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ORIGINAL RESEARCH

Analysis of Risk Factors and Development of a Predictive Model for Prognosis in Early-Stage Rectal Cancer Patients

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Background: Early-stage rectal cancer remains a significant clinical challenge due to variable patient outcomes. Identifying prognostic factors and developing an accurate predictive model is essential for optimizing treatment strategies and improving survival.

Methods: This retrospective study enrolled 156 patients with histologically confirmed early-stage rectal cancer treated from January 2016 to December 2019. Patients with complete clinical, pathological, and laboratory data and a minimum follow-up of 5 years were included. Data on demographics, body mass index, carcinoembryonic antigen levels, tumor characteristics, and lymph node status were extracted from electronic medical records. Univariate survival analysis was performed using the Log rank test, followed by multivariate analysis via Cox proportional hazards regression. A prognostic nomogram was constructed using the rms package, and its performance was evaluated with the concordance index and Hosmer–Lemeshow test. Internal validation was conducted through 1000 bootstrap resampling iterations.

Results: Univariate analysis demonstrated that factors such as age, BMI, CEA levels, T stage, lymph node metastasis, tumor histology, and lymph node retrieval significantly influenced 5-year overall survival. Multivariate analysis confirmed these variables as independent prognostic factors. The resulting nomogram, incorporating seven risk factors, exhibited robust discriminative ability with a corrected C-index of 0.806 (95% CI, 0.768–0.861) and excellent calibration (Hosmer–Lemeshow $\chi^2 = 2.865$, $P = 0.891$).

Conclusion: The predictive nomogram developed in this study provides a practical and reliable tool for individualized risk assessment and treatment planning in early-stage rectal cancer patients, potentially enhancing clinical decision-making and patient outcomes.

Keywords: rectal cancer, early-stage, prognostic factors, nomogram, survival prediction, risk assessment

Introduction

Rectal cancer remains a significant public health challenge worldwide, with early-stage disease representing a critical window for intervention. Despite advances in diagnostic techniques and therapeutic strategies, accurate prognostication in early-stage rectal cancer patients remains a clinical necessity. Early-stage rectal cancer, typically classified as stage I or II according to the tumor-node-metastasis (TNM) system, generally presents a favorable prognosis compared to advanced disease.[1,2] However, heterogeneity in tumor biology and patient-specific characteristics can lead to variations in outcomes, even within this subgroup. Traditional prognostic models based solely on pathological stage have limitations, as they often fail to capture the complex interplay between clinical, pathological, and molecular factors. Therefore, there is a growing interest in incorporating a wider range of variables into prognostic models to enhance predictive accuracy.[3–5]

Recent studies have identified several potential risk factors that may influence survival outcomes in early-stage rectal cancer patients.[6,7] These factors include, but are not limited to, patient demographics (such as age and sex), comorbid conditions, tumor characteristics (including tumor size, histological grade, and lymphovascular invasion), and molecular markers. The integration of these diverse factors into a single predictive framework is essential to address the

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multifactorial nature of rectal cancer prognosis. Nomograms have emerged as a robust statistical tool to predict clinical outcomes by integrating multiple prognostic variables. Unlike conventional staging systems, nomograms generate individualized risk estimates based on the weighted contribution of each factor. This model facilitates clinical decision-making by providing a more nuanced assessment of patient prognosis. The development of a nomogram for early-stage rectal cancer involves several methodological considerations, including the selection of relevant risk factors, statistical validation, and calibration of the predictive model. A rigorous analytical approach is necessary to ensure that the nomogram reliably discriminates between patients with different prognostic profiles and accurately predicts survival outcomes.[8,9]

This study aims to analyze risk factors and develop a nomogram model to predict prognosis, thereby providing a quantitative tool to guide individualized treatment decisions and surveillance strategies. The findings may have implications for tailoring treatment plans, determining the need for adjuvant therapies, and designing follow-up protocols, ultimately improving patient outcomes in early-stage rectal cancer.

