Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

REACT: A Novel Scoring Model for Predicting Recurrence Risk in Rectal Cancer Following Neoadjuvant Therapy and Curative Intent Surgery

Azmi LALE

dr.azmilale@gmail.com

Erciyes Üniversitesi Tıp Fakültesi Hastaneleri

Umit Kaya

Fırat Üniversitesi Hastanesi

Ahmet Aslan

Fırat Üniversitesi Hastanesi

Mehmet Fatih Ebiloglu

Fırat Üniversitesi Hastanesi

Birgul Karahan

Fırat Üniversitesi Hastanesi

Veysel Karahan

Fırat Üniversitesi Hastanesi

Turkmen Bahadir Arikan

Erciyes Üniversitesi Tıp Fakültesi Hastaneleri

Erhan Aygen

Fırat Üniversitesi Hastanesi

Research Article

Keywords: Rectal cancer, prognostic score, risk stratification, inflammatory markers, recurrence prediction, survival analysis

Posted Date: July 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9917235/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

This study aimed to identify clinicopathologic and serum-based inflammatory variables associated with tumor recurrence in patients with rectal cancer treated with neoadjuvant chemoradiotherapy (CRT) followed by curative-intent resection, and to develop a practical, recurrence-oriented scoring system.

Methods

A cohort of 129 patients with rectal adenocarcinoma was included in the study. Univariate and multivariate logistic regression analyses were used to evaluate associations with tumor recurrence. Kaplan-Meier and ROC analyses were applied to assess the predictive accuracy of the proposed scoring model.

Results

Multivariate analysis identified elevated preoperative neutrophil-to-lymphocyte ratio (NLR) (NLR > 3.0 HR:2.884; *p* = 0.006) and systemic-inflammatory-index (SII) (SII > 750 HR:4.557; *p* = 0.001), presence of extra-nodal extension (ENE) (HR: 6.831; *p* = 0.002), CEA level > 5.0 (HR:5.975; *p* = 0.018), and pT3 (HR:7.349; *p* = 0.012) and pT4 (HR:15.320; *p* = 0.003) as independent predictors of recurrence. Patients were categorized into low-, intermediate-, and high-risk groups using the REACT score, a three-tiered risk model. In Kaplan-Meier analysis, the REACT score was substantially correlated with disease-free survival (DFS) ($p < 0.001$) and showed high prognostic discrimination (AUC: 0.812). 7.9% of low-risk, 32.1% of intermediate-risk, and 100% of high-risk patients experienced a recurrence.

Conclusion

The REACT score provides a low-cost, easily applicable, and clinically relevant method for perioperative recurrence risk stratification in rectal cancer.

INTRODUCTION

Rectal cancer continues to be a major global health burden, accounting for a substantial portion of cancer-related morbidity and mortality globally. Disease recurrence continues to impact a significant portion of patients, particularly in the initial years following curative surgery, despite recent advancements in multimodal treatment approaches, such as neoadjuvant chemoradiotherapy, innovations in surgical tools and techniques, and the use of customised adjuvant therapies [1, 2]. The biochemical and immunological complexity of the disease and the variety in individual patient characteristics are not adequately reflected by the recent conventional staging systems, such as the

TNM classification, which provide a standardized method for treatment planning [3]. Even among identical staging profiles, recurrence risk and long-term survival results might differ significantly, highlighting the shortcomings of stage-based treatment approaches and highlighting the need for better prognostic methods.

For colorectal malignancies, a number of nomograms and models have been created recently to improve personalized prognostic risk prediction and aid in therapeutic decision-making. By adding additional variables such tumor regression grade, perineural invasion, and preoperative carcinoembryonic antigen (CEA) levels, it was intended to surpass conventional staging systems using these techniques [4–6]. However, the need for postoperative data, the exclusion of patient-related biological markers, and the computational complexity that prevents these models from being used in standard clinical practice limit their strength of demonstration capabilities [3]. These drawbacks highlight the need for practical prognostic methods that are based on easily available clinical data, physiologically informative, and perioperatively applicable.

The prognostic significance of systemic inflammatory responses and immunological state in patients with rectal cancer has been highlighted by mounting research in recent years. Numerous studies have demonstrated consistent relationships between preoperative markers including the neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and prognosis nutritional index (PrNI) with prognostic outcomes and treatment response [7–16]. Concurrently, the potential of histopathological indications such as extra-nodal extension (ENE) to offer additional prognostic value beyond conventional staging methods has been recognized [17]. The integration of inflammatory indicators and histopathologic features is still being investigated, despite the fact that a number of current models have improved prognostic prediction by adding clinicopathologic variables. The accuracy of preoperative risk stratification may be improved and more individualized therapeutic decision-making supported by the further development of prognostic methods that fully reflect both tumor biology and immunologic response.

Therefore, the main goal of this research was to create a prognostic score system that could accurately predict the likelihood of recurrence in individuals having curative surgery for rectal cancer. This model was created to be economical, easily accessible, therapeutically useful, and physiologically significant. Crucially, in order to improve its predictive accuracy, it sought to incorporate both host-derived systemic biological indicators and tumor-related pathological factors. A key objective was to construct a scoring system that relies on routinely available clinical data, without the need for additional laboratory testing or advanced radiological examinations which was intended to guide risk-adapted treatment or surveillance strategies in rectal cancer management.

METHODS

Study design and patient characteristics

This is a single-center, retrospective cohort study conducted at a tertiary hospital. Patients who underwent consecutive elective, curative-intent low anterior resection (LAR) or abdominoperineal resection (APR) with total mesorectal excision (TME) following neoadjuvant chemoradiotherapy (nCRT) for locally advanced rectal cancer between January 2015 and January 2022. Eligible patients met the following criteria: 1) Histologically confirmed primary rectal adenocarcinoma; 2) Clinically staged as cT3-T4 and/or N+ (Stage II-III) disease based on pretreatment MRI and/or CT; 3) Received standard neoadjuvant 5-fluorouracil (5-FU)-based chemotherapy combined with long-course radiotherapy (total dose 45-50.4 Gy in 25-28 fractions over 5-6 week); 4) Underwent LAR or APR with TME. 5) Received adjuvant treatment (FOLFOX or CAPEOX) 12-16 weeks. Exclusion criteria were: 1) Missing key clinical, laboratory, or histopathological data; 2) Synchronous distant metastasis (Stage IV) at the time of diagnosis; 3) Clinical evidence of infection; 4) Systemic inflammatory or hematologic disorders; 5) Emergency surgery such as obstruction, bleeding, or perforation; 6) History of another primary malignancy; 7) Patients who were unable to complete adjuvant chemotherapy due to toxicity, poor tolerance, or patient refusal. After inclusion and exclusion criteria a total of 129 patients were included in the final study cohort.

