ORIGINAL ARTICLE

Evaluating the role of pre-operative hemoglobin, albumin, lymphocyte, and platelet scores in predicting perioperative morbidity in rectal cancer patients

Evaluando el rol de los puntajes preoperatorios hemoglobina, albúmina, linfocitos y plaquetas en la predicción de la morbilidad perioperatoria en pacientes con cáncer rectal

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Abstract

Objective: *Our study aims to explore the predictive value of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score, calculated from routine blood tests measuring HALP levels, for perioperative morbidity in rectal cancer surgery patients.* **Method:** *We conducted a retrospective study focusing on patients who underwent elective rectal cancer surgery from January 2017 to September 2023. The study analyzed demographic, clinical, and laboratory data, including the HALP score, to assess its correlation with perioperative morbidity using logistic and linear regression analyses.* **Results:** *Univariate analysis showed no correlation between the HALP score and perioperative morbidity. Intriguingly, an increase of each centimeter in tumor size was associated with a significant reduction in the HALP score ($p = 0.042$), and operation time exhibited an inverse relationship with HALP scores ($p < 0.001$). Further, our study identified sex (male, $p = 0.017$) and age (> 65, $p = 0.016$) as significant predictors of perioperative morbidity.* **Conclusions:** *Our study found that pre-operative HALP scores did not significantly predict perioperative morbidity or local recurrence in rectal cancer surgery, challenging their presumed prognostic value. However, a notable association was observed between higher HALP scores, reduced tumor size, and shorter operative times, suggesting a potential indirect relationship of HALP in surgical outcomes.*

Keywords: *Rectum cancer. Perioperative morbidity. Immunonutritional status.*

Resumen

Objetivo: *Explorar el valor predictivo del puntaje HALP, calculado a partir de análisis de sangre sistemáticos que miden los niveles de hemoglobina, albúmina, linfocitos y plaquetas, para la morbilidad perioperatoria en pacientes de cirugía de cáncer rectal.* **Método:** *Estudio retrospectivo de pacientes sometidos a cirugía electiva de cáncer rectal desde enero de 2017 hasta septiembre de 2023, analizando datos demográficos, clínicos y de laboratorio para evaluar la correlación del puntaje HALP con la morbilidad perioperatoria mediante análisis de regresión logística y lineal.* **Resultados:** *No se encontró correlación entre el puntaje HALP y la morbilidad perioperatoria. El aumento por cada centímetro en el tamaño del tumor redujo significativamente el puntaje HALP ($p = 0.042$), y el tiempo de operación se relacionó inversamente con los puntajes HALP ($p < 0.001$). El sexo (masculino, $p = 0.017$) y la edad (> 65 años, $p = 0.016$) fueron predictores significativos de morbilidad perioperatoria.* **Conclusiones:** *Los puntajes HALP preoperatorios no predijeron significativamente la morbilidad perioperatoria ni la recurrencia local en la cirugía de cáncer rectal, cuestionando su valor pronóstico. Sin embargo, se observó una notable asociación*

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entre los puntajes HALP más altos, el menor tamaño del tumor y los tiempos quirúrgicos más cortos, sugiriendo una relación indirecta potencial del puntaje HALP en los resultados quirúrgicos.

Palabras clave: *Cáncer rectal. Morbilidad perioperatoria. Estado inmunitario y nutricional.*

Introduction

Rectal cancer is a prevalent type of cancer and a significant health concern[1,2]. Despite the development of additional modalities, surgery remains the primary treatment element[3]. Rectal cancer surgery is associated with high morbidity rates. Neoadjuvant and adjuvant treatments, according to the stage of cancer, can have a negative impact on the patient's physiological reserve and physical condition[4,5]. It can be tough to minimize surgical complications and achieve excellent oncological outcomes in rectal cancer surgery[6]. Identifying situations with a high potential for perioperative morbidity during surgical planning is crucial for achieving successful outcomes[7].

The literature highlights that assessing the inflammatory response induced by tumors in colorectal cancer can be beneficial for predicting prognosis[8,9]. Furthermore, the literature has examined the impact of nutritional status on the disease prognosis and perioperative morbidity[10]. At that point, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a combined parameter utilized to evaluate the patient's inflammatory and nutritional status. The HALP score is calculated from the values of hemoglobin, albumin, lymphocytes, and platelets, which are available in routine blood tests, and its implications for prognosis and survival have been studied in many types of cancer[11-13].