Methods

Study Design

This retrospective study included patients treated at our institution between January 2016 and December 2019. The study population comprised patients with histologically confirmed rectal cancer who were diagnosed with early-stage disease, defined as stage I or II according to the tumor-node-metastasis (TNM) classification system. Only patients with complete clinical, pathological, and laboratory data—including both preoperative and postoperative parameters—were included, and at least five years of documented follow-up, or observation until the occurrence of death or confirmed disease recurrence (whichever came first), was required to ensure robust evaluation of survival outcomes and disease recurrence. Patients who received any form of neoadjuvant therapy, such as chemotherapy, radiotherapy, or chemoradiotherapy, were excluded to eliminate potential confounding effects on pathological assessments and survival outcomes. Additionally, individuals with a history of synchronous or metachronous malignancies or those who underwent palliative or non-curative interventions were excluded to maintain a focus on long-term prognosis following curative treatment. Ultimately, a total of 156 early-stage rectal patients were enrolled in this study. Informed consent was obtained from all subjects and/or their legal guardian(s). Our study was comprehensively reviewed and approved by our hospital's ethics committee, adhering to all applicable guidelines and regulations. The design, execution, and reporting of the research were conducted in strict compliance with the ethical standards outlined in the Declaration of Helsinki for studies involving human subjects. To ensure confidentiality and privacy, all personal identifiers were anonymized before data analysis.

Data Collection

Data was extracted from the hospital's electronic medical record management system, enabling the collection of comprehensive clinical, pathological, and follow-up data. The dataset included patient demographics such as age and sex; anthropometric measurements, notably body mass index (BMI); and relevant laboratory parameters including carcinoembryonic antigen (CEA) levels. Detailed tumor characteristics were also obtained, encompassing tumor type, histological differentiation, T stage, presence or absence of lymph node metastasis, tumor location, and the total number of lymph nodes retrieved during surgical procedures. Tumour grade was recorded according to the World Health Organization three-tier histological grading system (WHO three-tier system)—well differentiated (G1), moderately differentiated (G2), and poorly/undifferentiated (G3–4); for analysis, G3–4 were classified as "low differentiated" and G1–2 as "non-low differentiated" owing to the small number of G3–4 cases.[10,11] Postoperative follow-up was systematically conducted through both telephone interviews and outpatient clinic visits, with all patients monitored until December 31, 2024.

Statistical Analysis

All analyses were performed using SPSS version 27.0 and R version 4.3.0. Categorical variables are presented as frequencies and percentages, with group comparisons conducted via the chi-square test. Univariate survival analysis

employed the Log rank test; variables with $P < 0.05$ were entered into a multivariate Cox proportional hazards regression. Five-year overall survival was estimated by the Kaplan–Meier method. Optimal cut-points for continuous variables were identified with maximally selected rank statistics (Youden index). Data-derived values (age 59.3 y, BMI 24.8 kg/m², retrieved nodes 11.6) were rounded to the nearest guideline-endorsed clinical thresholds (60 y, 25 kg/m², 12 nodes) to enhance interpretability; CEA retained the conventional 5 μg/L limit of normal. In R, the rms package was used to construct the prognostic nomogram from independent predictors. Internal validation was carried out by bootstrap resampling (n = 1000), with calibration curves plotted and the concordance index (C-index) computed to assess model agreement. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Clinical Characteristics and Survival Outcomes

A total of 156 early-stage rectal cancer patients were included in the study based on the predefined inclusion and exclusion criteria. The cohort comprised 88 males (56.4%) and 68 females (43.6%), with patient ages ranging from 21 to 86 years and a mean age of 60.91 ± 10.9 years. According to the TNM classification, 28 patients (17.9%) were categorized as stage I, while 128 patients (82.1%) were classified as stage II. Lymph node metastasis was identified in 29 patients, corresponding to an 18.6% metastasis rate. The follow-up period extended to 31 December 2024, with a median duration of 63.1 months and an observed range of 12–80 months—the lower bound reflecting the 14 patients who died within five years of surgery. During this period, the median overall survival was 53.98 months, and the estimated 5-year overall survival rate was 79.49%.

Univariate Analysis of Prognostic Factors

Univariate analysis was performed to evaluate the impact of various clinicopathological factors on 5-year overall survival in 156 early-stage rectal cancer patients. Age was a significant prognostic factor; patients aged <60 years exhibited a markedly higher survival rate (90.7%) compared to those aged ≥60 years (72.9%; $\chi^2 = 15.51$, $P < 0.001$). Similarly, a BMI <25 kg/m² was associated with superior survival (83.8% vs 73.7%; $\chi^2 = 5.15$, $P = 0.025$). Elevated carcinoembryonic antigen (CEA) levels (≥5 μg/L) significantly correlated with poorer outcomes, with a 5-year survival rate of only 64.1% compared to 83.7% in patients with CEA <5 μg/L ($\chi^2 = 14.7$, $P < 0.001$). In terms of tumor characteristics, T stage was significant; T1 tumors were linked to a 93.3% survival rate, whereas T2 tumors had a rate of 76.2% ($\chi^2 = 9.13$, $P = 0.003$). Lymph node metastasis dramatically reduced survival (55.2% vs 84.3% in node-negative cases; $\chi^2 = 28.31$, $P < 0.001$). Moreover, patients with adenocarcinoma, non–low differentiation, and retrieval of ≥12 lymph nodes demonstrated significantly better survival compared to their respective counterparts (all $P < 0.001$ for tumor type and differentiation, and $P = 0.001$ for lymph node retrieval). Sex and tumor location, however, were not significantly associated with survival outcomes ($P = 0.6$ and $P = 0.253$, respectively) (Table 1).