Data Collection

To determine the independent prognostic factors of rectum cancer, all demographic parameters, laboratory tests, intraoperative data, histopathological findings, and postoperative follow-up results were obtained retrospectively from a prospectively recorded database. Patient-related demographic parameters such as gender, age, body mass index (BMI), co-morbidities, American Society of Anesthesiologists classification (ASA) physical status score, serum-based laboratory tests and associated systemic inflammatory indicators, preoperative radiological examination such as MRI and CT findings were analyzed. Clinicopathological features as tumor size, histological type, tumor stage, morphological differentiation, lymphovascular invasion (LVI), perineural invasion (PNI), harvested lymph node count, radial and distal margin distance and status (R0/R1/R2), and ENE status in metastatic lymph nodes were collected. Furthermore, duration of operation, intraoperative estimated blood loss, surgical procedures (open/laparoscopy), ileal diversion performing status were recorded. All postoperative clinical outcomes and anastomotic leakage status were also recorded. All specimens were examined for histopathological TNM classification and staging was determined according to 8th American Joint Committee on Cancer classification for rectum cancer after surgery [18]. The well and moderately differentiated carcinomas were categorized as well differentiation morphology.

Serum Based Indicators and Calculations

Preoperative blood samples were collected within one week before the surgery to measure hemoglobin, lymphocyte, neutrophil, platelet, albumin, mean platelet volume (MPV), C-reactive protein (CRP), tumor marker as carcinoembryonic antigen (CEA), alkaline-phosphatase (ALP) levels. In order to identify the inflammation related prognostic indicators, the following calculations were performed:

CAR: CRP (mg/L) / albumin (g/dL) count,

PLR: total platelet (/L) / total lymphocyte (/L),

MPR: MPV (fL) / total platelet (/L) × 10^6,

NLR: Total neutrophil (/L) / total lymphocyte (/L),

HALP: [Hemoglobin (g/L) × albumin (g/dL) × lymphocytes (/L)] / total platelet (/L)

PrNI: 10 × albumin (g/dL) + 0.005 × total lymphocyte (/L).

SII: [Total platelet (/L) x total neutrophil (/L)]/ total lymphocyte (/L),

Surgical Procedures

The time interval between neoadjuvant CRT and surgery was 6-8 weeks. All the patients underwent bowel preparation prior to surgery and received oral and intravenous prophylactic antibiotics and subcutaneous low molecular weight heparin 4000IU the day before surgery. Standardized open and laparoscopic LAR or APR with TME procedures were performed to all patients. Splenic flexure mobilization was performed, inferior mesenteric artery was high ligated, and inferior mesenteric vein was high ligated below the pancreatic inferior border. Surgical approaches were selected as lateral-to-medial in open cases, medial-to-lateral approach was selected in laparoscopic procedures. In patients undergoing LAR, TME was performed by sharp dissection, a linear stapler was used for rectal division in open procedures and endo-stapler was used in laparoscopic procedures. Reconstruction technique was dictated handsewn coloanal or stapled colorectal due to the length of residual rectum. Pneumatic air-leak test or endoscopic evaluation was performed to all anastomoses for leakage test. In patients with low anastomoses distal to the peritoneal reflection, a temporary diverting ileostomy was routinely performed. In patients undergoing APR, TME was performed en-bloc with the anal canal and sphincter complex. A permanent colostomy was constructed in all APR cases. The decision to perform APR was based on tumor invasion of the sphincter or levator-ani complex, or inadequate response to neoadjuvant therapy that precluded sphincter preservation.

Surveillance

Post-operative follow-up was conducted in accordance with the NCCN Clinical Practice Guidelines and included clinical history, physical examination, serum CEA testing, and imaging studies such as chest, abdominal, and pelvic CT or ultrasonography, as well as colonoscopy assessment. Accordingly, patients were monitored every 3 months following surgery for the first two years, every 6 months for years 3 to 5, and then annually. Disease-free-survival (DFS) was defined as the time from surgery to the first documented recurrence, which was confirmed by imaging studies (e.g., CT, MRI, or PET-CT), significant CEA elevation with supportive radiological findings, or histopathological confirmation when available. Overall survival (OS) defined as the period between surgery and death from any cause or last known follow-up. At the time of their last clinical contact, patients who were lost to follow-up were censored. The cohort-wide median follow-up time was computed and compared between recurrence risk groups.

Recurrence Risk Stratification Using the REACT Score

In order to assess the likelihood of postoperative tumor recurrence after LAR in patients with rectal cancer, the REACT Score was created as a semi-weighted prognostic model. The model's primary parameters—rectal cancer, ENE, Advanced T stage, CEA, and tumor inflammation markers (NLR and SII)—are the source of the acronym REACT Score. Based on five clinically and statistically significant variables—CEA, SII, NLR, ypT stage, and ENE—the overall score varied from 0 to 9. A score based on the hazard ratio and clinical significance of each variable was determined using Cox regression analysis. In particular, raised SII (>750) and elevated NLR (>3.0) received one point each, while CEA >5 ng/mL and ENE positive received two points each because of their strong correlation with recurrence (HR >4). The tumor stage was graded according to its gradient influence on recurrence risk: ypT1–2 = 0, ypT3 = 2, and ypT4 = 3 (Table 1).

Based on their overall REACT scores, patients were then divided into three risk groups: Low-risk (0–2 points), Intermediate-risk (3–5 points), and High-risk (6–9 points) are the three categories. The observed score distribution, Kaplan–Meier survival estimates, and ROC curve analysis were used to determine this tripartite categorization. The low-risk boundary was built using the ROC analysis's recommended cut-off value of ≥3 points for differentiating recurrence risk. This classification was further corroborated by Kaplan–Meier analysis, which showed significant variations in DFS across the three categories. Interestingly, after follow-up, the high-risk group showed a 100% recurrence rate, which supported its distinction from intermediate scores. To prevent collinearity and redundancy, the REACT Score was not entered into the multivariate Cox model alongside its component variables. Instead, its predictive utility was evaluated independently using ROC analysis and survival comparisons between risk groups.

Statistical Analysis

The IBM SPSS statistical software for Windows, version 25 (SPSS Inc., Chicago, United States) was used to perform all analyses. For descriptive analysis, categorical variables were expressed as frequencies and percentages, whereas continuous variables were reported as median and min–max values. Comparisons of categorical variables were performed using the Chi-square test or Fisher’s exact test, as appropriate based on data distribution. For comparison of continuous variables, The Mann–Whitney U test was employed. In order to identify the optimal cut-off values and the area under the receiver operating characteristic (ROC) curve (AUC) for NLR, PLR, CAR, MPR, SII, PrNI, and HALP, ROC curve analysis was performed. Univariate and multivariate analyses with the Cox proportional hazards regression model were performed to identify the DFS and OS related indicators. Significant variables in the univariate analysis were entered in multivariate analyses. Odds ratios (OR) with 95% confidence intervals (CI) were given. The Kaplan-Meier method was performed to analyze survival outcomes and the Log-Rank test was used to compare the survival differences between the groups. The significance level in multivariate analyses was accepted as $p<0.1$, while in all other analyses the p value was accepted as <0.05.

