

Application of the REAL-score prognostic index in decision making in rectal cancer surgery

Aplicación del índice pronóstico REAL-score en la toma de decisiones en cirugía del cáncer de recto

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Abstract

Background: Colorectal anastomosis leak (AL) is the most feared complication of rectal cancer surgery (1-19%) as it increases morbidity and mortality and worsens oncological outcomes in terms of local recurrence and survival. The publication of the REAL-score index makes it possible to predict the risk of AL and compare the expected results with those obtained.

Method: Observational, descriptive, longitudinal and retrospective study of patients operated on for rectal cancer at the Miguel Servet University Hospital, in Zaragoza, Spain, in 2019. Statistical analysis of morbidity and mortality outcome variables and the REAL-score index using ROC curves. **Results:** Of 80 patients operated on for rectal cancer, colorectal anastomosis was performed in 52 and temporary ileostomy in 11 (21.2%). Morbidity was high (38.4%), but severe only in 7.7% (Clavien-Dindo IIIb), with no deaths. There were four dehiscences: one type B and three type C. A direct relationship between high risk of AL and the practice of temporary stoma is observed when the cut-off point of the REAL-score exceeds 14.74%.

Conclusions: REAL-score can help in decision-making in rectal cancer surgery. Above a cut-off point, the risk of AL would imply a selective ileostomy.

Keywords: Anastomotic leakage. Colorectal cancer. REAL-score.

Resumen

Antecedentes: La dehiscencia de la anastomosis colorrectal (DA) es la complicación más temida de la cirugía del cáncer de recto (1-19%), pues incrementa la morbilidad y empeora los resultados oncológicos en términos de recidiva local y supervivencia. La publicación del índice REAL-score permite predecir el riesgo de DA y comparar los resultados esperados con los obtenidos. **Método:** Estudio observacional, descriptivo, longitudinal y retrospectivo, de pacientes intervenidos de cáncer de recto en el Hospital Universitario Miguel Servet, en Zaragoza, España, en 2019. Análisis estadístico de variables resultado de morbilidad y del índice REAL-score mediante curvas ROC. **Resultados:** De 80 pacientes intervenidos de cáncer de recto, se realizó anastomosis colorrectal en 52 e ileostomía temporal en 11 (21.2%). La morbilidad fue alta (38.4%), pero grave solo en el 7.7% (Clavien-Dindo IIIb), sin ningún fallecimiento. Hubo cuatro dehiscencias: una de tipo B y tres de tipo C. Se observa una relación directa entre alto riesgo de DA y la práctica de estoma temporal cuando el punto de corte del REALscore supera el 14.74%. **Conclusiones:** El REAL-score puede ayudar en la toma de decisiones en la cirugía del cáncer de recto. Por encima de un punto de corte, el riesgo de DA implicaría ileostomía selectiva.

Palabras clave: Dehiscencia anastomótica. Cáncer de recto. REAL-score.

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Introduction

Since the year 2017, colorectal cancer has been the most frequently diagnosed neoplasm in Spain. According to estimates of the Spanish Society of Medical Oncology (SEOM), in 2020, more than 44 000 new cases were diagnosed, with one third of them being rectal in location¹. The optimal approach to colorectal cancer is currently decided within multidisciplinary teams that offer different therapeutic options based on the patient, stage, and tumor location. This has improved the outcomes in terms of local recurrence and 5-year survival. However, despite the advances made in surgical techniques, high postoperative morbidity (20% up to 30%)² is still reported, with colorectal anastomotic leakage (CAL) being the most feared complication, with an incidence rate of 10.6% in Mexico³.

CAL is a well-established concept defining a defect in the continuity of the intestinal wall in an anastomosis connecting the intra and extraluminal compartments. Its clinical presentation varies widely, ranging from asymptomatic to causing severe symptoms. Therefore, there is significant variability in reporting its incidence and the need to classify it postoperatively into several grades according to its clinical relevance and required treatment (types A, B, and C)^{4,5}. CAL increases morbidity and mortality, the length of stay, and health care spending due to the high rate of reinterventions required. CAL has also been shown to have a negative long-term impact by increasing local recurrence rates and reducing overall survival, disease-free survival, and cancer-specific survival^{6,7}.

