ORIGINAL ARTICLE

Results of the fecal immunochemical test in a colorectal cancer screening program in Mexico

Resultados de la prueba inmunoquímica fecal en un programa de escrutinio para cáncer colorrectal en México

*Shareni Gálvez-Ríos[1], Sergio Sobrino-Cossío[2], Ana Siu[3], Marlene Chaurand[4], Miguel Abdo-Francis[5], Aurelio López-Colombo[6], Eduardo Fenocchi[7], Elymir Galvis-García[2,8], Óscar Teramoto-Matsubara[9], Arturo Meixueiro-Daza[1], Peter Grube-Pagola[1], Paulo C. Gómez-Castaños[1], Olivia Rascón-Sosa[1], Xaira J. Rivera-Gutiérrez[1], Orestes Cobos-Quevedo[1], Enrique Pérez-Luna[1], and José M. Remes-Troche[1]**

[1]Physiology Laboratory, Institute of Medical-Biological Research, Universidad Veracruzana, Veracruz; [2]Endodoscopy Department, Hospital Ángeles del Pedregal, Mexico City; [3]Endoscopy Department, Clínica Médica Siu, Tuxtla Gutiérrez, Chiapas; [4]Endoscopy Department, Hospital Regional de Alta Especialidad de la Península de Yucatán, Yucatán; [5]Endoscopy Department, Hospital Ángeles Acoxpa, Mexico City; [6]Directorate of Teaching, Specialty Hospital, Centro Médico Nacional Manuel Ávila Camacho, Instituto Mexicano del Seguro Social, Puebla de Zaragoza, Puebla. Mexico; [7]Department of Endoscopy, Digestive Cancer Center, Instituto Nacional del Cáncer, Montevideo, Uruguay; [8]Endoscopy Department, Hospital General de México Dr. Eduardo Liceaga, Mexico City; [9]Endoscopy Department, Centro Médico ABC, Mexico City. Mexico

Abstract

Background: *Colorectal cancer (CRC) is one of the main five causes of morbidity and mortality by oncologic diseases in our country and worldwide. Recently, fecal immunochemical test (FIT) has proven to be a non-invasive screening test that allows to select patients most likely to have a pre-malign lesion to perform a colonoscopy.* **Objective:** *The aim of the study was to report the findings of a CRC screening program using FIT in our country population.* **Method:** *A multicentric study was performed, by inviting open population older than 50 years to participate in a CRC screening. Quantitative FIT specific for human hemoglobin was used, with a cut point of 100 ng/mL or higher to consider as positive. Those patients with positive results were asked to undergo a colonoscopy. In the cases where polypoid lesions were found, biopsies were performed.* **Results:** *In total, 751 FIT was processed, and 51 (6.8) of those were positive, with a rate of 15.9 premalign lesions for 1000 individuals, and 1.3 patients with CRC for every 1000.* **Conclusions:** *The present study matches worldwide reports, supporting the initiative of establishing a formal and standardized CRC screening program in the public health sector.*

Keywords: *Colorectal cancer. Screening. Fecal immunochemical test.*

Resumen

Antecedentes: *El cáncer colorrectal (CCR) es una de las cinco primeras causas de morbimortalidad por cáncer en nuestro país y en todo el mundo. La prueba inmunoquímica fecal (FIT, fecal immunochemical test) es una herramienta de tamizaje no invasiva que permite seleccionar a los sujetos con mayor probabilidad de lesión premaligna en la colonoscopia.* **Objetivo:** *Reportar los resultados del programa de escrutinio para CCR mediante FIT en población abierta en México.* **Método:** *Estudio multicéntrico nacional en población abierta mayor de 50 años a través de medios de difusión masiva para participar en un programa de escrutinio de CCR. Se utilizó FIT cuantitativa específica para detectar hemoglobina*

Correspondence:
*José M. Remes-Troche
Iturbide s/nCol. Centro CP. 91700,
Veracruz, Ver. México
E-mail: jose.remes.troche@gmail.com