RESULTS

Patient Demographics and Clinicopathological Characteristics

A total of 129 patients with histologically confirmed rectal cancer were included in the study. The median age was 62 years (range: 21–85), with 71 (55.0%) male and 58 (45.0%) female patients. The median follow-up duration was 46.4 months (range: 9–116 months). The median BMI was 26.7 kg/m² (range: 20.3–34.9). Comorbid conditions were present in 34 (26.4%) patients, most commonly hypertension in 26 (20.2%) and diabetes mellitus in 19 (14.7%) patients. Laboratory findings revealed elevated CEA levels were observed in 36 (27.9%) patients, and elevated ALP levels in 33 (25.6%) patients. Histopathological analysis revealed adenocarcinoma in 114 (88.4%) patients and mucinous adenocarcinoma in 15 (11.6%) patients. Advanced tumor stages were frequent, with 72 (55.8%) patients having ypT3 disease, 14 (10.9%) patients having ypT4 disease and 16 (12.4%) patients presenting with ypN2 involvement. Poor morphological differentiation was noted in 12 (9.3%) patients, LVI in 62 (48.1%) patients, PNI in 44 (34.1%) patients. Among the 60 patients with metastatic lymph nodes, ENE was detected in 14 (23.3%) patients.

Surgical approaches included open surgery in 65 (50.4%) patients and laparoscopic surgery in 64 (49.6%) patients. A diverting ileostomy was performed in 88 (77.9%) in LAR patients. The median estimated blood loss was 50 mL (range: 25–1200 mL). Anastomotic leakage occurred in 7 (6.2%) patients. During the follow-up period, tumor recurrence was observed in 34 (26.4%) patients, most commonly in the liver, affecting 20 (15.5%) patients. A detailed summary of the patient characteristics, laboratory data, histopathological and surgical findings is shown in table 2.

Roc Analysis for Systemic Inflammatory Indicators

While for 5-year OS analysis cancer-specific death was accepted as the end point, tumoral recurrence status was accepted as the end point for 3-year DFS. ROC analysis was performed to identify the optimal cut-off point of the systemic inflammatory parameters with the highest sensitivity and specificity (fig. 1). Accordingly, the cut-off values determined associated with 5-year OS for NLR was 3.0 (AUC:0.651, sensitivity: 64.5%, specificity: 63.3%; p = 0.011) for PLR was 190 (AUC:0.477, sensitivity: 51.6%, specificity: 50.0%; p = 0.696), for CAR was 1.73 (AUC:0.589, sensitivity: 42.9%, specificity: 46.4%; p = 0.470), for MPR was 29.0 (AUC:0.509, sensitivity: 48.4%, specificity: 48.0%; p = 0.877), for SII was 816 (AUC:0.612, sensitivity: 61.3%, specificity: 60.2%; p = 0.061), for PrNI was 42.0 (AUC:0.454, sensitivity: 48.0%, specificity: 46.1%; p = 0.483), and for HALP was 0.14 0 (AUC:0.561, sensitivity: 72.0%, specificity: 51.7%; p = 0.355). The cut-off values determined associated with 3-year DFS for NLR was 3.0 (AUC:0.662, sensitivity: 66.7%, specificity: 57.3%; p = 0.006), for PLR was 195 (AUC:0.530, sensitivity: 51.5%, specificity: 51.0%; p = 0.612), for CAR was 1.7 (AUC:0.250, sensitivity: 20.0%, specificity: 43.3%; p = 0.077), for MPR was 29.0 (AUC:0.490, sensitivity: 51.5%, specificity: 51.0%; p = 0.867), for SII was 750 (AUC:0.653, sensitivity: 78.8%, specificity: 60.4%; p = 0.009), for PrNI was 42.0 (AUC:0.516, sensitivity: 58.6%, specificity: 49.4%; p = 0.802), and for HALP was 0.14 (AUC:0.536, sensitivity: 62.1%, specificity: 49.4%; p = 0.560).

Univariate and Multivariate Analysis of DFS and OS

In the univariate Cox regression analysis elevated carcinoembryonic antigen (CEA) levels were a strong negative prognostic factor (HR: 5.337; 95% CI: 2.255–12.633; $p < 0.001$) for DFS. Systemic inflammation markers such as neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) were also significantly correlated with shorter DFS (HR: 2.884; 95% CI: 1.362–6.107; $p = 0.006$ and HR: 4.557; 95% CI: 1.870–11.102; $p = 0.001$, respectively) (Table 3). Among histopathological features, mucinous adenocarcinoma morphology (HR: 3.021; 95% CI: 1.183–7.713; $p = 0.021$), tumor size ≥5 cm (HR: 2.404; 95% CI: 1.107–5.221; $p = 0.027$), advanced T and N stages (pT4: HR: 9.022; 95% CI: 2.689–30.272; $p < 0.001$; pN2: HR: 11.530; 95% CI: 4.586–28.988; $p < 0.001$), poor differentiation (HR: 2.444; 95% CI: 1.042–5.733; $p = 0.040$), lymphovascular invasion (HR: 3.637; 95% CI: 1.569–8.433; $p = 0.003$), perineural invasion (HR: 3.198; 95% CI: 1.537–6.653; $p = 0.002$), and extranodal extension (HR: 4.044; 95% CI: 1.652–9.897; $p = 0.002$) were significantly associated with worse DFS outcomes (Table 4).

Male sex (HR: 2.209; 95% CI: 1.013–4.819; $p = 0.046$), cardiac comorbidities (HR: 2.569; 95% CI: 1.071–6.162; $p = 0.034$), elevated CEA (HR: 4.240; 95% CI: 1.764–10.194; $p = 0.001$), high NLR (HR: 2.445; 95% CI: 1.170–5.109; $p = 0.017$), increased ALP (HR: 2.329; 95% CI: 1.007–5.387; $p = 0.048$), high HALP (HR: 2.449; 95% CI: 1.021–5.873; $p = 0.045$) were found to significantly predict poorer OS (Table 3). Tumor-related factors such as mucinous histology (HR:,2.731; 95%CI: 1.085-6.876; $p = 0.033$), ypT3 stage (HR: 8.931; 95%CI: 2.098-38.016; p = 0.003), ypT4 stage (HR: 14.695; 95% CI: 3.032–71.218; $p = 0.001$), pN2 status (HR: 5.864; 95% CI: 2.379–14.457; $p < 0.001$), poor differentiation (HR: 3.951; 95% CI: 1.809–8.633; $p = 0.001$), presence of LVI (HR: 2.197; 95%CI: 1.033-4.675; p = 0.041) and ENE (HR: 2.527; 95% CI: 1.053–6.062; $p = 0.038$) were significantly associated with decreased OS (Table 4).

