed an LCA and an open splenectomy were performed. The patient had an uneventful post-operative recovery.* **Conclusion:** *LCA is a rare tumor, with atypical presentation often associated with other malignancies or immunologic conditions. Diagnosis is challenging, and so far, splenectomy is the gold standard treatment.*

Keywords: *Littoral cell angioma. Vascular tumor. Myelodysplastic syndrome. Spleen tumor. Case report.*

Resumen

Introducción: *El angioma de células litorales es un nuevo subtipo de tumor vascular, el cual ha sido reportado con poca frecuencia en todo el mundo. Se asocia con neoplasias malignas viscerales y otras condiciones inmunitarias.* **Caso clínico:** *Varón caucásico de 70 años con antecedentes de síndrome mielodisplásico de 6 años de evolución, que fue investigado por esplenomegalia y pancitopenia. Los exámenes radiológicos e histopatológicos revelaron un angioma de células litorales y se realizó una esplenectomía abierta. El paciente tuvo una recuperación posoperatoria sin incidentes.* **Conclusión:** *El angioma de células litorales es un tumor raro, con presentación atípica y frecuentemente asociado con otras neoplasias malignas o condiciones inmunitarias. El diagnóstico es un desafío y, hasta ahora, la esplenectomía es el tratamiento estándar.*

Palabras clave: *Angioma de células litorales. Tumor vascular. Síndrome mielodisplásico. Tumor de bazo. Reporte de caso.*

Correspondence:
Orestis Ioannidis
E-mail: telonakos@hotmail.com

Date of reception: 23-05-2022
Date of acceptance: 08-07-2022
DOI: 10.24875/CIRUE.M22000802

Cir Cir (Eng). 2024;92(6):809-814
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

Littoral cell angioma (LCA) is a new subtype of vascular tumor, which has been reported variably and infrequently in the medical literature[1,2]. There are approximately 160 cases presented internationally and very few in the Hellenic Population. LCA has been recently associated with numerous autoimmune diseases and malignancies. In fact, there are only two previously reported cases of LCA in myelodysplastic syndrome (MDS) patients in the medical literature, none of these in Europe[3,4].

We report the case of a 70-year-old male patient with a history of MDS who presented with pancytopenia and splenomegaly. The following case report is presented in accordance with the Surgical Case Report guidelines[5]. We also review the relevant literature regarding the presentation and overall management of LCA.

Case report

A 70-year-old Caucasian man, with a known 6-year history of MDS and several previous hospital admissions for pancytopenia, presented to the Emergency Department due to pruritus and several ecchymoses all over the body. He was hemodynamically stable (blood pressure: 110/70 mmHg and heart rate: 95 bpm), oxygen saturation was 98% and temperature 36.7°C. Clinical examination revealed normal bowel sounds, soft and non-tender abdomen, dull to percussion left costal margin, without liver enlargement and non-palpable cervical, axillary and inguinal lymph nodes. His medical history included arterial hypertension, hypercholesterolemia, hypothyroidism on replacement therapy, allergic rhinitis, and asthma. The patient underwent laboratory examinations, which revealed normocytic normochromic anemia (hemoglobin = 8.8 g/dL), thrombocytopenia (88,000/μL), and leukopenia (2400 K/uL). The patient was admitted to the Department of Internal Medicine for further evaluation.

Additional blood results disclosed normal liver and kidney function, inflammatory markers within normal limits and negative serum immunological tests for *Toxoplasma*, Cytomegalovirus, Human Immunodeficiency Virus (HIV), and Epstein-Barr virus. In addition, a bone marrow biopsy revealed erythroid hyperplasia, although peripheral blood smear was normal. Further evaluation with an ultrasound of the upper abdomen was performed, demonstrating spleen enlargement (6 × 12 × 15 cm) and several hyperechoic lesions, without any other pathological findings. These results were subsequently confirmed with an abdominal computed tomography (CT) scan, where these multiple lesions appeared hypodense throughout the spleen (Fig. 1).

Taking all of the above into consideration, in combination with the patient's history of MDS, these multifocal splenic masses were believed to represent extramedullary involvement (EMI) of his blood cancer to the spleen. Moreover, the differential diagnosis included lymphoid and vascular spleen tumors. Thus, CT scans of the brain, lungs and neck were obtained and the possibility of metastasis was excluded from the study.

Following a surgical review, a decision was made to proceed with a splenectomy without obtaining a biopsy, due to its potential hemorrhagic complications. Vaccines against *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b were administered 4 weeks before the elective surgery. Intraoperatively, we performed a midline incision and then entered the peritoneal cavity. An enlarged spleen with a reddish appearance and multiple tiny dark spots was recognized. We first clamped and lighted the splenic artery, and afterward, the splenic vein was clamped and lighted. The spleen was removed to its entirety and the abdomen was closed with a closed suction drain.