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humana con un punto de corte de 100 ng/mL (prueba positiva). Se realizó colonoscopia a los positivos. Se tomaron biopsias dirigidas de las lesiones premalignas/cáncer para análisis histopatológico. **Resultados:** *Se procesaron 751 FIT, de las cuales 51 (6.8%) fueron positivas, con una tasa de 15.9 lesiones premalignas por cada 1,000 sujetos evaluados, y 1.3 pacientes con CCR por cada 1,000 pacientes.* **Conclusiones:** *Nuestro estudio concuerda con lo reportado en la literatura mundial, apoyando así la iniciativa de fomentar el establecimiento de un tamizaje formal y estandarizado dentro del sector de salud pública.*

Palabras clave**:** *Cáncer colorrectal. Escrutinio. Prueba inmunoquímica fecal.*

Introduction

Colorectal cancer (CRC) is the third cause of cancer morbidity and mortality in the world, both in men and women. According to the GLOBOCAN registry, estimated incidence in 2012 was 17.2 new cases per 100,000 population, with a mortality rate of 8.4/100,000, which increased to 9.2% in 2018[1-3].

In the American continent, estimated incidence is 246,000 new cases, with a mortality of approximately 112,000 persons every year. Incidence and mortality rates in Latin America and the Caribbean are lower than in the United States of America and Canada, except for Uruguay, Argentina, Barbados, and Trinidad and Tobago, whose figures are higher than in the rest of Latin America and similar to those in North America. In Mexico, CRC is ranked third in incidence among oncological diseases in both genders, and fifth in mortality in men and sixth in women[1,2].

Cancer incidence and mortality are rapidly growing throughout the world. According to the World Health Organization (WHO) 2015 estimates, CRC represented the third cause of death in general and the second cause of cancer deaths in adults older than 70 years. The GLOBOCAN registry estimated for 2018 a detection of 18.1 million new cases and 9.6 million cancer deaths in the world. The American continent accounts for 21% of the incidence of cancer and for 14.4% of its mortality[3,4].

The differences in mortality patterns can be explained by the differences in health infrastructures, treatment and access to medical care, and higher diagnostic costs[4]. Countries transitioning to higher levels of human development, such as those in Central and South America and Eastern Europe, have shown an increase in the incidence of CRC. Countries of Central and South America (including Cuba) are undergoing rapid sociodemographic and epidemiological changes, and the nature of health problems is transitioning from infectious diseases to chronic diseases, including cancer[5]. Recent estimates indicate that 15% of colon cancers and 8% of rectal cancers will occur in Latin America (including the Caribbean)[4,5].

CRC can be divided into hereditary and sporadic. In most cases, it shows a progressive development from a premalignant lesion (adenomatous), which after a period of about 10 years gives rise to a malignant lesion, which is known as “adenoma-carcinoma sequence”[6,7]. Therefore, given to the presence of a “window period”, it is possible for premalignant lesions, and even early-stage cancer, to be timely detected and treated, which has a positive impact on life expectancy and health sector expenditure.

It is important to remember that CRC only has symptoms at advanced stages of the disease. In general, the patient seeks medical care in the presence of warning signs (usual clinical diagnosis). The magnitude of hemorrhage is variable and is a consequence of trauma to the neoplastic tissue due to the passage of stools through the colon, that is, it is a warning sign associated with tumor growth. It is regarding this problem that lies the importance of establishing screening programs for the general population, in asymptomatic, older than 50 years individuals. The tests used in screening programs should ideally have a low cost, good sensitivity and specificity, be easy to apply, non-invasive, and have good adherence[8-10].

The tests used for CRC screening in different countries include fecal occult blood tests, flexible rectosigmoidoscopy, colonoscopy, and computed tomography colonography. However, only guaiac-based fecal occult blood test and flexible sigmoidoscopy have been shown to reduce the incidence and mortality of this type of cancer in randomized and controlled trials[11-16].

The least invasive, less costly, and therefore most accepted diagnostic procedures among the population are fecal occult blood tests. The most recent advance for evaluating fecal occult blood is fecal immunochemical test (FIT). Its predecessor, the guaiac test, is based on the detection of peroxidase in blood, and for this reason, it can also nonspecifically react to

peroxidase present in foods such as red meat, fruits, and some vegetables and can also yield false negative results if the patient is consuming high doses of Vitamin C, which blocks peroxidase reaction. On the other hand, FIT is based on a specific antigen-antibody reaction for detecting human globin and has the advantage of being more specific for the lower gastrointestinal bleeding, since upper gastrointestinal tract globin is degraded by digestive enzymes before reaching the lower tract[13].