In the multivariate Cox proportional hazards model, regarding DFS, elevated CEA levels (HR: 4.411; 95% CI: 1.848–10.529; $p = 0.001$), high SII (HR: 3.204; 95% CI: 1.083–9.483; $p = 0.035$); ypT3 (HR: 7.349; 95% CI: 1.543–34.997; $p = 0.012$) and ypT4 (HR: 15.320; 95% CI: 2.487–94.384; $p = 0.003$), stage III (HR: 5.059; 95% CI: 1.074–23.823; $p = 0.040$), stage IV (HR: 7.371; 95% CI: 1.154–47.100; $p = 0.035$) and extra nodal extension (ENE) (HR: 6.831; 95% CI: 2.060–22.650; $p = 0.002$) were independent predictors of recurrence. For OS in the multivariate Cox regression analysis, independent prognostic indicators included male gender (HR:3.825; 95%CI: 0.818-17.890; $p = 0.088$), elevated CEA (HR: 5.975; 95% CI: 1.364–26.172; $p = 0.018$), elevated ALP (HR: 6.496; 95%CI: 1.309 – 32.244; $p = 0.022$), high NLR (HR: 6.672; 95%CI: 0.919-48.453; $p = 0.061$), TNM stage III (HR: 5.059; 95%CI: 1.074-23.823; p = 0.040), TNM stage IV (HR: 7.371; 95% CI: 1.154–47.100; $p = 0.035$), poor tumor differentiation (HR: 20.863; 95% CI: 4.955–87.850; $p < 0.001$) and LVI (HR: 4.194; 95% CI: 0.964-18.246); $p = 0.056$) were independently associated with worse OS (table 3-4).

Survival Analysis

In the present study the 1-, 3-, and 5-year OS rates were 99.2%, 67.4%, and 30.2% respectively. The 1-, and 3-year DFS rates were 94.5%, 79.1%. According to Kaplan–Meier survival analysis of the 3-year DFS, patients with high CEA levels (23% vs. 69%; $p < 0.001$) and SII levels (38% vs. 76%; $p < 0.001$) had

significantly poorer outcomes compared to those with normal levels. Histopathologic features including advanced tumor depth (ypT3-T4) (33% vs. 88%; p = 0.001) and presence of ENE (12% vs. 50%; p = 0.001) were significantly associated with disease recurrence risk (Fig. 2). The 5-year OS rate was significantly lower in patients with elevated preoperative CEA levels (18% vs. 74%; p < 0.001), elevated ALP levels (33% vs. 63%; p = 0.042), and elevated NLR levels (38% vs. 59%; p = 0.014) compared to those with normal levels. Among the demographic parameters, only the male gender was associated with shorter 5-year survival compared to females (41% vs. 61%; p = 0.041). Histopathologic features including poor tumor differentiation (25% vs. 52%; p < 0.001), the presence of LVI (60% vs. 74%; p = 0.036), and TNM III and IV stages (36% vs. 57%; p < 0.001) were all significantly correlated with worse OS (Fig. 3).

Operative Procedures and Perioperative Findings

Surgical procedures and techniques, estimated blood loss, operative time, ileal diversion status or anastomotic leakage were not significantly associated with DFS and OS (Table 5).

Performance of the REACT Score in Predicting Recurrence

The prognostic performance of the REACT Score was assessed using ROC curve analysis and Kaplan–Meier survival estimates. The AUC for the ROC curve of the REACT Score in predicting tumor recurrence was 0.813 (95% CI: 0.731–0.894, p < 0.001). Based on ROC curve characteristics, a score of ≥3 provided the optimal cut-off value, yielding a sensitivity of 84.8% and specificity of 60.4% for predicting tumor recurrence. Kaplan–Meier survival analysis revealed a significant difference in DFS across the three groups (*log-rank p* <0.001) (Fig. 4). The mean estimated DFS was 107.1 months in the low-risk group, 76.1 months in the intermediate-risk group, and 49.3 months in the high-risk group. Notably, only 5 patients (7.9%) in the low-risk group and 18 patients (32.1%) in the intermediate-group experienced recurrence, while the high-risk group demonstrated a 100% recurrence rate experienced recurrence during follow-up. None of the high-risk group patients achieved 3- or 5-year DFS (Table 6).

DISCUSSION

In this retrospective cohort study, we identified several perioperative and histopathological variables that independently predict DFS and OS in patients with rectal cancer undergoing LAR following NACT. By integrating serum based systemic inflammatory markers, tumoral histopathological features, and clinical variables, we developed a novel prognostic scoring system - REACT - that enables effective recurrence risk stratification. The score also reflects the model's clinical objective - to react early to recurrence risk - by integrating biological behavior, tumor burden, and inflammatory indicators into a unified prognostic index. In this context, the REACT score produced a strong prognostic performance, with a high area under the ROC curve (AUC = 0.813), and reliably distinguished patients with markedly different recurrence risks. This study's findings offer a clinically applicable, easily reproducible scoring model that addresses a critical need for individualized risk prediction beyond conventional TNM staging. Moreover, to our knowledge, it has not been previously researched in this specific configuration integrating ENE, systemic inflammatory response, and conventional prognostic indicators.

Age, sex, BMI, and comorbidities are examples of demographic variables that have been identified as significant predictors of oncologic outcomes in rectal cancer. In the present study, advanced age was not an independent predictor of DFS or OS, consistent with previous studies suggesting that age alone may not directly impact on oncological outcomes when appropriate treatment is administered [19]. However, other reports have associated advanced age with reduced tolerance to NACT and increased surgery related risk, particularly in frail patients with multiple comorbidities [20]. It was observed that there is a trend toward worse outcomes in male patients, which aligns with prior findings indicating higher recurrence rates and lower survival in male gender, potentially due to pelvic anatomical constraints during surgery and differential immune-inflammatory responses [21]. Some studies in the literature link obesity with adverse pathological features and reduced disease control [22, 23], whereas others emphasize the role of visceral adiposity and sarcopenic obesity on prognosis rather than BMI [24]. However, no significant relation was found between BMI and prognosis in our study.