Colorectal cancers exhibit heterogeneity due to their tumor localization, structure, and genetic characteristics[14,15]. Therefore, diverging from existing literature, we specifically investigated the relationship between the HALP score and perioperative morbidity in patients undergoing surgery for rectal cancer.

Method

We obtained approval from the Bursak Yüksek İhtisas Training and Research Hospital Ethics Committee for our study, decision number 2011-KAEK-25 2023/11-17.

The patient, who was diagnosed with rectal cancer as a result of elective procedures at the clinic, underwent assessment and received treatment from a multidisciplinary tumor council. The surgical procedure of total mesorectal excision can be conducted either openly or laparoscopically, depending on the predilection of the surgeon and the specific clinical requirements of the patient.

We included patients who were 18 years or older and had undergone surgery for rectal cancer between January 2017 and September 2023. Patients who underwent emergency surgery, abdominopelvic resection, adjacent organ invasion, metastatic disease, liver failure, and those with insufficient medical records, including operation time and pathological records, were excluded (Fig. 1).

Data on patient' characteristics, including age, sex, American Society of Anesthesiologists (ASA) score, and body mass index (BMI), as well as information on pathological factors, such as tumor size, lymphovascular invasion status, T stage, and pathological stage, were collected. Surgical data, including operation time, perioperative morbidity, number of dissected lymph nodes, and mortality, were also compiled. In addition, clinical data such as duration of stay, local recurrence, and readmission, as well as laboratory data including hemoglobin, albumin, lymphocyte count, platelet count, and HALP score, were included in the study. Due to the limited duration of our study and the low mortality rate, we did not analyze the survival data.

The HALP score is an immunonutritional marker and is calculated as hemoglobin x albumin x lymphocyte count/platelet count[16-18]. Our hypothesis suggests a correlation between the immunonutritional status of patients and the occurrence of perioperative morbidity and surgical outcomes in individuals undergo elective rectal cancer surgery. We assessed the patients' immunonutritional status using the HALP score as a numerical metric and examined its correlation with variables such as operation time, length of hospital stay, readmission rate, perioperative morbidity, mortality, and local recurrence. Perioperative morbidity was defined as the occurrence of a complication that required treatment within 1 month after the operation. It was assessed using the Clavien–Dindo score.

Within the scope of the statistical analysis, categorical variables were presented as numbers and percentages. Continuous variables are expressed as mean±standard deviation (SD), and median values. The effects of the patients' clinical and surgical characteristics on morbidity

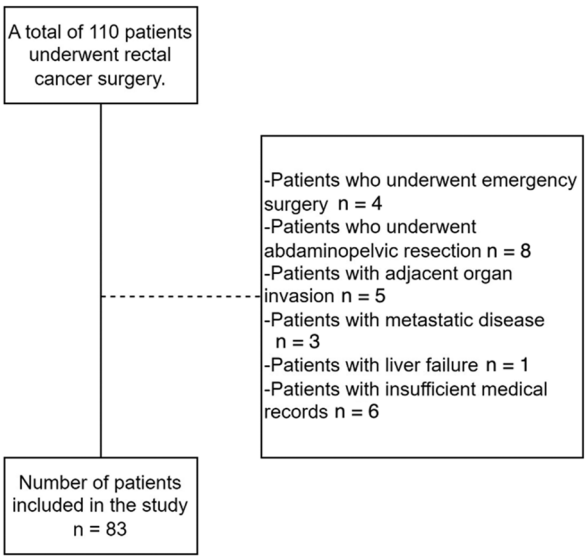

Figure 1. *Flow chart of patients included in the study.*

and recurrence development were examined using logistic regression models. Age, sex, certain clinical features, and laboratory results on morbidity and recurrence were analyzed using the univariate logistic regression (LR) method, followed by the analysis of significant variables with stepwise multivariable LR (Enter method). The median values of the quantitative variables were determined as the cutoff point and added to the logistic regression model. The relationship between the dependent variable, HALP score, and patient characteristics was investigated using univariable and multivariable linear regression models. Multivariable linear regression variables were included in the analysis using the enter method. Moreover, multicollinearity was examined for factors with variance inflation factor (VIF) of < 5 and included in the model. All statistical calculations were performed using SPSS software (version 29.0; SPSS Inc., Chicago, IL, USA). All reported p-values were calculated based on two-tailed hypotheses, and statistical significance was set at $p < 0.05$.