Subsequently, the spleen was sent for further histopathological and immunohistochemical studies. It measured a total of 14.5 × 9.5 × 7 cm, weighted 452 g and appeared reddish with homogenous texture. Macroscopically, sections through the specimen showed multifocal small dark lesions, the largest measuring 0.5 cm. Microscopically, the findings were consistent with a LCA of the spleen. More specifically, histopathological examinations revealed several non-encapsulated but well-circumscribed tiny masses, that consisted of anastomosing vascular channels (Fig. 2A), resembling splenic sinusoids, lined by histiocytes and eosinophils, with papillary projections (Fig. 2B) and cyst-like spaces (Fig. 3A), containing red blood cells (Fig. 3B), and widespread deposition of hemosiderin granules (Fig. 3C). No marked nuclear atypia or prominent mitotic figures were displayed (Fig. 4). Immunohistochemical characterization demonstrated that lining cells were positive for CD31 (Fig. 5A) and CD68 markers and negative for CD34, whereas cells within papillary projections were

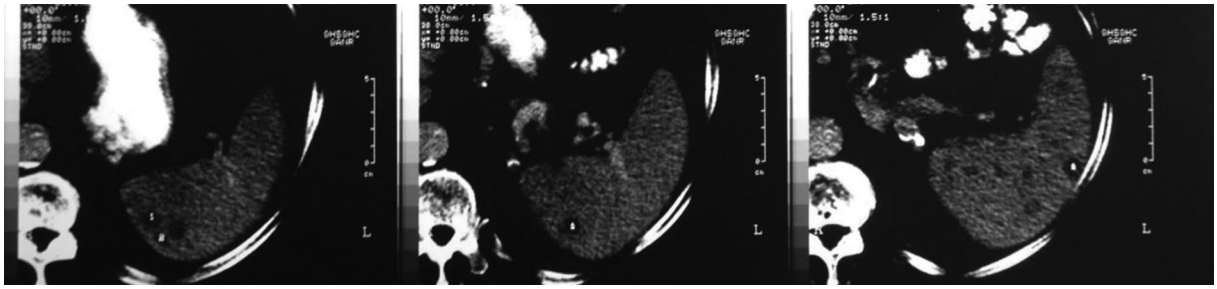

Figure 1. *Abdominal computed tomography scan showing multiple hypodense lesions throughout the spleen.*

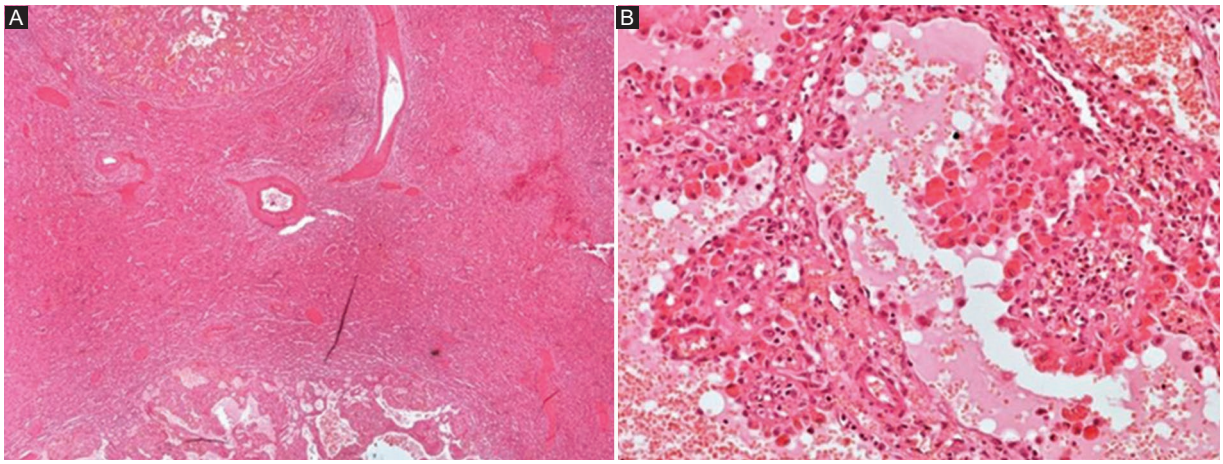

Figure 2. *Histopathological examinations revealed several non-encapsulated but well-circumscribed tiny masses, that consisted of anastomosing vascular channels* **(A)** *with papillary projections lined by tall endothelial cells* **(B)**.

positive for CD34 (Fig. 5B). The final diagnosis of LCA was established. The patient had an uneventful post-operative recovery and remained well at 12 months of post-operative follow-up.

Prophylactic antimicrobial therapy was indicated and oral amoxicillin was prescribed to be taken twice daily in the first 2 years after the splenectomy.

Discussion

LCA, first described by Falk et al.[6] in 1991, is a very rare vascular tumor located only in the spleen, that arises from the littoral cells of the red pulp sinuses[7], which have features similar to both endothelial cells and macrophages[2]. According to literature, it occurs mostly in the age range of 35-60 years, without sex-based predilection[8]. Here, we present a case of a 70-year-old Caucasian male, aiming to emphasize the rarity of the tumor, its atypical presentation with a MDS background and its diagnostic challenges.

Despite its uncertain etiology, it has been suggested that immunologic deregulation may play a significant role in the development of the tumor. Indeed, ankylosing spondylitis, Crohn's disease, Wiskott-Aldrich syndrome, and MDS are, among others, medical conditions associated with LCA. At first, it was thought to be a benign neoplasm; however, recent studies have proved that it exhibits malignant potential[9]. Moreover, it may be associated with several visceral malignancies, such as colorectal, pancreatic, renal, and lung carcinomas[10].