With all the available information, currently, the surgical community is focusing its efforts on preventing CAL by identifying risk factors and implementing measures to reduce its incidence or, at least, its consequences. In this context, the REAL-score (REctal Anastomotic Leakage)⁸ was developed in June 2019, providing a simple yet accessible online resource (<https://www.real-score.org>) that quantifies the preoperative probability for developing CAL after rectal cancer surgery based on the analysis of different risk factors (Fig. 1). The REAL-score could facilitate patient management by serving as a tool for surgical planning, aiding in decision-making on when to perform colorectal resection with or without anastomosis, with or without a temporary stoma. However, despite the described potential contributions, there is no literature applying the REAL-score in their series.

The objective of our study is to apply the REAL-score prognostic index to patients undergoing rectal cancer surgery in 2019 to quantify the risk of CAL and analyze the agreement between the number of predicted leakages with the REAL-score and those observed, all within the context of investigating our clinical outcomes in terms of 30-day morbidity and mortality.

Method

This was an observational, descriptive, longitudinal, and retrospective study based on the registry of patients who underwent rectal cancer surgery from January 1 through December 31, 2019, at the Hospital Universitario Miguel Servet (HUMS), a tertiary referral center with more than 1200 acute care beds and a catchment population of more than 375 000 inhabitants. The project was approved by the Research and Innovation Commission of Sector Zaragoza II, meeting conditions of clinical research quality and applicability in the health care setting.

This study includes a complete annual series. Patients were admitted for elective surgery for curative intent rectal cancer. All patients were previously assessed by a multidisciplinary team to discuss the clinical, radiological, and pathological diagnosis of rectal cancer, staging, and therapeutic proposal following standardized criteria set by national and international specialty societies. Patients who did not give their prior written informed consent, minors younger than 18 years, and those undergoing endoscopy procedures, minimally invasive endoanal surgery, rectal amputation, pelvic exenteration, or palliative intestinal diversion were excluded from the study.

Data collection was performed from the registry of rectal cancer surgical interventions at the colorectal surgery unit of the general surgery and digestive system department of HUMS. The selected variables were entered into an Excel database registry for integration and subsequent processing (Table 1). The evaluation period ranged from the day of surgical intervention to postoperative day 30. After discharge, follow-up information was retrieved from outpatient consultation reports.

Statistical analysis was conducted using IBM-SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, United States), including descriptive statistics, with continuous variables being expressed as mean and standard deviation, and categorical variables as

Welcome to Real-Score webapp. You will be able to determine your RealScore directly through this website. The WebApp uses R as engine to determine the score of the patient.

Form

Interval from NeoAdjuvant Therapy to surgery: days

Age > 65: ☐ Yes ☐ No

Gender: ☐ M ☐ F

Smoke: ☐ Yes ☐ No

Short course RT: ☐ Yes ☐ No

Previous Abd. Surgery: ☐ Yes ☐ No

BMI:

Diabetes: ☐ Yes ☐ No

ASA: ☐ 1 ☐ 2 ☐ 3 ☐ 4

Hemoglobin: g/dl mmol/L

TNM: T N M

Anastomotic distance from anal verge: cm

Figure 1. REAL-score (REctal Anastomotic Leakage) prognostic index. Available online: <http://www.real-score.org>.

Table 1. Study variables

Epidemiological variables	Intervention variables	Follow-up variables
Health record number Gender Date of birth	Colorectal anastomosis Protective stoma	Anastomotic dehiscence
Pre-intervention variables	Post-intervention variables	Applied prognostic indices
Body mass index Smoking Diabetes mellitus Anesthetic risk (ASA) Hemoglobin Tumor staging (TNM) Distance from lesion to anal margin Previous abdominal surgery Short-course neoadjuvant radiotherapy Time since neoadjuvancy	Surgical morbidity and mortality (Clavien-Dindo surgical complication classification) Anastomotic dehiscence (ISREC grades B and C) Time elapsed until dehiscence	REAL-score

ASA: American Society of Anesthesiologists; ISREC: International Study Group of Rectal Cancer; TNM: tumor, nodes, metastasis.

frequencies and percentages. The Kolmogorov-Smirnov test was used to determine the normal distribution of continuous quantitative variables, and Levene's test was used to compare the homogeneity of variances. ANOVA (Analysis Of Variance) was used for hypothesis testing, and post hoc multiple comparison tests were conducted to determine differences between categories. An intersubject effects test was conducted to establish the relationship between the Clavien-Dindo morbidity scale and stoma, as well as with the REAL-score. To confirm the relationship between the stoma (dependent variable) and the REAL-score (independent variable), the omnibus test of the model coefficient was used, while the Hosmer-Lemeshow test was performed to make sure

that the sample data were well represented by the logistic model. The variables in the equation determined whether there was a relationship between the stoma and the REAL-score. Finally, mean comparison was performed using the non-parametric Wilcoxon test.