Results

When the socio-demographic and clinical characteristics of the cases were examined (Table 1), it was determined that 69.9% were male, the average age was 66.75 ± 12, and the average BMI was 26.16 ± 3.74. It was observed that 43.9% of the patient had an ASA score of 2, laparoscopic surgery was performed in 57.8%, and the tumor was located in the upper rectum

Table 1. General characteristics of the patients

Parametres	n (%) or mean ± SD (M)
Gender	
Male	58 (69.9)
Female	25 (30.1)
Age	66.75 ± 12 (65)
BMI kg/m^2	26.16 ± 3.74 (26)
ASA score	
2	36 (43.9)
3	45 (54.9)
4	1 (1.2)
Neoadjuvant treatment	
Receive	40 (48.1)
Not-receive	43 (51.8)
Operation type	
Open	35 (42.2)
Laparoscopic	48 (57.8)
Tumor localization	
Lower rectum	31 (37.3)
Middle rectum	17 (20.5)
Upper rectum	35 (42.2)
T stage	
T0	2 (2.4)
Tis	2 (2.4)
T1	8 (9.6)
T2	16 (19.3)
T3	44 (53)
T4	11 (13.3)
Pathologic stage	
0	4 (4.8)
1	22 (26.5)
2A	17 (20.5)
2B	4 (4.8)
3A	12 (14.5)
3B	13 (15.7)
3C	11 (13.3)
Adjuvant treatment	
Receive	49 (62)
Not received	29 (35.4)
Average tumor size (cm)	4.08 ± 2.58 (3.5)
Lymphovascular invasion	25 (30.1)
Average number of lymph nodes	15.82 ± 7.68 (15)
Open	16.17 ± 6.8 (16)
Laparoscopic	15.56 ± 8.33 (14)
Average operation time (min)	245 ± 68.69 (240)
Open	247.71 ± 51.1 (240)
Laparoscopic	243.02 ± 79.58 (240)
Average length of stay (day)	9.71 ± 5.73 (8)
Open	11.57 ± 5.52 (10)
Laparoscopic	8.35 ± 5.55 (7)
Average hemoglobin level HB mg/dL	122.87 ± 21.95 (123)
Average lymphocyte level LYM 10^3/L	1.51 ± 0.69 (1.4)
Average platelet level PLT 10^3/L	266.97 ± 147.97 (237)
Average albumin level ALB gr/dL	42.91 ± 40.33 (39)

(Continues)

Table 1. General characteristics of the patients *(continued)*

Parametres	n (%) or mean ± SD (M)
Average HALP score	29.39 ± 18.48 (26)
Anastomotic leak	8 (9.6)
Readmission	13 (16.5)
30 day morbidity	30 (36.1)
Local recurrence	17 (21.8)
Mortality	5 (6)

(n = 83); HALP: hemoglobin, albumin, lymphocyte, and platelet; BMI: body mass index; M: median; ASA: American Society of Anesthesiologists.

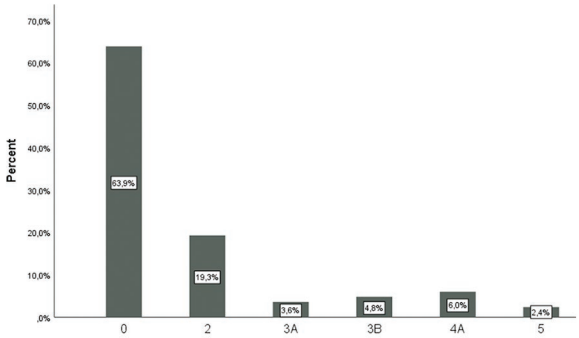

Figure 2. *Bar graph of the distribution of surgical morbidity according to the Clavian-Dindo classification.*

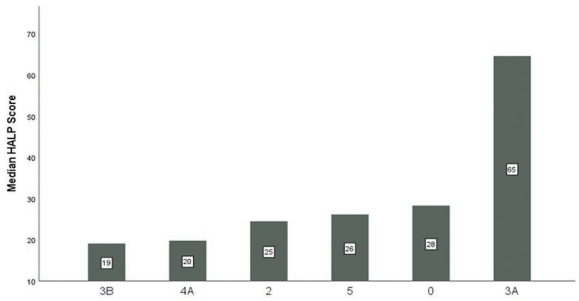

Figure 3. *Median hemoglobin, albumin, lymphocyte, and platelet scores according to the Clavien–Dindo classification.*