More specifically, MDS are clonal hematopoietic disorders involving morphologic defects and peripheral-blood cytopenias, with a high risk of progression to acute myeloid leukemia (AML)[11]. EMI in AML is reported in 2.5-9.1% of affected patients. The involved sites include soft tissue, gastrointestinal tract, bone and lymph nodes, where spleen counts for 2% of all the locations. The appearance of EMI in the course of AML is a very complex phenomenon, and it is associated with several clinical and laboratory features,

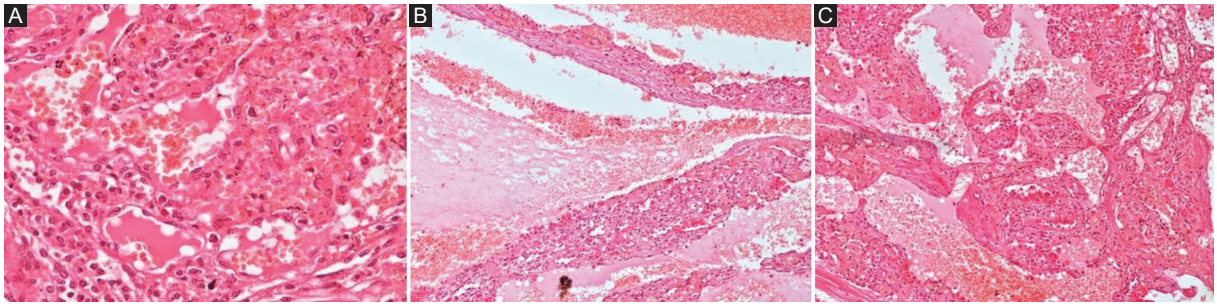

Figure 3. A: *irregular channel lumina and cystic spaces.* **B:** *cystic spaces filled with blood. Few sloughing endothelial cells.* **C:** *intracytoplasmic hemosiderin pigment.*

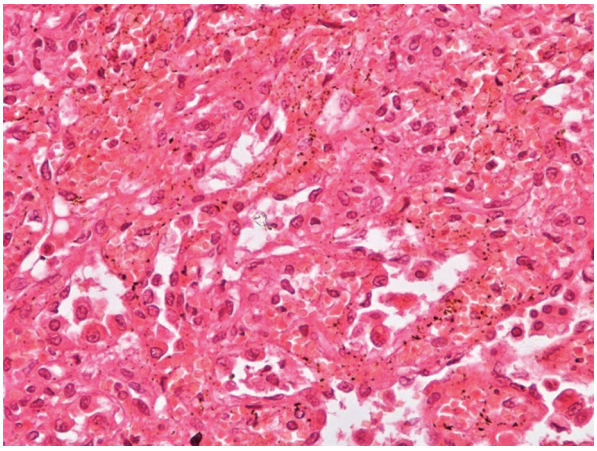

Figure 4. *No prominent mitotic figures were displayed.*

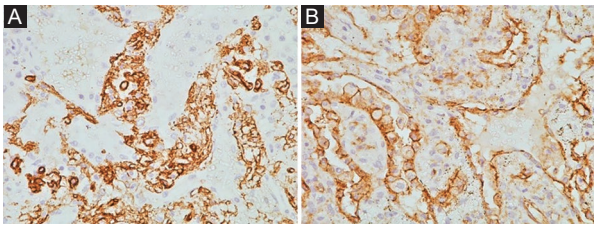

Figure 5. *Immunohistochemical characterization of littoral cell angioma.* **A:** *lining cells positive for CD31.* **B:** *papillary projections positive for CD34.*

such as increased levels of lactate-dehydrogenases (LDH) and leukocytosis[12]. As a result, spleen lesions in our case could be considered as extramedullary sites of blood cancer, but neither LDH levels nor leucocyte count was significantly associated with EMI, excluding this possibility.

Furthermore, LCA has specific immunophenotypic and morphologic characteristics, which differentiate it from other vascular splenic neoplasms, such as lymphangioma, hemangioma, hemangioendothelioma, and hemangiosarcoma[13].

LCA has no characteristic clinical manifestations and it might be incidentally detected during imaging studies in asymptomatic patients. However, in some cases, LCA may be manifested with splenomegaly, abdominal pain, weakness and fatigue, fever of unknown origin, or pancytopenia[8,14]. In our case, LCA manifested with spleen enlargement and laboratory evidence of hypersplenism.

Due to its atypical clinical appearance, imaging studies, such as ultrasonography, CT and magnetic resonance imaging (MRI) scan, could play a significant role in differential diagnosis, as they can detect splenic lesions. More specifically, the sonographic appearance is variable, including hypoechoic, isoechoic or hyperechoic lesions in an enlarged spleen[2]. On abdominal CT scans, obtained without contrast material, LCA typically appears as well- or poorly-circumscribed multiple hypodense lesions, while after contrast material administration, they may be presented as hypoattenuating in the early portal venous phase. However, these features may also be presented in other primary splenic neoplasms, metastatic disease, lymphoma, Kaposi's sarcoma, sarcoidosis or infectious processes, which lead to microabscess formation[1]. In our patient, absence of abdominal and thoracic neoplasm, lymph nodes' involvement or granulomas on CT scans, as well as negative screening tests for HIV and other infections, led the diagnosis primarily to splenic neoplasms. On MRI, it mostly appears slightly hypointense on T1- and T2-weighted pulse sequences, a finding that reflects the presence of hemosiderin in the lesions due to the hemophagocytic capacity of neoplastic cells[2,8,15]. Unfortunately, this fairly specific imaging feature is present only in a few cases[16]. One case shows inhomogeneously

hyperintensity on unenhanced T2-weighted images, as well as in hemangioma of the spleen[15]. We did not proceed to an MRI in our case, due to patient's right knee arthroplasty implants.