The cutoff point with the best discriminative power of the REAL-score for CAL was defined using analysis through ROC curves (Receiver Operating Characteristic). According to the obtained coefficients, it was considered excellent ≥ 0.90 , good = 0.80-0.90, fair = 0.70-0.80, poor = 0.60-0.70, and very limited = 0.50-0.60. The Youden index (sensitivity + specificity - 1) was used to calculate the optimal cutoff point. Statistical significance was established at $p < 0.05$.

Results

A total of 80 patients underwent rectal cancer surgery at HUMS from January 1 through December 31, 2019. A total of 28 patients without colorectal anastomosis were excluded from the study: 20 with abdominoperineal amputation, 6 with minimally invasive endoanal surgery, and 2 with pelvic exenteration. The general characteristics of the resulting sample of 52 patients are detailed in table 2.

The location of the rectal tumor determined by magnetic resonance imaging showed a lesion in the upper rectum (10-15 cm from the anal margin) in 28 patients (53.8%), in the middle rectum in 20 patients (38.5%), and in the lower rectum (< 5 cm from the anal margin) in 4 (7.7%). According to the tumor committee's decision, based on the tumor location and stage, 17 patients (32.7%) received neoadjuvant treatment with short-cycle radiotherapy prior to surgery, with the interval to surgery being 51.8 ($\pm$ 13.7) days. Anterior rectal resection with partial mesorectum excision was performed in upper rectal tumors, while complete mesorectum excision was performed in middle and lower rectal tumors. Colorectal anastomosis was associated with temporary diverting ileostomy in 11 patients (21.2%). Laparoscopic approach was completed in 46 patients (88.5%), with conversion to laparotomy being necessary in 2 cases (3.8%).

Postoperative morbidity at 30 days is summarized in table 3. There were no admissions to the intensive care unit, or any deaths recorded either. The postoperative incidence of CAL was 4 cases (7.7%): 2 type B (1.9%), resolved with conservative treatment, and 3 type C (5.8%), which required surgical reintervention and colostomy. The mean time from surgery to CAL was 4.5 ($\pm$ 0.96) days. None of these patients were thought to require temporary diverting ileostomy.

In our study, patients were categorized into three groups: a) with colorectal anastomosis, b) with colorectal anastomosis + protective ileostomy, and c) with anastomosis + tube ileostomy. The relationship between the different groups of the sample was calculated, and statistically significant differences were found between a) anastomosis group vs b) anastomosis group + ileostomy group (p = 0.021) and between a) anastomosis group vs c) anastomosis group + transcecal ileostomy group (p = 0.044). Conversely, no differences were found between the stoma categories, i.e., between b) and c) (p = 0.942); therefore, both groups (b and c) were grouped into one. As expected, group a) had lower REAL-score values vs the other 2 stoma categories.

Table 2. Overall characteristics of the sample

Variables (n = 52)	
Age in years: mean (SD), median (range)	68.5 ($\pm$ 11), 69 (35-87)
Gender: male/female (%)	30 (57.7%)/22 (42.3%)
Body mass index: mean (SD), median (range)	27.5 ($\pm$ 5), 27 (18-44)
Preoperative hemoglobin: g/dl (SD), median (range)	13.6 ($\pm$ 1), 13.6 (10.8-16.7)
Type 2 diabetes mellitus, n (%)	10 (19.2%)
Smoking, n (%)	7 (13.5%)
Previous abdominal surgery, n (%)	21 (40.4%)

SD: standard deviation.

Once the clinical parameters were collected and patients with similar characteristics were grouped, the relationship between the expected CAL estimates according to the predictive REAL-score index and the performance of protective stomas during surgery was analyzed, finding statistical significance between them (p = 0.003) (Table 4). In conclusion, we determined that the variability of performing a stoma during surgery is associated with a REAL-score obtained between 16.2% (Cox and Snell R-squared) and 24.8% (Nagelkerke R-squared).