in 42.2%, 53% in stage 3, 26.5% in stage 1, and 62% in adjuvant therapy. The average tumor size of the cases was 4.08 ± 2.58 cm, the average number of lymph nodes was 15.82 ± 7.68, the average operation time was 245 ± 68.69 min, the average hospital stay was 9.71 ± 5.73 days, the average HB was 122.87 ± 21.95 mg/dL, the average LYM was 1.51 ± 0.69 10^3/L, the average PLT was 266.97 ± 147.97 10^3/L, the average ALB was 42.91 ± 40.33 gr/dL, and the average HALP score was calculated as 29.39±18.48. In addition, anastomotic leakage was observed in 30.1% of the cases, re-admission in 9.6%, morbidity in 36.1%, and mortality in 6%. The surgical mortalities of the cases are presented with a bar graph, and it was determined that according to the Clavien–Dindo classification, 63.9% of the cases had a morbidity score of 0, 19.3% had 2, 6% had 4A, and 2.4% were classified as 5 according to the Clavien–Dindo classification (Fig. 2).

The effects of the patients' clinical and surgical characteristics on morbidity were investigated using logistic regression models (Table 2). Univariate LR (Logistic Regression) analysis identified sex and age as statistically significant risk factors for morbidity ($p = 0.017$ and $p = 0.016$, respectively). Males carried a 4.266 times higher morbidity risk than females (95% CI: 1.3-13.992, $p = 0.017$), and patients aged over 65 carried a 3.323 times higher morbidity risk (95% CI: 1.256-8.795, $p = 0.016$). The significant factors observed in the univariate LR analysis were further examined together in a multivariate LR (enter method) model to determine their combined effect on morbidity risk. Accordingly, it was determined that age and sex significantly contributed to morbidity risk at a statistical level ($p = 0.029$ and $p = 0.031$, respectively).

The median HALP scores according to the Clavien–Dindo classification are summarized in Fig. 3. Accordingly, it was determined that the cases in the 3A morbidity class had the highest median HALP score, while the lowest median HALP score was seen in 3B cases, according to the Clavian-Dindo classification.

Univariate and subsequent multivariate linear regression analyses identified factors that were significantly associated with HALP scores. In the univariate linear regression models, operation duration and tumor size were determined to be factors that significantly affected the variation in HALP scores ($p < 0.05$) (Table 3). A 1 cm increase in tumor size was associated with an average decrease of 1.62 units in the HALP score ($R^2 = 0.024$; $p = 0.042$), while a 1-min increase in operation time led to an average decrease of 0.07 units in the HALP score ($R^2 = 0.062$; $p < 0.001$). In the multivariate linear regression model, only operation duration and tumor size continued to have a significant relationship with the change in the HALP score, with their respective coefficients being $\beta = -1.57$, $p = 0.044$, and $\beta = -0.06$, $p = 0.025$.

The effects of the patients' clinical and surgical characteristics on local recurrence were investigated using logistic regression models (Table 4). Univariate

Table 2. Investigation of the impact of clinical and surgical characteristics on perioperative morbidity through the utilization of univariate and multivariate logistic regression analyses

Parametres	Univariate LR		Multivariate LR	
	OR (95% CI)	p	OR (95% CI)	p
Gender male (ref: female)	4.266 (1.3-13.992)	0.017	3.864 (1.146-13.031)	0.029
Age > 65 (ref ≤ 65)	3.323 (1.256-8.795)	0.016	3.027 (1.11-8.255)	0.031
BMI > 26 (ref ≤ 26)	2.286 (0.916-5.705)	0.076		
ASA (ref = 2)	1	0.353		
3	0.508 (0.202-1.275)	0.149		
4	2.021 (0.01-235.56)	0.990		
Localization of tumor (ref = lower)	1	0.415		
Middle	0.426 (0.113-1.608)	0.208		
Upper	0.818 (0.304-2.201)	0.691		
Pathological stage > 2 ([ref ≤ 2])	1.233 (0.5-3.038)	0.649		
Operation type (open [ref = lap])	1.65 (0.667-4.082)	0.279		
Operation duration > 240 min ([ref ≤ 240])	1.193 (0.475-2.997)	0.707		
Number of lymph node > 15 ([ref ≤ 15])	1.141 (0.464-2.806)	0.773		
T stage > 2 ([ref ≤ 2])	0.649 (0.254-1.655)	0.365		
HALP score > 26 ([ref ≤ 26])	0.511 (0.206-1.270)	0.116		

HALP: hemoglobin, albumin, lymphocyte, and platelet; LR: logistic regression; OR: odds ratio; ASA: American Society of Anesthesiologists; BMI: body mass index.