Systemic inflammatory response to tumoral cells has been revealed as a biological mechanism influencing cancer progression and treatment response in colorectal malignancies. Accumulating evidence supports the prognostic value of inflammation-based indices such as the NLR, PLR, PrNI, and SII in rectal cancer [7, 11, 14, 16, 25–27]. In the present study, higher SII and NLR values were significantly associated with decreased DFS, reinforcing the hypothesis that heightened systemic inflammatory response reflects an aggressive tumor microenvironment and impaired host immunity. These findings are consistent with recent meta-analyses demonstrating that high NLR and SII levels predict poor DFS and OS across various stages of rectal cancer [7, 11, 14]. Moreover, combined indices incorporating inflammatory and nutritional parameters, such as SII+PrNI or SIRI+PrNI, have been shown to outperform single biomarkers in prognostic accuracy [12, 13]. Our results further validate the utility of integrating such markers into comprehensive prognostic models for risk stratification in clinical practice.

In our group, NLR and SII were found to be the most reliable prognostic markers among the systemic inflammatory measures. In Cox regression analysis, both indicators were linked to poor DFS, indicating their potential use as easily accessible, non-invasive surrogates of tumor aggressiveness and immune response. In addition to their statistical significance, SII and NLR were included in the REACT score due to their cost-effectiveness, repeatability, and ease of interpretation in standard clinical settings. The advantage of SII over other inflammatory indicators like PLR or CAR in predicting recurrence and survival has also been shown by recent research in the literature [11, 14]. Moreover, poor tumor-infiltrating lymphocyte activity and unfavorable histologic characteristics may be linked to increased NLR, connecting local immune evasion mechanisms with systemic inflammation [7]. These results support the potential significance of these indicators in directing postoperative surveillance and adjuvant treatment approach decisions in the management of rectal cancer and offer further validity for their inclusion in structured prognostic models.

The biological behavior of rectal cancer and its tendency to recur are known to be determined by tumoral histological features. In line with known findings in the literature, the presence of ENE and advanced ypT stage (T3–T4) were observed to be independently related with worse DFS in the recent study [27].

Notably, ENE has been found to be a very aggressive pathological characteristic that indicates a large tumor burden outside of the capsule. Recent research indicates that ENE is substantially associated with early tumor recurrence and poor long-term outcomes, especially when evaluated using preoperative radiological examinations, despite the paucity of evaluations in the literature data [12]. Beyond traditional nodal staging, the incorporation of ENE into the REACT score improves risk discrimination by adding a potent signal of pathogenic feature.

Several perioperative surgery related factors, including surgical technique, operative time, intraoperative blood loss, the presence of diverting ileostomy, and postoperative complications as anastomotic leakage, have been investigated for their potential influence on long-term oncologic outcomes in rectal cancer. In the present study, despite their association with postoperative morbidity, none of these parameters showed a statistically significant relation with DFS or OS which aligns with recent reports suggesting that these parameters may not directly affect oncological outcomes in standardized surgical settings [19]. Regarding surgical techniques, there were no significant differences in survival outcomes between patients undergoing laparoscopic versus open LAR. This is consistent with findings from large-scale meta-analyses and long-term randomized trials as 10-year follow-up of the COREAN trial [1, 24]. Although anastomotic leakage was rare in our cohort and there was no significant association with survival outcome, recent literature has linked this complication to increased local recurrence and impaired long-term oncologic outcomes [6]. While the recent study's findings emphasized that not all surgical parameters independently predict oncologic outcomes, their indirect effects—particularly through modulation of postoperative morbidity—should be considered in planning treatment strategies and recurrence risk assessment according to literature data.

Many prognostic models have been defined as conventional nomograms and machine learning–based recurrence prediction tools in the management of rectal cancer [4–6]. While these nomograms and scoring models have advanced risk estimation by incorporating multiple clinicopathologic features, many remain limited by their reliance on postoperative variables, lack of inflammatory inputs, or complexity that restricts their use in clinical practice For example, nomograms created by Zhang et al. and Weiser et al. place less emphasis on biological or inflammatory activity and more on tumor stage, nodal status, and pathological response to neoadjuvant therapy [3, 4]. On the other hand, our REACT score combines systemic and tumor-driven inflammatory variables into a platform that is both practically applicable and accessible during surgery. Additionally, REACT provides a tri-level categorization that more accurately reflects clinical heterogeneity, whereas many prediction models stratify risk continuously or with cutoffs. The REACT score may also help the doctor make decisions about preoperative oncological treatment length and protocols, such as choosing between total neoadjuvant therapy (TNT) and standard chemoradiotherapy, due to its practicality and predictive usefulness for recurrence risk. REACT offers a unique, multidisciplinary approach to the prognostic scoring system in rectal cancer by filling in the gaps in the current predictive models. This opens the door for additional validation and possible incorporation into structured clinical models.

Limitations:

There are a number of limitations to this study that should be noted. First, the results may not be as applicable to wider patient populations due to the retrospective and single-center methodology, which may induce selection bias. Second, the REACT score was created and validated within a single cohort, despite the fact that it includes clinically easily accessible and serum-based inflammatory relevant variables. External validation in independent datasets is necessary to verify its applicability and assess the degree of influence across various clinical settings. Although the REACT model showed good predictive accuracy in this investigation, further prospective-randomized research is needed to determine its potential usefulness in directing postoperative monitoring procedures and treatment decision-making.

CONCLUSION

In this retrospective cohort analysis, we created a straightforward but reliable methodology that may efficiently stratify patients based on recurrence risk by including perioperative characteristics into a novel composite scoring model, the REACT score. In contrast to many current nomograms or prognostic scoring systems, REACT offers a more complete picture of the behavior of rectum cancer by incorporating both tumoral histopathologic criteria and serum-based inflammatory markers. The model's potential utility in normal practice and customized treatment planning is highlighted by its strong discriminatory competence and ease of clinical application. The findings of this study robustly support the REACT score as a promising prognostic instrument that may enhance personalized oncologic treatment management in patients with rectal cancer.

Declarations

Ethics: This study was approved by the Firat University Faculty of Medicine Scientific Research Ethics Committee (Approval date and No: 14.05.2025-34457) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. This article does not contain any experiments involving human participants or animals performed by any of the authors.

Informed Consent: Owing to the retrospective design of the study, the requirement for obtaining written informed consent from each patient was waived by the ethics committee.

Acknowledgements: None

Funding: No source of funding or research and/or publication. Authors declare they have nothing to disclose.

Conflict of interest: Authors declare no conflicts of interest or financial ties to disclose.

Data availability statement: The data in the study will be available upon reasonable request to the corresponding author.

Conflicts of Interest: All authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

The manuscript has not been published elsewhere in any language.