Histopathologically, non-encapsulated multiple or solitary nodules, variant in terms of size, texture and color, are revealed in macroscopic examination[8]. As for the color, it ranges from red to black, an appearance which reflects the presence of blood products of variable age[17].

Microscopically, the lesions contain several anastomosing vascular channels, lined with flat and tall endothelial cells, and irregular lumina, usually accompanied by papillary projections and cyst-like spaces. They might slough off into the vascular lumina and show hemophagocytosis. The neoplastic LCA cells, due to their dual endothelial and histiocytic differentiation, express antigens of both types. In contrast to normal endothelial cells, LCA cells express not only factor VIII antigen but also CD31, CD68, KP1, lysozyme, CD21, and CD163. The immunohistochemical pattern is negative for CD8, CD34, and S-100 antigens[8]. Our case was not an exception, as anastomosing vascular channels, resembling splenic sinusoids, with widespread deposition of hemosiderin were observed.

Taking into consideration the atypical clinical and imaging characteristics of LCA, as well as the high risk of hemorrhage after performing a fine-needle aspiration biopsy, the final diagnosis of this rare tumor depends on histological and immunohistochemical examinations post-operatively[8].

Regarding the treatment of LCA, open splenectomy or hand-assisted laparoscopic total splenectomy is the gold standard. This is mandatory due to the tumor's large size or diffuse nature, while it also serves the purpose of preserving enough tissue for histological and immunohistochemical examinations[18]. Although total splenectomy, both diagnostic and therapeutic, is the most widely performed procedure, there has been described a case in the international literature where a partial splenectomy was preferred for a localized tumor, preserving the advantage of patient's post-operative intact immune function[19]. Regarding the best surgical approach, recent studies have shown laparoscopic splenectomy to be superior to open splenectomy, in terms of decreased need of pain relievers and length of stay, as well as earlier oral intake[1]. However, in our case, we proceeded with an open approach, due to surgeon's preference, followed by an uneventful post-operative course.

Conclusion

LCA is a recently described vascular tumor of the spleen, associated with other malignancies, and may itself also have malignant potential. Its diagnosis is very challenging to make pre-operatively, but it should always be considered in the differential diagnosis of splenic lesions. So far, splenectomy is the gold standard treatment of vascular splenic tumors, including the LCA.

Funding

No funding was received for the present study.

Conflicts of interest

The authors declare no competing financial interests.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Blansfield JA, Goldhahn RT Jr., Josloff RK. Littoral cell angioma of the spleen treated by laparoscopic splenectomy. JSLS. 2005;9:222-4.
2. Liu YP, Cheng SM, Huang JK. Littoral cell angioma of the spleen: a case report. Chinese J Radiol. 2005;30:241-6.
3. Erçin C, Gürbüz Y, Hacıhanefioğlu A, Karakaya AT. Multiple littoral cell angioma of the spleen in a case of myelodysplastic syndrome. Hematology. 2005;10:141-4.
4. Bierenbaum J, Alapat DV, Godinez C, Park AE, Zhao XF, Baer MR. Littoral cell angioma: a correctable cause of progressive pancytopenia in a patient with myelodysplastic syndrome. Leuk Res. 2010;34:e117-9.
5. Agha RA, Fowler AJ, Saeta A, Barai I, Rajmohan S, Orgill DP et al. The SCARE statement: consensus-based surgical case report guidelines. Int J Surg. 2016;34:180-6.
6. Falk S, Stutte HJ, Frizzera G. Littoral cell angioma. A novel splenic vascular lesion demonstrating histiocytic differentiation. Am J Surg Pathol. 1991;15:1023-33.
7. Borch WR, Aguilera NS, Brissette MD, O'Malley DP, Auerbach A. Practical applications in immunohistochemistry: an immunophenotypic approach to the spleen. Arch Pathol Lab Med. 2019;143:1093-105.
8. Lin XY, Li JM, Wang QX, Feng JZ, Zhao MQ, Zhong WX, et al. Littoral cell angioma of the spleen: report of three cases and a review of the literature. Chin Med J (Engl). 2011;124:3423-6.
9. Tee M, Vos P, Zetler P, Wiseman SM. Incidental littoral cell angioma of the spleen. World J Surg Oncol. 2008;6:87.

10. Roldan-Vasquez E, Roldan-Vasquez A, Jarrin-Estupiñan X, Roldan-Crespo J. Case report: infrequent littoral cell angioma of the spleen. Int J Surg Case Rep. 2021;85:106242.
11. Cazzola M. Myelodysplastic syndromes. N Engl J Med. 2020;383: 1358-74.
12. Fianchi L, Quattrone M, Criscuolo M, et al. Extramedullary involvement in acute myeloid leukemia. A single center ten years' experience. Mediterr J Hematol Infect Dis. 2021;13:e2021030.
13. Kinoshita LL, Yee J, Nash SR. Littoral cell angioma of the spleen. Am J Roentgenol. 2000;174:467-9.
14. Tan YM, Chuah KL, Wong WK. Littoral cell angioma of the spleen. Ann Acad Med Singapore. 2004;33:524-6.
15. Schneider G, Uder M, Altmeyer K, Bonkhoff H, Gruber M, Kramann B. Littoral cell angioma of the spleen: CT and MR imaging appearance. Eur Radiol. 2000;10:1395-400.
16. Wang YJ, Li F, Cao F, Sun JB, Liu JF, Wang YH. Littoral cell angioma of the spleen. Asian J Surg. 2009;32:167-71.
17. Chourmouzi D, Psoma E, Drevelegas A. Littoral cell angioma, a rare cause of long standing anaemia: a case report. Cases J. 2009;2:9115.
18. Du J, Shen Q, Yin H, Zhou X, Wu B. Littoral cell angioma of the spleen: report of three cases and literature review. Int J Clin Exp Pathol. 2015;8:8516-20.
19. Mac New HG, Fowler CL. Partial splenectomy for littoral cell angioma. J Pediatr Surg. 2008;43:2288-90.