There are two types of FIT: qualitative and quantitative. The former yields a positive or negative result, while the latter indicates globin concentration. Quantitative FIT is the test of choice for population screening, since it offers the advantage of selecting a cutoff point for test positivity depending on the characteristics of the equipment itself (manufacturer recommendations) and the risk level of the population being screened and, therefore, those patients who are candidates for colonoscopy exploration can more reliably be selected, that is, it allows the clinician to select a balance between sensitivity and specificity depending on the population under study and on available endoscopic resources[13-16].

At present, there is no universal recommendation for CRC screening, but most guidelines and consensuses recommend starting it from 50 years of age onward in low-risk people and at age 40 in high-risk individuals. Worldwide, the procedure that is most widely recommended and used is colonoscopy; however, it is important to point out that this is more common in developed countries, while in developing countries, the most common recommendation for screening is fecal occult blood identification. In Mexico, the CRC screening program based on fecal occult blood is aimed at people with low risk, older than 50 years, and performing the test (guaiac or immunochemistry) annually is recommended; in case, this test shows anomalies, colonoscopy should be carried out[14-16].

The purpose of this study is to report the findings of a screening program for CRC using FIT in a sample of the general population in Mexico to determine the prevalence of early lesions associated with CRC.

Methods

A cross-sectional, prospective, descriptive, and multicenter study was carried out, with the participation of the States of Mexico, Veracruz, Chiapas, Yucatán and Puebla, which was started in May 2015 and concluded in January 2016. By announcing the study at health centers of different levels of care and through mass media, general population older than 50 years of age was invited to participate in a screening program for colon cancer. Patients with a personal history of CRC, inflammatory bowel disease, melena, hemorrhoids with active bleeding, or warning signs, such as unjustified weight loss, were excluded from the study. Patient personal data were collected. An identification number was provided, by means of which the device for taking the stool sample was labeled, and the process for sample collection at home was explained. Once the sample was collected, it was stored in refrigeration and later was sent to a reading center in Mexico City, where analysis of the samples was carried out in a centralized manner. A quantitative FIT specific for human hemoglobin (Hb) was performed, which was processed using the OC FIT-CHEK® automated test method (Polymedco-Endomedica S.A. de C.V.)[17,18]. The cutoff point was established at 100 ng/mL for the test to be considered positive, according to the supplier's recommendations. Patients with positive results were contacted for the performance of a colonoscopy, which was carried out once informed consent was granted and after intestinal preparation.

In the cases where polyps were identified during colonoscopy or with suspected malignancy, biopsies were collected for subsequent histopathological analysis.

The study protocol was approved by the Institutional Ethics Committee and patients' rights continued to be safeguarded in accordance with the Declaration of Helsinki. There was no financial support or remuneration for the study subjects, who voluntarily agreed to participate.

Descriptive statistics were used for analysis, and for the comparison of variables with abnormal distribution between groups, Mann–Whitney's U-test was used. The SPSS statistical package, version 11.00, was used, and statistical significance was established with p-value < 0.05.

Results

The use of 1000 quantitative FITs was projected, out of which 900 (90%) were applied and, finally, 751 (75%) were returned and processed (Fig. 1). Of the processed tests, 51 were positive (≥ 100 ng/mL), that is, 6.8% (95% confidence interval: 5.5-8.2), with variations according to regions, from 4.2% in Yucatan to 10.2% in Mexico City, depending also on total

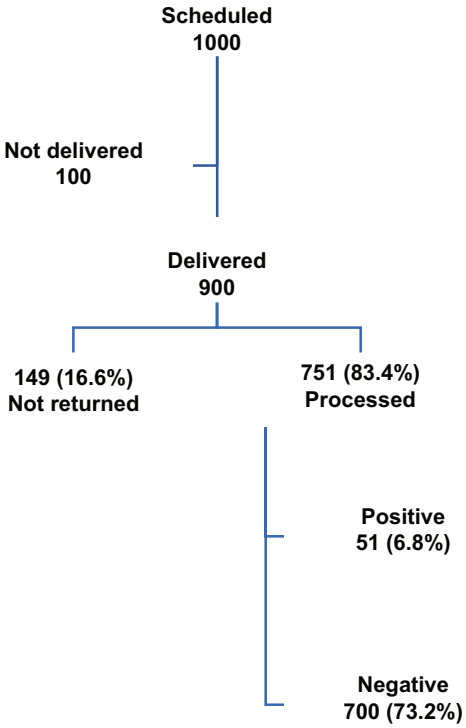

Figure 1. *Projection and processing after 1000 quantitative fecal immunochemical tests were applied for fecal occult blood detection.*