Table 3. Univariate and multivariate linear regression analyses for HALP score

Parametres	Univariate linear regression			Multivariate linear regression	
	β (95% CI)	R^2	p	β (95% CI)	p
Gender	–1.66 (–10.50-7.19)	0.1%	0.710		
Age	0.12 (–0.22-0.46)	0.1%	0.486		
ASA score	–1.19 (–9.04-6.65)	0.1%	0.763		
Tumor size	–1.62 (–3.21- –0-60)	0.2%	0.042	–1.57 (–3.11- –0.04)	0.044
Tumor stage	–0.62 (–4.43-3.19)	0.1%	0.001		
Operation time	–0.07 (–0.12- –0.01)	3%	0.023	–0.06 (–0.12- –0.01)	0.025
Anastomotic leak	–9.05 (–22.66-4.57)	2%	0.190		
readmission	–490 (–16.35-6.55)	0.1%	0.397		
Length of stay	0.38 (–0.33-1.09)	0.1%	0.291		
Morbidity	–0.95 (–9.40-7.51)	0.1%	0.825		
Local recurrence	–2.25 (–12.68-8.18)	0.1%	0.669		

HALP: hemoglobin, albumin, lymphocyte, and platelet; ASA: American Society of Anesthesiologists; CI: confidence interval.

LR analysis identified age and readmission variables as significant risk factors for recurrence (p = 0.013 and p = 0.005, respectively). On examination of the results, it was found that patients aged over 65 carried a 5.5 times higher risk of recurrence (95% CI: 1.433-21.106, p = 0.013), and patients who were readmitted had a 6.3 times higher risk of recurrence (95% CI: 1.748-22.711, p = 0.005). The significant factors observed in the

Table 4. Investigation of the impact of clinical and surgical characteristics on local recurrence through the utilization of univariate and multivariate logistic regression analyses

Parametres	Univariate LR		Multivariate LR	
	OR (95% GA)	p	OR (95% GA)	p
Age > 65 (ref ≤ 65)	5.5 (1.433-21.106)	0.013	4.654 (1.160-18.669)	0.030
Gender male (ref: female)	1.206 (0.388-3.743)	0.746		
ASA score (ref = 2)	1	0.866		
3	0.733 (0.236-2.276)	0.592		
4	0.010 (0.001-345.45)	0.990		
Tumor size > 3.5 cm (ref ≤ 3.5)	1.476 (0.497-4.384)	0.483		
T stage > 2 (ref ≤ 2)	1.435 (0.476-4.328)	0.521		
Lymphovascular invasion (1)	1.172 (0.357-3.848)	0.794		
Anastomotic leak (1)	0.573 (0.064-5.114)	0.618		
Readmission	6.3 (1.748-22.711)	0.005	4.903 (1.279-18.792)	0.020
Length of stay > 8 day (ref ≤ 8)	0.806 (0.269-2.417)	0.700		
Perioperative morbidity	0.646 (0.214-1.956)	0.440		
Halp score > 26 (ref ≤ 26)	0.919 (0.313-2.695)	0.877		

LR: logistic regression; OR: odds ratio; ASA: American Society of Anesthesiologists.

univariate LR analysis were further examined together in a multivariate LR (enter method) model to determine their combined effect on recurrence risk. Accordingly, it was determined that age and readmission variables significantly contributed to the risk of recurrence at a statistical level (p = 0.030 and p = 0.020, respectively).

Discussion

This retrospective observational study aimed to explore the predictive value of pre-operative HALP scores for perioperative morbidity in patients undergoing rectal cancer surgery. Contrary to our hypothesis and the existing literature suggesting a potential link between HALP scores and outcomes in various cancers[11], our findings did not demonstrate a statistically significant correlation between pre-operative HALP scores and perioperative morbidity in rectal cancer patients. This discrepancy underscores the potential limitations of the HALP scores in capturing the nuanced interplay of factors that contribute to surgical risks and complications.

On comparing our surgical outcomes with those in the existing literature, it can be asserted that we exhibit similarity in terms of the average duration of operations[19-21] and the average quantity of lymph nodes harvested[22-24]. Nevertheless, the anastomotic leak rate observed in our study is notably elevated compared to the existing literature[18,25], while the local recurrence frequency aligns with the findings reported in the literature[14]. Based on the existing literature, it can be inferred that the quality of oncological surgery is acceptable. However, there is a need for improvement in terms of anastomotic leakage reduction.