LETTER TO THE EDITOR

Nationwide reduction in COVID-19 mortality among patients with asthma and other chronic diseases in Mexican adults according to epidemic wave

Reducción nacional en la letalidad por COVID-19 en pacientes con asma y otras enfermedades crónicas en adultos mexicanos según la ola epidémica

Martín Bedolla-Barajas[1] and Jaime Morales-Romero[2]*

[1]Servicio de Alergia e Inmunología Clínica, Nuevo Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Jalisco; [2]Instituto de Salud Pública, Universidad Veracruzana, Instituto de Salud Pública, Xalapa, Veracruz. Mexico

At the beginning of the pandemic, the available information suggested that asthma did not appear to increase lethality from COVID-19;[1] instead, chronic conditions such as chronic obstructive pulmonary disease (COPD), diabetes, and hypertension, among others, were associated with a higher risk of death[1]. The differences in mitigation and containment strategies adopted by each country may have contributed to the variations observed in COVID-19 lethality. Therefore, we conducted a study aimed at analyzing the trend in COVID-19 lethality in patients with asthma and comparing its behavior with that observed in other chronic diseases.

By analyzing data from the COVID-19 Epidemiological Surveillance System in Mexico (February 2021 to August 2022), we compared COVID-19 lethality in patients with asthma and other chronic diseases at each peak point of the five epidemic waves. Our research adhered to the ethical principles for using health databases proposed by the Declaration of Helsinki.

The highest overall COVID-19 lethality was observed in chronic kidney disease (6,953/22,613; 30.7%), followed by COPD (3,974/15,660; 25.4%), cardiovascular disease (4,515/22,937; 19.7%), diabetes (33,996/220,161; 15.4%), hypertension (41,279/303,602; 13.6%), and obesity (17,721/238,806; 7.4%), with the lowest lethality being observed in asthma (1,501/46,155; 3.3%).

Overall, all the chronic diseases analyzed showed a trend toward decreasing lethality (Table 1). In the case of asthma, during the peak of the 1st wave, lethality rate was 9.3%, and then showed a sustained trend toward reduction, which became noticeable from the 2nd to the 5th wave. In contrast, the other diseases showed a slight increase in lethality during the 2nd wave, followed by a significant decrease from the 4th wave onward.

During the 5 epidemic waves in Mexico, asthma clearly showed lower lethality from COVID-19 vs the other diseases analyzed. This event puts into perspective that patients with asthma may have a lower risk of acquiring SARS-CoV-2[2] infection, but they may have a higher risk of dying from COVID-19 or of dying vs other chronic diseases[1]. Therefore, deaths in this group may have primarily occurred in patients with more severe or uncontrolled asthma[3]. The inflammatory profile of asthma patients, the use of inhaled steroids for asthma control, or the use of COVID-19 vaccines are some of the limitations that should be considered when interpreting these findings.

***Correspondence:**
Martín Bedolla-Barajas
E-mail: drmbedbar@gmail.com

Date of reception: 13-11-2022
Date of acceptance: 20-12-2022
DOI: 10.24875/CIRUE.M22000779

Cir Cir (Eng). 2024;92(6):815-816
Contents available at PubMed
www.cirugiaycirujanos.com

Table 1. Reduction in COVID-19 lethality in patients with asthma and other chronic diseases in Mexican adults (February 2021 to August 2022)