References

1. Park JW, Kang SB, Hao J, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): 10-year follow-up of an open-label, non-inferiority, randomised controlled trial. Lancet Gastroenterol Hepatol. 2021;6(7):569–77.
2. Detering R, Rutgers MLW, Bemelman WA, et al. Prognostic importance of circumferential resection margin in the era of evolving surgical and multidisciplinary treatment of rectal cancer: A systematic review and meta-analysis. Surgery. 2021;170(2):412–31.
3. Weiser MR, Chou JF, Keshinro A, Colorectal Cancer Disease Management Team of Memorial Sloan Kettering Cancer Center, et al. Development and Assessment of a Clinical Calculator for Estimating the Likelihood of Recurrence and Survival Among Patients With Locally Advanced Rectal Cancer Treated With Chemotherapy, Radiotherapy, and Surgery. JAMA Netw Open. 2021;4(11):e2133457.
4. Zhang C, Zhao S, Wang X. A Prognostic Nomogram for T3N0 Rectal Cancer After Total Mesorectal Excision to Help Select Patients for Adjuvant Therapy. Front Oncol. 2021;11:698866.
5. Jeon Y, Kim YJ, Jeon J, et al. Machine learning based prediction of recurrence after curative resection for rectal cancer. PLoS ONE. 2023;18(12):e0290141.
6. Saadoun JE, Meillat H, Zemmour C, et al. Nomogram to predict disease recurrence in patients with locally advanced rectal cancer undergoing rectal surgery after neoadjuvant therapy: retrospective cohort study. BJS Open. 2022;6(6):zrac138.
7. Hamid HKS, Davis GN, Trejo-Avila M, et al. Prognostic and predictive value of neutrophil-to-lymphocyte ratio after curative rectal cancer resection: A systematic review and meta-analysis. Surg Oncol. 2021;37:101556.
8. Gawiński C, Mróz A, Roszkowska-Purska K, et al. A Prospective Study on the Roles of the Lymphocyte-to-Monocyte Ratio (LMR), Neutrophil-to-Lymphocyte Ratio (NLR), and Platelet-to-Lymphocyte Ratio (PLR) in Patients with Locally Advanced Rectal Cancer. Biomedicines. 2023;11(11):3048.
9. Nishi M, Shimada M, Tokunaga T, et al. Lymphocyte to C-reactive protein ratio predicts long-term outcomes for patients with lower rectal cancer. World J Surg Oncol. 2021;19(1):201.
10. Wang Y, Yang L, Bao H, et al. Utility of ctDNA in predicting response to neoadjuvant chemoradiotherapy and prognosis assessment in locally advanced rectal cancer: A prospective cohort study. PLoS Med. 2021;18(8):e1003741.
11. Tan Y, Hu B, Li Q, Cao W. Prognostic value and clinicopathological significance of pre-and post-treatment systemic immune-inflammation index in colorectal cancer patients: a meta-analysis. World J Surg Oncol. 2025;23(1):11.

12. Li KJ, Zhang ZY, Sulayman S, et al. Prognostic value of combined systemic inflammation response index and prognostic nutritional index in colorectal cancer patients. World J Gastrointest Surg. 2024;16(12):3794–805.
13. Li H, Sun W, Fu S, et al. Prognostic value of the preoperative prognostic nutritional and systemic immunoinflammatory indexes in patients with colorectal cancer. BMC Cancer. 2025;25(1):403.
14. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol. 2017;23(34):6261–72.
15. Martín-Carnicero A, Ramalle-Gomara E, Rubio-Mediavilla S, et al. Prognostic and Predictive Biomarkers in Patients with Locally Advanced Rectal Cancer (LARC) Treated with Preoperative Chemoradiotherapy. J Clin Med. 2022;11(20):6091.
16. Yamamoto T, Kawada K, Obama K. Inflammation-Related Biomarkers for the Prediction of Prognosis in Colorectal Cancer Patients. Int J Mol Sci. 2021;22(15):8002.
17. Li QY, Yang D, Guan Z, et al. Extranodal Extension at Pretreatment MRI and the Prognostic Value for Patients with Rectal Cancer. Radiology. 2024;310(3):e232605.
18. Amin MB, Edge S, Greene F, et al. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing; 2017.
19. Høydahl Ø, Edna TH, Xanthoulis A, et al. The impact of age on rectal cancer treatment, complications and survival. BMC Cancer. 2022;22(1):975.
20. Georgescu DE, Patrascu T, Georgescu TF et al. Diabetes Mellitus as a Prognostic Factor for Locally Advanced Rectal Cancer. In Vivo. 2021 Jul-Aug;35(4):2495–2501.
21. Samawi HH, Yin Y, Speers CH, Cheung WY. Sex Disparities in Outcomes of Early Stage Colorectal Cancer: A Population-Based Study. Clin Colorectal Cancer. 2018;17(4):e711–7.
22. Zhu Y, Guo X, Zhang Q, Yang Y. Prognostic value of sarcopenia in patients with rectal cancer: A meta-analysis. PLoS ONE. 2022;17(6):e0270332.
23. Nguyen L, Shanmugan S. A Review Article: The Relationship Between Obesity and Colorectal Cancer. Curr Diab Rep. 2024;25(1):8.
24. Kong M, Chen H, Shan K, et al. Comparison of Survival Among Adults With Rectal Cancer Who Have Undergone Laparoscopic vs Open Surgery: A Meta-analysis. JAMA Netw Open. 2022;5(5):e2210861.
25. Rossi S, Basso M, Strippoli A, et al. Are Markers of Systemic Inflammation Good Prognostic Indicators in Colorectal Cancer? Clin Colorectal Cancer. 2017;16(4):264–74.
26. Fagarasan G, Seicean R, Bintintan V, et al. The Value of Preoperative C-Reactive Protein to Albumin Ratio as a Prognostic Biomarker in Colon Cancer Patients. Med (Kaunas). 2024;60(7):1054.
27. Chen K, Collins G, Wang H, Toh JWT. Pathological Features and Prognostication in Colorectal Cancer. Curr Oncol. 2021;28(6):5356–83.

Tables

Tables 1 to 6 are available in the Supplementary Files section.