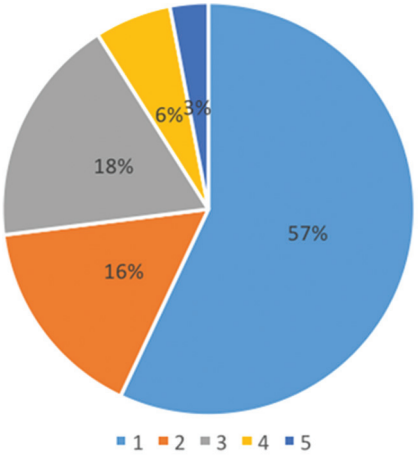

Figure 2. *Percentage of samples analyzed by each State of the Republic. 1: Veracruz, Veracruz. 2: Mexico City. 3: Tuxtla Gutiérrez, Chiapas. 4: Mérida, Yucatán. 5: Puebla, Puebla.*

Table 1. Fecal immunochemical tests (FIT) for occult blood detection and colonoscopies that were performed

State	Performed FITs n (%)	Positive FITs n (%)	Performed colonoscopies
Tuxtla Gutiérrez, Chiapas	133 (18)	12 (9)	12
Mexico City	118 (16)	12 (10.2)	8
Veracruz, Veracruz	430 (57)	25 (5.8)	18
Puebla, Puebla	22 (3)	0 (0)	0
Merida, Yucatan	48 (6)	2 (4.2)	2
Total	751	51 (6.8)	40 (78.4%)

number of samples provided by each region (Fig. 2 and Table 1). Four hundred and forty-seven of total included subjects (59.5%) were women and mean age was 57 years, with an average body mass index of 27 kg/m^2 (Table 2).

All 51 patients with positive results were contacted and 40 (78.4%) of them underwent follow-up with colonoscopy. Among the 40 endoscopic procedures that were performed, in five (12.5%), there were no findings of colorectal lesions. For analysis, subjects were divided in two groups according to the colonoscopy result: patients with findings of non-neoplastic lesions and patients with neoplastic lesions (polyps without and with malignant potential, and already established cancer).

In 20 patients, there were only non-neoplastic findings, such as proctitis (2), hemorrhoidal disease (12), diverticular disease (5), non-specific chronic ulcerative colitis (2), angiodysplasia (2), and amoebic colitis (2). In 15 patients, there were neoplastic findings, such as polyps with no atypia (2), 10-mm and 4-mm hyperplastic polyps in the rectum (1), < 5-mm tubular adenomas without dysplasia (4), tubular adenomas with mild dysplasia (4), tubulovillous adenomas with mild dysplasia (2), serrated adenoma (1), and moderately-differentiated invasive adenocarcinoma of the rectum (1). In the latter group of patients, non-neoplastic findings were also reported, such as diverticula (2), hyperplastic polyp (1), chronic non-specific ulcerative colitis (2), and anal fissure (1).

Of 751 processed tests, 51 (6.8%) were positive, but only in 40 of these patients was a colonoscopy carried out, with premalignant lesions being found in 11 of them, which corresponds to 1.4% of total subjects included in the study, and there was one patient with

Table 2. Sociodemographic characteristics of the population sample

	Veracruz, Veracruz	Tuxtla Gutiérrez, Chiapas	Mexico City	Mérida, Yucatán	Puebla, Puebla	Total
N (%)	430 (57%)	133 (19%)	118 (17%)	48 (6%)	22 (3%)	751 (100%)
Age, years (SD)	59.9 (5.2)	56.3 (4.4)	57.9 (9.3)	55.2 (5.5)	56.1 (4.3)	57.0 (5.7)
Males	140	50	80	22	12	304
Male: female ratio	0.48	0.6	2.1	0.84	1.2	0.68
Body mass index, kg/m^2	28.2	27.0	26.4	27.2	26.3	27.0

SD: standard deviation.