Disease	Pandemic wave					p*
	I (n/N) % (95%CI)	II (n/N) % (95%CI)	III (n/N) % (95%CI)	IV (n/N) % (95%CI)	V (n/N) % (95%CI)	
Respiratory						
Asthma	431/4649 9.3% (8.4 to 10.1%)	536/6683 8.0% (7.4 to 8.7%)	317/5508 5.8% (5.1 to 6.4%)	200/21,597 0.9% (0.8 to 1.1%)	17/7,718 0.2% (0.1 to 0.3%)	< 0.0001
COPD	973/2659 36.6% (34.8 to 38.4%)	1,320/3468 38.1% (36.5 to 39.7%)	740/2292 32.3% (30.4 to 34.2%)	831/5128 16.2% (15.2 to 17.2%)	110/2113 5.2% (4.3 to 6.2%)	< 0.0001
Metabolic						
Obesity	4955/33,745 14.7% (14.3 to 15.1%)	7106/46,766 15.2% (14.9 to 15.5%)	3741/36,227 10.3% (10.0 to 10.6%)	1780/88,261 2.0% (1.9 to 2.1%)	139/33,807 0.4% (0.3 to 0.5%)	< 0.0001
Diabetes	8121/29,820 27.2% (26.7 to 27.7%)	12,756/46,803 27.3% (26.9 to 27.7%)	7119/33,769 21.1% (20.7 to 21.5%)	5418/75,774 7.2% (7.0 to 7.3%)	582/33,995 1.7% (1.6 to 1.8%)	< 0.0001
Cardiovascular						
Hypertension	9569/37,381 25.6% (25.2 to 26.0%)	16,082/61,952 26.0% (25.6 to 26.3%)	8,162/42,358 19.3% (18.9 to 19.6%)	6,737/112,026 6.0% (5.9 to 6.2%)	729/49,885 1.5% (1.4 to 1.6%)	< 0.0001
CVD	1085/3,459 31.4% (29.8 to 32.9%)	1497/4695 31.9% (30.6 to 33.2%)	822/2920 28.2% (26.5 to 29.8%)	976/8314 11.7% (11.0 to 12.4%)	135/3549 3.8% (3.2 to 4.4%)	< 0.0001
Renal						
CKD	1439/3403 42.3% (40.6 to 43.9%)	2112/4666 45.3% (43.8 to 46.7%)	1391/3553 39.2% (37.5 to 40.8%)	1781/8078 22.0% (21.1 to 23.0%)	230/2913 7.9% (6.9 to 8.9%)	< 0.0001

CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; 95%CI: 95% confidence interval for proportions calculated by the Wald method; CKD: chronic kidney disease; n: subjects who died from COVID-19; N: total subjects with the specified comorbidity.

*Mantel-Haenszel chi-square test for trend.

Source: Open data from the General Directorate of Epidemiology of the Government of Mexico. Available at: https://www.gob.mx/salud/documentos/datos-abiertos-152127. Consulted on August 12, 2022.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Morales-Romero J, Bedolla-Barajas M. Asthma is not a risk factor for severity of SARS-CoV-2 infection in the Mexican population. J Asthma. 2022;59:2314-21.
2. Sunjaya AP, Allida SM, Di Tanna GL, Jenkins CR. Asthma and COVID-19 risk: a systematic review and meta-analysis. Eur Respir J. 2022;59:2101209.
3. Dolby T, Nafilyan V, Morgan A, Kallis C, Sheikh A, Quint JK. Relationship between asthma and severe COVID-19: a national cohort study. Thorax. 2023;78:120-7.

LETTER TO THE EDITOR

Extracorporeal membrane oxygenation (ECMO) in lung transplantation

Oxigenación por membrana extracorpórea (ECMO) en trasplante pulmonar

Enrique Monares-Zepeda[1], Uriel Chavarria-Martínez[2], Sergio S. Sánchez-Salazar[2], Guillermo Cueto-Robledo[3,4], Christopher Barrera-Hoffmann[5], and Manuel Wong-Jaén[6]*

[1]Servicio de Medicina Crítica Obstétrica, Hospital General de México Dr. Eduardo Liceaga, Mexico City; [2]Medicina Interna, Medicina Crítica y Neumología, Hospital de Alta Especialidad Christus Muguerza, Monterrey, Nuevo León; [3]Urgencias Cardiopulmonares, Hospital General de México Dr. Eduardo Liceaga, Mexico City; [4]Clínica de Circulación Pulmonar, Hospital General de México Dr. Eduardo Liceaga, Mexico City; [5]Medicina Crítica, Hospital General Regional No. 1 Lic. Ignacio García Téllez, Mérida, Yucatán; [6]Cirugía Torácica y Trasplantes, HospitaL de Alta Especialidad Christus Muguerza, Monterrey, Nuevo León. Mexico

To the Editor,

Since the first report of intraoperative extracorporeal membrane oxygenation (ECMO) during a lung transplant in 1978, ECMO has become an essential component of transplant protocols[1]. There are two main approaches: one aims to avoid extracorporeal circulation entirely, while the other adopts a protocol of initiating ECMO before beginning the transplant[2].

Major centers with extensive experience that favor ECMO in transplants argue four significant advantages[3], as shown in figure 1. While it is preferable to perform a lung transplant without any form of extracorporeal support[4], this approach significantly limits the cases, excluding patients at high risk of right ventricular failure and requieing rushed procedures in critical situations. The use of extracorporeal techniques broadens the range of patients who can benefit from transplantation. ECMO offers several advantages over cardiopulmonary bypass, including reduced inflammation, the ability to be used both preo- and postoperatively, and the suspension of heparin during surgery. In a global registry of 800 patients, 50% underwent transplantation without extracorporeal support, 20% with cardiopulmonary bypass, and 30% with ECMO. Although cases without extracorporeal support had the best prognosis, those requiring extracorporeal support were more complex, and when comparing cases of similar complexity, the prognosis for ECMO-supported cases was much better than for those with cardiopulmonary bypass[4].

The use of perioperative ECMO reduces the incidence of primary graft dysfunction, possibly because it avoids cardiopulmonary bypass, resulting in a lower systemic inflammatory response and better control of hypoxia and reperfusion levels. The treatment of choice for moderate to severe dysfunction is to place the patient on ECMO[5], which is its main indication post-transplant; delaying this therapy beyond 48 hours significantly increases morbidity and mortality. On the other hand, perioperative ECMO complicates the classification of dysfunction severity, as the criterion of hypoxemia cannot be used.