When our short-term surgical and clinical parameters, such as average length of stay (11.5 day open, 8.3 day laparoscopic), readmission rate (16.5%), and perioperative morbidity rate (%36), are compared with the existing literature, it becomes evident that our average length of stay is above that of the literature (7 days open, 6 days laparoscopic)[26], and our readmission rate is beyond that of the literature series (6.4%)[27]. The observed rate of perioperative morbidity in our study seems to be higher than that reported in other studies[28]. Based on the data presented, it is evident that certain areas exist within the clinical management of patients that require improvement.

When analyzing the literature on perioperative morbidity in low anterior resections, anastomotic leaks are commonly highlighted as a significant factor. A study conducted by Matthiessen et al.[29] identified several independent risk factors, namely, low anastomosis, preoperative radiation, presence of intraoperative adverse events, and male sex. In a separate investigation, the

use of pre-operative steroids, extended duration of surgical procedures, and contamination of the operative field were identified as distinct risk factors[30]. In addition, Malika et al.[31] conducted a study on perioperative morbidity in the context of rectal cancer surgery. Their findings revealed a statistically significant requirement for perioperative transfusion. In our analysis, we found that age 65 years and male gender were associated with perioperative morbidity. This raises important considerations for pre-operative assessment and risk stratification, indicating that a more comprehensive approach that potentially incorporates a wider range of clinical and biological markers may be necessary to accurately predict and manage perioperative risks.

Notably, our study sought to understand the relationship between pre-operative HALP scores and the risk of local recurrence post-surgery. Despite the expectation that lower HALP scores would correlate with higher recurrence rates given the association between poor nutritional and immunological status and cancer aggressiveness, our data did not reveal a statistically significant link. This lack of correlation may suggest that while HALP scores can provide a snapshot of a patient's general health status, they might not be sufficiently sensitive to specifically predict local recurrence in rectal cancer. Waldenstedt et al.[32] identified several factors associated with local recurrence. These factors include intraoperative adverse events, non-radical resection, high pathological T stage, and the presence of lymph node metastases. Another study revealed a correlation between tumor size, T stage, and local recurrence[33]. The findings of our study indicated a significant association between age, readmission, and local recurrence.

The HALP score has been assessed in the literature with regard to survival in colorectal cancer, and its statistical significance has been established[34]. The study conducted by Yalav et al. revealed that there was no significant association between the HALP score and surgical morbidity in patients with colorectal cancer[35]. Based on our data, there is no correlation between HALP score and surgical morbidity or local recurrence. However, a high HALP score is associated with reduced tumor size and shorter operative time.

Our study has certain limitations. The limitations of this study include its retrospective design, the contribution of multiple surgeons in clinical operations, and the inability to establish a relationship between our data and survival due to the study's specific date range. The findings also prompt a reevaluation of the role of systemic inflammation and nutritional status in rectal cancer surgery outcomes. Although HALP scores were not predictive of morbidity in our cohort, this does not negate the importance of these factors in patient care. Instead, this may indicate the need for more sensitive or specific markers to assess and address these dimensions of patient health.

Conclusions

Our retrospective observational study explored the predictive value of pre-operative HALP scores on perioperative morbidity and local recurrence in rectal cancer surgery. Contrary to our hypothesis and the previous literature, we did not find a statistically significant correlation between pre-operative HALP scores and perioperative morbidity or local recurrence rates. This outcome challenges the presumed universal applicability of HALP scores as a prognostic tool in oncological surgeries and underscores the necessity of considering a multifaceted approach to risk assessment and management in patients with rectal cancer.

Interestingly, our study revealed a significant positive correlation, where a higher HALP score was associated with a reduced tumor size and shorter operative time. This finding suggests that while HALP scores may not directly predict perioperative morbidity or the likelihood of local recurrence, they may still offer valuable insights into certain aspects of the surgical outcome, such as the potential for a less complex surgical procedure and favorable tumor pathology.

The significant associations between perioperative morbidity and factors such as age and sex reinforce the importance of a multifaceted approach to pre-operative risk assessment. Future studies should aim to develop and validate comprehensive models that integrate a broad spectrum of clinical, nutritional, and inflammatory markers to better predict and mitigate the risk of perioperative morbidity in rectal cancer surgery.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. Artificial intelligence (AI) assistance was employed for grammatical review and language editing of this manuscript. Specifically, AI tools were utilized to ensure clarity, coherence, and grammatical accuracy in the text. The scientific content, data analysis, and interpretation of results were exclusively carried out by the authors, without any influence or contribution from AI. The authors take full responsibility for the originality, accuracy, and integrity of the manuscript's content.

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