Table 3. Average hemoglobin in feces (ng/mL) on fecal immunochemical test (FIT) for occult blood detection

Colonoscopies	Positive FITs				p
Total	Total	No colorectal lesions	Non-neoplastic lesions	Neoplastic lesions	
N	40	5	20	15	
Percentage	100	12.5	50	37.5	
Hemoglobin (ng/mL)	842	245	609.9	1350,2	0.014
Standard deviation	916	213	604.9	1186.6	

Table 4. Comparisons between hemoglobin figures in feces according to histopathological findings

Findings	P (Mann–Whitney's U-test)
Negative versus positive	0.027
Negative versus neoplastic lesions	0.001
Neoplastic versus non-neoplastic lesions	0.014

an invasive adenocarcinoma (0.13%). A rate of 15.9 patients with neoplastic lesions with potential for malignancy and cancer per 1000 evaluated subjects was calculated, as well as 1.3 patients with CRC per 1000 evaluated subjects, according to the previous studies' methodology.

Regarding the comparison of Hb quantification between groups, a statistically significant difference was reported between patients with positive FIT without colonoscopy findings of colorectal lesions and those with positive FIT in whom, there were colonoscopy findings, both neoplastic and non-neoplastic (p = 0.027, Mann–Whitney's U-test). Similarly, when Hb figures were compared between patients without endoscopic findings and patients with only neoplastic findings, an even larger statistical significance was recorded (p = 0.001, Mann–Whitney's U-test). A significant difference was demonstrated when Hb levels were compared between patients with neoplastic findings and subjects with non-neoplastic findings (p = 0.014, Mann–Whitney's U-test) (Tables 3 and 4).

Discussion

At present, there is enough evidence worldwide for asserting that FIT is more sensitive and specific for the detection of neoplastic colorectal lesions than the guaiac test, and that it also favors higher adherence to screening programs due to its practicality, cost-benefit ratio, and non-invasiveness[13]. In this study, for the first time in Mexico, we demonstrated that this test should be used in the general population throughout the country, since we found that 6.8% of tests are positive and that 1.4% and 0.13% of our population might have premalignant lesions or invasive adenocarcinoma, respectively.

In 1996, a pilot study was carried out in Uruguay, with the first screening with FIT being performed in asymptomatic population of Latin America, a model on which we based ourselves for the development of the present study[19]. They prospectively included 1000 asymptomatic users of Uruguayan public health

Table 5. Comparison of results between countries according to the world literature

	Uruguay 199619	Uruguay 200620	Thailand 201313	Mexico 2015
FIT				
Total number	1000	60,405	127,301	900
Processed	805 (8.5%)	56,262 (93.1%)	80,012 (62.9%)	751 (83.4%)
Positive	117 (14.6%)	5299 (9.4%)	873 (1.1%)	51 (6.8%)
Colonoscopies	70	3234	627	40
Number of neoplastic lesions	48 (68.5%)	1266 (39.1%)	188 (29.8%)	15 (37.5%)
Number of cancer cases*	No reportado	306 (9.4%)	23 (3.7%)	1 (2.5%)
Detection of advanced neoplasm per 1,000 cases*	No registrado	14.6	28.7	1.3

FIT: Fecal immunochemical Test for occult blood detection.
*Percentage with regard to the number of performed colonoscopies.

services, older than 50 years and without personal or family history of CRC (average risk). Eight hundred and five participants (80.5%) completed the study and, of them, 14.6% (117) were positive, with colonoscopy thus being indicated, which was carried out in 70 patients. Seventy-five colorectal lesions were found in 48 patients, with more than half corresponding to polyps, 28 of them adenomas. Subsequently, in 2006, the Uruguayan research group published the results of a national screening program with a sample of 60,405 subjects[20]. A comparison of the results obtained in different studies is shown in table 5.

The percentage of patients with a positive FIT result and endoscopic finding of neoplastic lesion was 37.5% in our study, in contrast to the figure of 35% published in 2015 in the first screening carried out in Mexico with colonoscopy as the only screening method[21]. However, this figure widely varies throughout the world, from 16% to up to 43%, according to different studies. Similarly, the rate of advanced neoplasm detection per 1000 evaluated subjects ranges from 1.1 to 21[15,16,22]; in the present study, it was 1.3 per 1000 subjects.