In conclusion, both approaches have advantages. Although vaoiding ECMO reduces the complexity and costs of the process, it limits the number of candidates to those at low risk of right ventricular failure and with good functional oxygen reserve. Using ECMO allows the inclusion of more complex patients and is a better option vs cardiopulmonary bypass. It is also highly beneficial

***Correspondence:**
Enrique Monares Zepeda
E-mail: enrique_monares@hotmail.com

Date of reception: 05-01-2024
Date of acceptance: 23-03-2024
DOI: 10.24875/CIRUE.M24000780

Cir Cir (Eng). 2024;92(6):817-818
Contents available at PubMed
www.cirugiaycirujanos.com

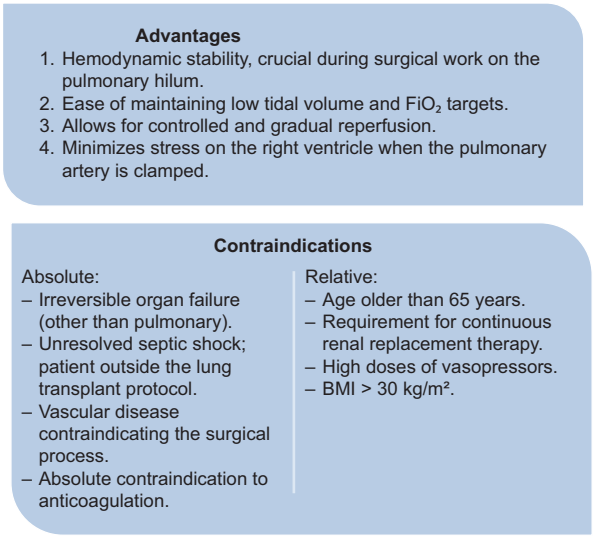

Figure 1. *Advantages and Contraindications of ECMO in Lung Transplantation.*

in complications such as primary graft dysfunction. Large lung transplant programs should consider ECMO as an option for pre-, intra-, and postoperative use.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Additionally, the authors have acknowledged and followed the recommendations outlined in the SAGER guidelines, depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in the writing of this manuscript [figures, graphs, tables or foot notes].

References

1. Faccioli E, Inci I. Extracorporeal life support as a bridge to lung transplantation: a narrative review. J Thorac Dis. 2023;15:5221-31.
2. Expert Consensus Panel. Hartwig M, Van Berkel V, Bharat A, Cypel M, Date H, Erasmus M, et al. The American Association for Thoracic Surgery (AATS) 2022 Expert Consensus Document: The use of mechanical circulatory support in lung transplantation. J Thorac Cardiovasc Surg. 2023;165:301-26.
3. Andreasson A, Hoetzenecker K. Commentary: Why a routine venoarterial extracorporeal membrane oxygenation support strategy is a good idea in lung transplantation. J Thorac Cardiovasc Surg. 2022;164:1363-4.
4. Loor G, Huddleston S, Hartwig M, Bottiger B, Daoud D, Wei Q, et al. Effect of mode of intraoperative support on primary graft dysfunction after lung transplant. J Thorac Cardiovasc Surg. 2022;164:1351-61.e4.
5. Snell GI, Yusen RD, Weill D. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading — A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36:1097-103.

LETTER TO THE EDITOR

Nutritional care of the patient after metabolic surgery: a misunderstood discipline

Cuidado nutricional del paciente posterior a cirugía metabólica: una disciplina incomprendida

*Emily S. Valadez-Méndez[1], Sol Ramírez-Ochoa[1], Leonardo Perales-Guerrero[1], Shaúl A. Navarro-Lara[1], Liliana B. Alcázar-García[1], Carlos J. Moreno-Bernardino[1], Javier Solís-Estrada[1], Silvia G. Esquivel-Razo[1†], Miguel A. Buenrostro-Ahued[1], and Enrique Cervantes-Pérez[1,2]**

[1]*Department of Internal Medicine, Hospital Civil de Guadalajara "Fray Antonio Alcalde", Health Sciences University Center, Universidad de Guadalajara, Guadalajara;* [2]*Centro Universitario de Tlajomulco, Universidad de Guadalajara, Tlajomulco de Zúñiga. Jalisco, México*

To the Editor:

Metabolic and bariatric surgery (MBS) is an efficient method of weight loss and has been linked to improvements in health conditions and quality of life related to obesity as well as a decrease in mortality. Reduced micronutrient absorption and changes in gut-brain hormonal control are two post-surgical anatomical and physiological changes that have a wide range of health-related effects. For long-term success, patients require continual evaluation of their physical and mental health. Internists, especially primary care physicians, are in a perfect position to monitor for non-serious consequences in the short and long term, adjust therapy of chronic diseases as necessary, and keep an eye on changes in mental health. In the United States, about 260,000 MBS treatments were carried out each year as of 2019[1]. In 2015, between 30% and 60% of all MBS procedures in the United States were laparoscopic Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (SG), respectively. The average weight loss after MBS is 25% to 30% of pre-operative weight 1 year after SG and 30-35% after RYGB[2].