Figures

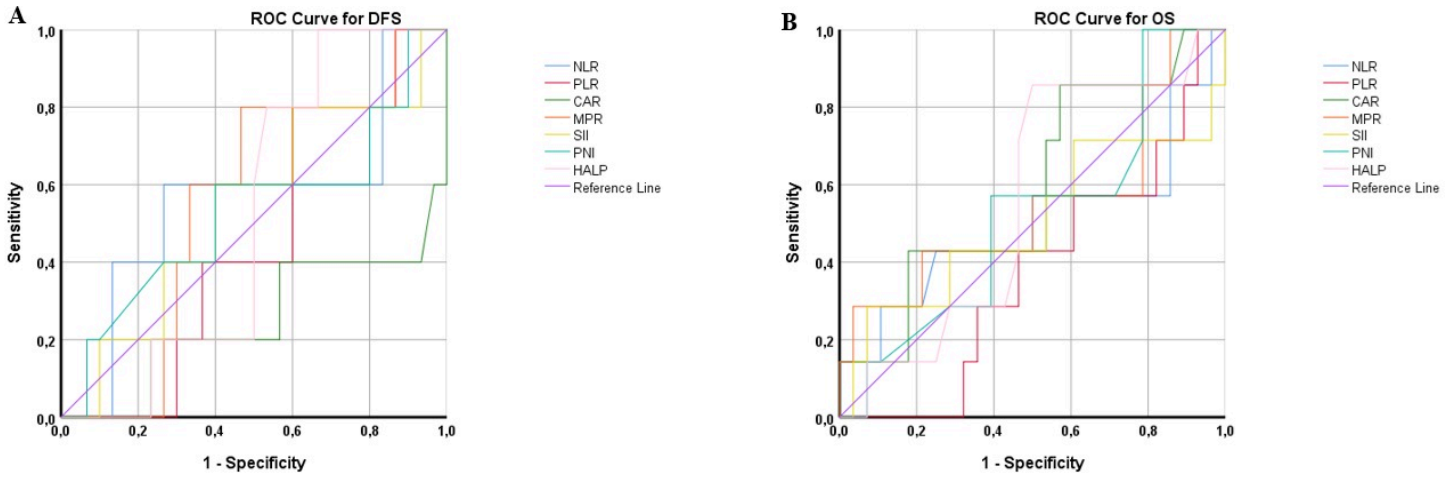


Figure 1

ROC Curve analysis of systemic inflammatory markers for **A)** DFS and **B)** OS in rectum cancer patients. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein-to-albumin ratio (CAR), MPV-to-platelet ratio (MPR), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), and hemoglobin-albumin-lymphocyte-platelet score (HALP).

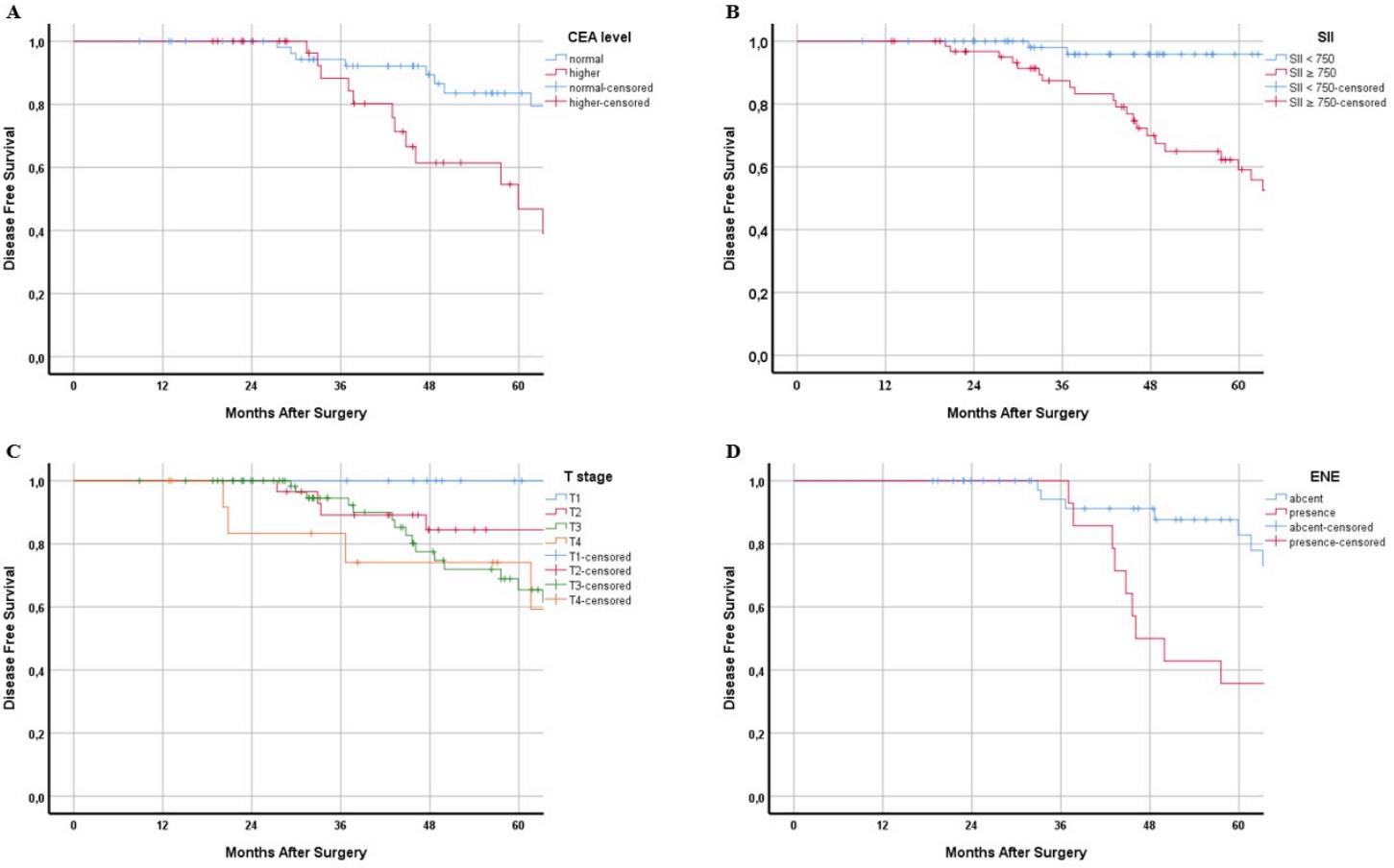


Figure 2

Disease-Free Survival (DFS) based on prognostic indicators of rectum cancer. Kaplan–Meier curves for DFS according to individual prognostic indicators. A) Carcinoembryonic antigen (CEA) level (normal vs. high). B) Systemic immune-inflammation index (SII) <750 vs. ≥750. C) pT stage (T1–T4). D) Presence vs. absence of extranodal extension (ENE).