The predictive capacity of CAL of the REAL-score based on population categories a) vs b) + c) was established by calculating the area under the ROC curve, which was 0.856 (Fig. 2).

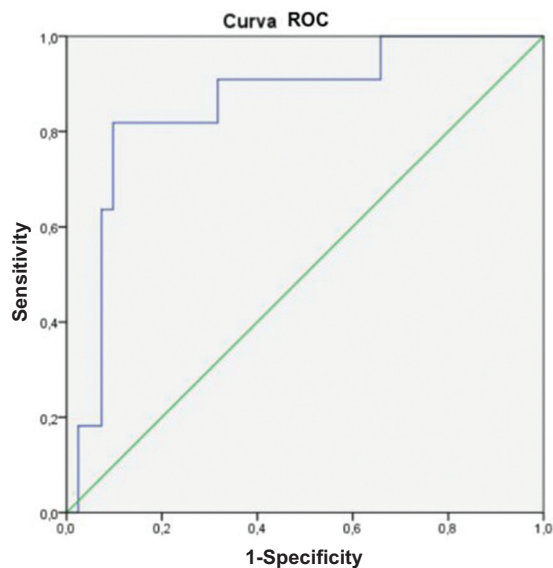
The value of the REAL-score of 14.74% showed the highest discriminative power, with a sensitivity rate of 82% and a specificity rate of 83% (Youden index: 0.989), hence, it was selected as the cutoff point from which the risk of postoperative CAL is significant enough to warrant protective ileostomy. Finally, when investigating postoperative outcomes regarding morbidity and mortality, according to the Clavien-Dindo classification, we can conclude that there is no statistically significant relationship between the REAL-score variable and the Clavien-Dindo classification (p = 0.536).

Discussion

Despite the extensive literature on morbidity following rectal cancer surgery and the importance of CAL,

Table 3. 30-day postoperative morbidity based on the Clavien-Dindo classification

Postoperative morbidity	No. of patients (Percentage)
Grade I	4 patients (7.7%)
Postoperative ileus (conservative treatment)	2 patients
Superficial surgical wound infection (local care)	1 patient
Self-limiting fever without focus	1 patient
Grade II	12 patients (23%)
Respiratory infection	2 patients
Urinary tract infection	2 patients
Anastomotic dehiscence type A and B (absolute diet + parenteral nutrition + antibiotic therapy)	2 patients
Septic thrombosis of the internal jugular vein	1 patient
Infection related to central venous catheter	1 patient
Hypertensive crisis	1 patient
Electrolyte imbalance decompensation	1 patient
Postoperative ileus (need for parenteral nutrition)	1 patient
Surgical wound infection (debridement and antibiotic therapy)	1 patient
Grade III	4 patients (7.7%)
Anastomotic dehiscence type C (emergency surgical reintervention)	3 patients
Postrenal kidney failure (double J catheter)	1 patient

**Figure 2.** ROC curve for the association between the stoma and the REAL-score.

there has traditionally been no uniform criteria to define it. Under these conditions, comparing studies on CAL using scientific methodology has been almost impossible. Without agreement on the definition, there is also no consensus on its incidence (which ranges from 1% up to 19% according to different series), postoperative mortality (4% up to 32%), or the associated increased hospital stays and health care spending⁹. To reduce this variability and understand the actual

Table 4. Correlation of expected anastomotic dehiscence (REAL-score), protective stoma, and observed anastomotic dehiscence

REAL-score	Stoma	Anastomotic dehiscence
3.38%	No	No
3.39%	No	No
4.71%	No	No
4.97%	No	No
5.19%	No	No
5.23%	No	No
6.58%	No	No
6.65%	No	No
6.87%	No	No
7.52%	No	No
7.57%	No	No
7.97%	No	No
8.02%	No	No
8.33%	No	Yes, type C
8.42%	No	No
8.44%	No	No
8.65%	No	No
8.85%	No	No
9.44%	No	No
9.49%	No	No

(Continues)

Table 4. Correlation of expected anastomotic dehiscence (REAL-score), protective stoma, and observed anastomotic dehiscence (continued)