Although the study by García-Osogobio et al.[21] was the first about a screening program for CRC reported in the country, it should be noted that it was carried out at tertiary care level in employees of a single private center in Mexico City and with a small sample (n = 123). Our study represents the first multicenter effort in different parts of the country and truly aimed at the general population, which represents the primary target of national screening programs for any neoplasm.

The cutoff point used in our study was 100 ng/mL, a measure based on Hb concentration in the buffer solution, as in the study carried out in Uruguay. However, international consensuses recommend standardization of the measuring unit to micrograms per gram (μg/g), that is, the amount of Hb for each gram of feces[22,23].

In various studies carried out throughout the world, average Hb quantification has been shown to increase according to the degree of lesion malignancy. For example, Fenocchi et al.[24] reported the following Hb averages according to the type of lesion: for adenoma, 320 ng/mL; for advanced adenoma, 608 ng/mL; for early cancer, 730 ng/mL; and for advanced cancer, 931 ng/mL. In our study, identifying this correlation was not possible, probably due to the small size of the entire sample in comparison with other studies, and the number of lesions that were found (only one patient with cancer). However, a statistically significant difference was demonstrated when Hb figures were compared between patients with neoplastic findings and those with non-neoplastic findings ($p = 0.014$, Mann–Whitney's U- test).

FIT sensitivity, specificity, and positive and negative predictive values for CRC detection have been reported to be 100%, 90%, 16%, and 100%, respectively, and for all neoplasms, 74%, 93%, 45%, and 98%, respectively. Fecal determination can detect 100% of CRCs and 74% of significant colorectal neoplasms[25]. On the other hand, FIT positivity rates of between 3% and 5.9% are acceptable for a population screening to be carried out[26,27]. In Japan, 6 million people (17% of eligible population) have undergone the test[27].

In developed countries (United States of America and Canada, Australia, New Zealand, and most European countries), the incidence and mortality of CRC have decreased or stabilized since the 1970s due to a reduction in exposure to risk factors, early detection and prevention, and treatment improvements, unlike what occurs in countries transitioning to higher levels of human development, such as those in Central and

South America and eastern Europe, where the presence of CRC has increased[3].

CRC has an incidence close to 5%, which is why it is considered a real public health problem. Screening programs are important tools for controlling the incidence of CRC. However, to be effective, they should target the right population. The objective is the detection of precancerous lesions and incipient CRC in an asymptomatic population with no history of cancer or precancerous lesions[28,29].

The WHO has implemented CRC screening programs in population policies. Breast cancer and CRC are the only malignancies with sufficient evidence of efficacy of their screening for preventing their occurrence or progression through proper treatment[28,29].

The rate of CRC detection can vary between 0.37 and 0.45 depending on Hb cutoff point (50-225 ng/mL), and the number of colonoscopies needed to detect one case of cancer has been reported to be 11.7 with the 100 ng/mL cutoff point[30].

Although our study represents a first major effort, it is important for some of its limitations to be mentioned. Despite being a multicenter study, a high heterogeneity can be observed in the performance of FIT and colonoscopies, and there are some referral and selection biases. On the other hand, it is important to point out that, when colonoscopy is performed, there are also multiple factors that can be difficult to control, such as the type of colonoscopy and its preparation, the technique and experience of the endoscopist or of the centers, and even the type of equipment that is used. Even so, the importance of our study lies in that the findings are similar to those reported in other places, and in the sites where more patients were recruited, Mexico City, Chiapas, and Veracruz, the positivity figures and the rate of premalignant lesions' detection were very similar.

Conclusions

In general terms, the results of our study are consistent with those reported in the world literature, thus supporting the initiative to encourage the establishment of formal screening within the public health sector. Follow-up and expansion of the sample size are required to assess the impact on long-term incidence and mortality.

Conflicts of interest

José M. Remes-Troche is member of advisory boards from Takeda Pharmaceuticals, Alfa-Wasserman, and Almirall and has served as speaker for Takeda Pharmaceuticals, Asofarma, Alfa-Wassermnan, Almirall, and Astra-Zeneca.

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Ethical disclosures

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

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 informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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