To maximize weight reduction, ameliorate coexisting diseases, lower the chance of gaining weight again, prevent malnutrition, and lessen gastrointestinal side effects, long-term dietary management is necessary. Long-term impacts of physiological and hormonal changes following MBS include weight loss, dietary intake and absorption, medication management, gastrointestinal problems, mental health, and reproductive health. Due to this, follow-up care should be interdisciplinary and involve primary care clinicians, the bariatric surgery team, mental health specialists, and dietitians[3]. Recommendations for macro- and micronutrient monitoring and supplementation after MBS are summarized in table 1[2,4]. Severe nutritional complications after bariatric surgery are potentially disabling and life-threatening, but they are often easily preventable. Despite this, it is challenging to determine the frequency of nutritional deficiencies brought on by surgery, and their reported prevalence varies widely depending on the patient's compliance with micronutrient supplements, amount of weight loss, pre-existing nutritional status, eating habits, measurement techniques, quality and length of follow-up, and type of bariatric procedure. After surgery, deficiencies can appear or worsen in as many as 60% of patients at 6 months and 100% of patients at 2 years. Due to this, nutritional post-bariatric efforts seem to be underrecognized, misunderstood, and underappreciated[5].

Treatment of nutrition deficiencies should begin before surgery in morbidly obese bariatric surgery patients since it is a challenging problem both pre- and postoperatively. Adequate and proper nutrition care and eating habit change are two of the most crucial

***Correspondence:**
Enrique Cervantes-Pérez
E-mail: enrique.cervantes@academico.udg.mx

Date of reception: 18-10-2022
Date of acceptance: 16-11-2022
DOI: 10.24875/CIRUE.M22000803

Cir Cir (Eng). 2024;92(6):819-820
Contents available at PubMed
www.cirugiaycirujanos.com

Table 1. Recommendations for macronutrients and micronutrients monitoring and supplementation after MBS

Macro and Micronutrient	Monitoring/Supplementation
Proteins	At least 60 g of protein daily (up to 0.8-1.2 g/kg of body weight), during periods of active weight reduction.
Vitamin A	Follow-up at post-operative months 1, 3, 6, and 12 and then once a year after RYGB, if necessary (e.g., signs of post-operative protein deficiency). Dose: 5000-10,000 IU/day
Vitamin D	Evaluate at months 1, 3, 6, and 12 following surgery, then every year. Dose: 3000 IU of Vitamin D daily from all sources to maintain a level over 30 ng/mL.
Vitamin E, K	Monitor at post-operative month 12 after RYGB and when clinically indicated. Dose: 15 mg of Vitamin E per day (19 mg in lactating patients); 90-120 mcg of Vitamin K daily.
Vitamin B12	Monitor B12, methylmalonic acid, with or without homocysteine at post-operative months 3, 6, and 12. Dose: 500-1000 mcg/day orally or 1000 mcg every month intramuscularly.
Vitamin B1	Monitor if clinically indicated (encephalopathy and ataxia) or risks are present (alcohol misuse or emesis). Dose: 50-100 mg daily.
Iron	Follow-up at post-operative months 1, 3, 6, and 12, then annually. Dose: 18 mg/d for men and women aged ≥ 51 years; 45-60 mg/d for women aged < 51 years.
Folate	Monitor if there is macrocytic anemia or mild pancytopenia. Dose: 400-800 mcg; 800-1000 mcg for women of childbearing age.
Zinc	Monitor levels if there is chronic diarrhea or dermatitis. Dose: 11 mg/d for men; 8 mg daily for women.
Copper	Monitor if clinically indicated (myeloneuropathy). Dose: 1 mg of copper per 8-15 mg of zinc per day to prevent copper deficiency.
Selenium	Monitor if there is skeletal muscle dysfunction or cardiomyopathy. Dose: 100 mcg daily.

MBS: metabolic and bariatric surgery; RYGB: roux-en-Y gastric bypass.

parts of post-bariatric follow-up. If patients receive multivitamin supplements, macroelements, and microelements on a regular basis, in addition to being regularly monitored, severe nutrition shortages can be avoided. Although effective collaboration between surgeons, internists, psychiatrists, and dietitians is necessary for multidisciplinary supervision, the patient is the key player in the fight against malnutrition, weight gain, and other consequences following bariatric surgery.

Acknowledgments

The authors would like to thank Dr. Silvia for her tireless work in the Department of Internal Medicine. You are an outstanding physician for your sensitivity to patient care and outstanding performance in medicine.

Funding

No external funding was received to support this work.

Conflicts of interest

The authors declare that there are no competing interests.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. American Society for Metabolic and Bariatric Surgery. Estimate of Bariatric Surgery Numbers, 2011-2019; 2021. Available from: https://asmbs.org/resources/estimate-of-bariatric-surgery-numberson27september2022
2. Mechanick JI, Apovian C, Brethauer S, Garvey WT, Joffe AM, Kim J, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures-2019 update: cosponsored by American association of clinical endocrinologists/American college of endocrinology, the obesity society, American society for metabolic and bariatric surgery, obesity medicine association, and American society of anesthesiologists-executive summary. Endocr Pract. 2019;25:1346-59.
3. Sioka E, Tzovaras G, Perivoliotis K, Bakalis V, Zachari E, Magouliotis D, et al. Impact of laparoscopic sleeve gastrectomy on gastrointestinal motility. Gastroenterol Res Pract. 2018;2018:4135813.
4. Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American society for metabolic and bariatric surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients. Surg Obes Relat Dis. 2017;13:727-41.
5. Nuzzo A, Czernichow S, Hertig A, Ledoux S, Poghosyan T, Quilliot D, et al. Prevention and treatment of nutritional complications after bariatric surgery. Lancet Gastroenterol Hepatol. 2021;6:238-51.