REAL-score	Stoma	Anastomotic dehiscence
9.87%	No	No
9.97%	No	Yes, type C
9.97%	No	No
10.18%	No	No
10.29%	No	No
10.52%	No	No
10.77%	No	No
10.90%	No	No
10.96%	No	No
11.57%	Yes	No
12.34%	No	No
13.84%	No	No
14.01%	No	Yes, type B
14.12%	No	No
14.25%	No	No
14.69%	No	No
14.79%	No	No
15.82%	No	No
16.13%	No	No
17.01%	Yes	No
18.47%	Yes	No
19.00%	No	No
20.67%	Yes	No
23.16%	Yes	No
23.34%	Yes	No
23.44%	Yes	No
24.66%	Yes	No
26.15%	No	No
30.53%	No	Yes, type C
32.47%	Yes	No
36.02%	Yes	No
53.01%	No	No

figures of CAL in Spain, the Spanish Association of Coloproctology (AECp) launched a multicenter accreditation program titled "Analysis of quality

indicators in colorectal cancer surgery of accredited units"³ back in 2018. Based on the study of the clinical results of 18 coloproctology units over 5 years (2013-2017), the overall rate of CAL in rectal surgery was found to be 10.6%. This figure is similar to that published in 2019 by the REAL-score working group, with 9.7% in nearly 10 000 patients recruited from a meta-analysis from 2000 through 2015⁸.

In our case series, a CAL rate of 7.7% was recorded, which puts us at the lower end compared to the available literature^{7,9}. However, it is necessary to continue using tools that allow preoperative clinical decision-making to achieve the ultimate goal of approaching a zero CAL rate. The publication of the REAL-score predictive index in June 2019 drew attention to the actual need for harmonizing different outcome publications. Designed in a clinical context different from ours, we had to find out if the implementation and extrapolation of results to our setting were possible. Thus, we initiated the retrospective application of the REAL-score to verify its adaptability to our case mix. The results of our series show that in patients with lower REAL-score scores, primary anastomosis without protective stoma is usually performed, while the number of protective stomas increases directly proportional to the REAL-score score. Therefore, it is confirmed that there is a statistically significant relationship between high scores and the clinical practice of creating a stoma ($p = 0.003$). Based on the described statistical analysis, this scale has good predictive power for CAL, with an area under the ROC curve of 0.856. Therefore, we understand that the REAL-score is applicable to our population and that, furthermore, the clinical decisions made by the surgeons in our center align with the predictions provided by this tool. We can qualify our orientation in performing protective ileostomy in colorectal anastomoses as very selective, as in 8 out of 11 patients who underwent ileostomy, the REAL-score score was > 20 .

The REAL-score could allow us to further refine the decision threshold, tilting the balance in favor of ileostomy or not from a certain score threshold. Thus, the incorporation of the REAL-score into the routine clinical practice would be significant support in the preoperative management of the patient, guiding the need for protective stoma based on objective data in addition to the professional experience of the surgeon and a series of technical factors. In the analysis of our data, the cutoff score from which the risk of postoperative CAL is significant enough to justify the performance of protective ileostomy was set at 14.74. Nonetheless, the surgeon must consider the implications of

performing an ileostomy for the patient (limitation of quality of life or the need for a second intervention for intestinal transit reconstruction, etc.), their interests, and the consequences of such decision, which are so diverse and of such magnitude (hydroelectrolytic alterations, wound infection, incisional hernia, etc.) that in the current stage of the study any cutoff point should not be interpreted in isolation or deterministically.^{10,11} The REAL-score is considered a tool that aids in decision-making but must be integrated with professional experience and previous knowledge. Another collateral effect of the REAL-score is that it allows for comparisons between different surgical teams by considering the case-mix of each series and objectively quantifying the risk of CAL.

The most common postoperative complications were postoperative ileus, nosocomial infection, surgical wound infection, and CAL, yet most patients (61.6%) did not present any complications during the postoperative period. As expected, there is no statistically significant relationship between the REAL-score and postoperative morbidity and mortality recorded based on the Clavien-Dindo classification ($p = 0.536$). In fact, it is not patients with the highest risk of CAL in the REAL-score who presented the most morbidity.

Conclusions

The REAL-score is a predictive index of CAL that adapts to our case mix of rectal cancer patients and allows for result comparison with other series. Above a certain cutoff point, it is useful as a tool to decide the need for temporary ileostomy, always accompanied by the analysis of the patient's clinical context. As this is a descriptive and retrospective study with a single-center series, further evidence is needed, possibly from prospective and multicenter studies, to validate the REAL-score and determine whether its implementation can help decrease the morbidity and mortality associated with a complication as fearsome as CAL.

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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 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.

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