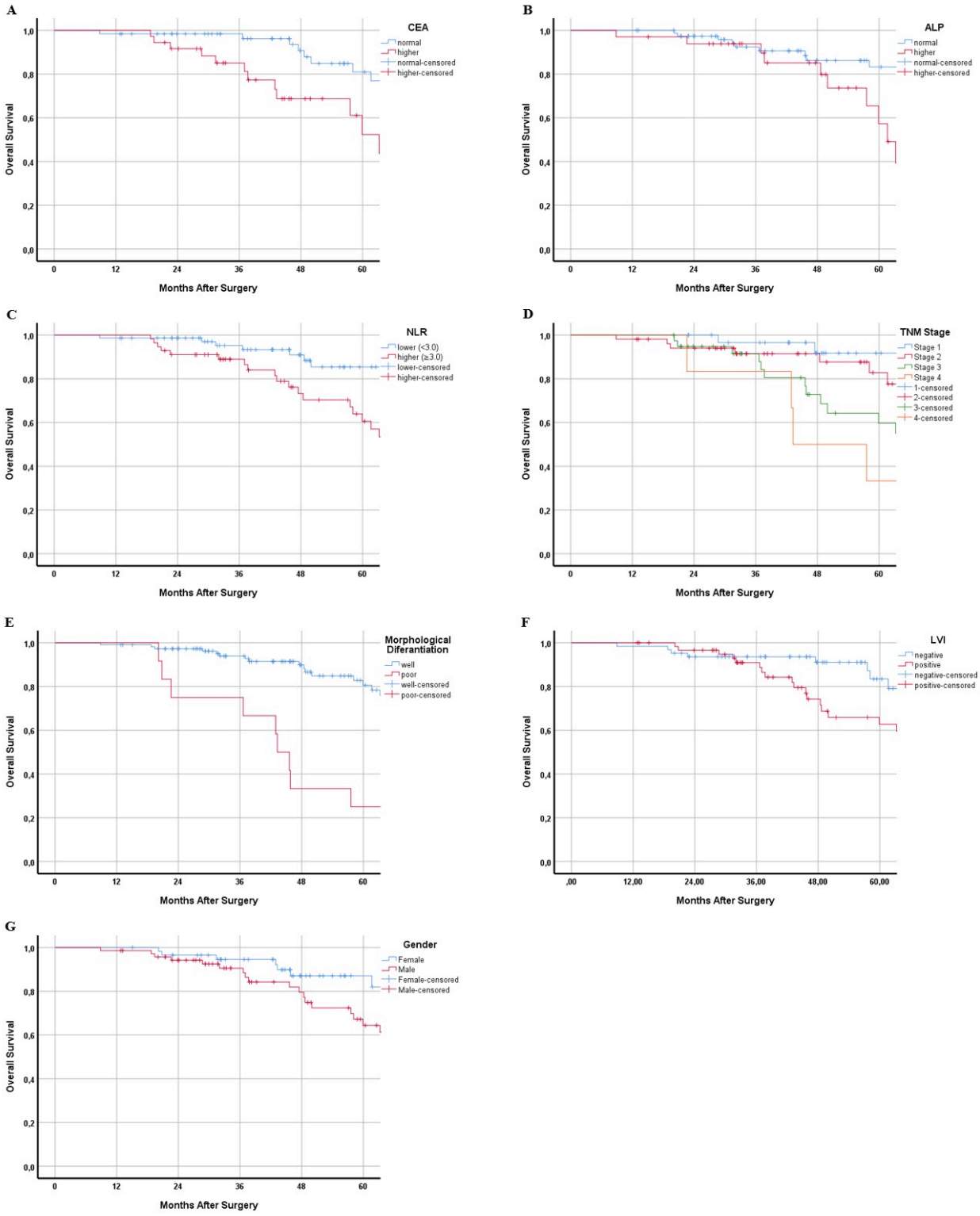


Figure 3

Overall Survival (OS) Based on Prognostic Indicators. Kaplan–Meier curves for OS based on various prognostic factors. **A)**Carcinoembryonic antigen (CEA) level (normal vs. high). **B)** Serum ALP level (normal vs. high). **C)** Neutrophil-to-lymphocyte ratio (NLR ≤3 vs. >3). **D)** TNM stage (I–IV). **E)** Tumor morphological differentiation (well vs. poor). **F)** Lymphovascular invasion (LVI) (negative vs. positive). **G)** Gender (female vs. male)

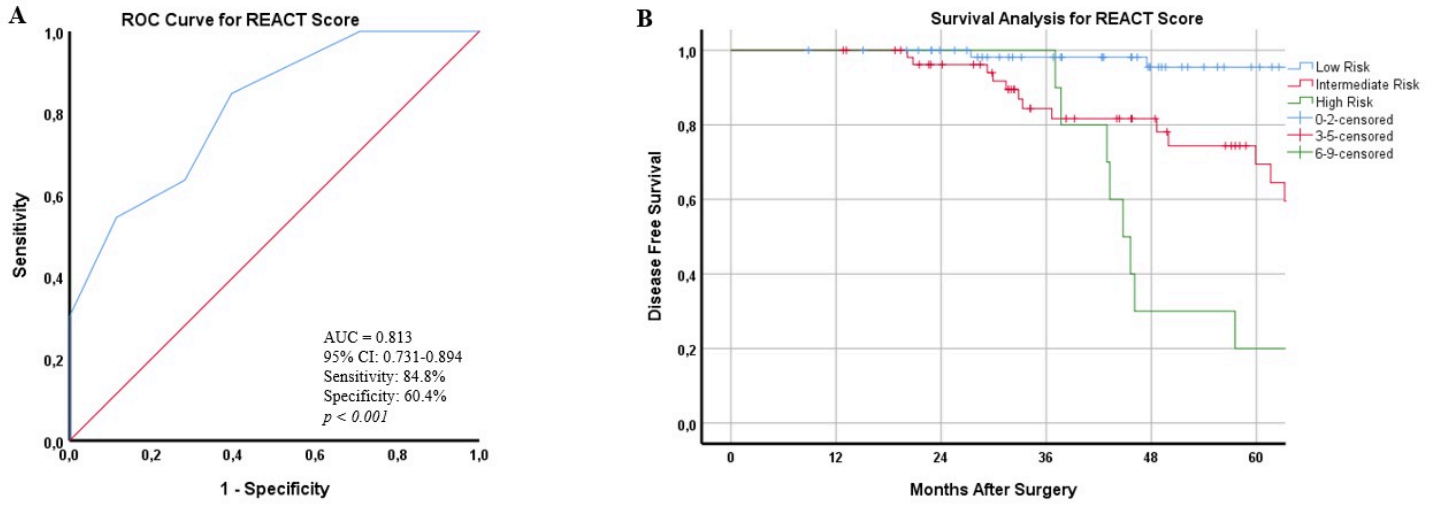


Figure 4

Prognostic performance of the REACT Score in predicting tumor recurrence. **A)** ROC curve of the REACT Score for predicting tumor recurrence. **B)** Kaplan–Meier curves for DFS according to REACT Score risk stratification. Patients were classified as low risk (0–2 points), intermediate risk (3–5 points), and high risk (6–9 points). DFS was significantly shorter in the higher score groups (*log-rank p* < 0.001).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.ComponentsandScoringSystemoftheREACTScore.docx
- Table2.Patientcharacteristics.docx
- Table3.systemicinflammatoryindicators.docx
- Table4.histopathologicalparameters.docx
- Table5.surgicalfindingsinrectumcancerpatients.docx
- Table6.TumorRecurrenceRiskStratificationREACTScore.docx