Multivariate Analysis of Independent Prognostic Factors

Cox multivariate regression analysis identified several independent risk factors influencing prognosis in early-stage rectal cancer patients. Notably, patients aged ≥60 years demonstrated a significantly elevated risk of adverse outcomes (OR 3.15, 95% CI: 1.75–5.95, $P < 0.001$). In addition, a BMI ≥25 kg/m² was independently associated with poorer survival (OR 2.10, 95% CI: 1.33–3.30, $P < 0.001$). Histological subtype also played a crucial role; mucinous adenocarcinoma conferred a significantly increased risk (OR 2.70, 95% CI: 1.35–5.42, $P < 0.001$). Elevated CEA levels (≥5 μg/L) further predicted worse outcomes (OR 1.70, 95% CI: 1.05–2.70, $P = 0.031$). Tumor stage was also an important determinant, with T2 stage associated with a higher risk (OR 2.60, 95% CI: 1.02–6.79, $P = 0.039$). The presence of lymph node metastasis markedly increased the risk (OR 3.80, 95% CI: 2.31–6.50, $P < 0.001$), as did retrieval of fewer than 12 lymph nodes (OR 1.96, 95% CI: 1.17–3.23, $P = 0.009$). In contrast, low differentiation did not reach statistical significance (OR 1.82, 95% CI: 0.86–3.80, $P = 0.118$) (Table 2).

Table 1 Univariate Analysis of Prognostic Factors Influencing Outcomes in Early-Stage Rectal Cancer Patients

Prognostic Factor	Category	n (n, %)	5-Year Survival Rate (%)	χ^2 Value	P value
Sex	Male	88 (56.4%)	77.3	0.31	0.6
	Female	68 (43.6%)	80.9		
Tumor Location	Low	66 (42.3%)	77.3	2.75	0.253
	Mid	76 (48.7%)	81.6		
	High	14 (9.0%)	64.3		
BMI (kg/m²)	<25	99 (63.5%)	83.8	5.15	0.025
	≥25	57 (36.5%)	73.7		
CEA (μg/L)	<5	117 (75.0%)	83.7	14.7	<0.001
	≥5	39 (25.0%)	64.1		
T Stage	T1	30 (19.2%)	93.3	9.13	0.003
	T2	126 (80.8%)	76.2		
Lymph Node Metastasis	No	127 (81.4%)	84.3	28.31	<0.001
	Yes	29 (18.6%)	55.2		
Tumor Type	Adenocarcinoma	147 (94.2%)	81.0	26.50	<0.001
	Mucinous adenocarcinoma	9 (5.8%)	33.3		
Differentiation	Non-low differentiated	146 (93.6%)	80.8	10.92	<0.001
	Low differentiated	10 (6.4%)	50.0		
Lymph Node Retrieval	<12	81 (51.9%)	71.6	11.36	0.001
	≥12	75 (48.1%)	86.7		
Age (years)	<60	97 (62.2%)	90.7	15.51	<0.001
	≥60	59 (37.8%)	72.9		

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; T, tumor; χ^2, chi-square.

Table 2 Cox Multivariate Regression Analysis of Independent Risk Factors for Prognosis in Early-Stage Rectal Cancer Patients

Factors	β Value	Standard Error Value	χ^2 Value	OR Value	95% CI for OR	P-value
BMI ≥25 kg/m²	0.750	0.238	9.40	2.10	1.33–3.30	<0.001
Mucinous adenocarcinoma	1.000	0.355	7.65	2.70	1.35–5.42	<0.001
CEA ≥5 μg/L	0.550	0.240	4.61	1.70	1.05–2.70	0.031
T2 stage	0.970	0.480	4.00	2.60	1.02–6.79	0.039
Lymph node metastasis	1.350	0.255	27.10	3.80	2.31–6.50	<0.001
Lymph node retrieval <12	0.700	0.260	6.63	1.96	1.17–3.23	0.009
Age ≥60 years	1.167	0.304	13.40	3.15	1.75–5.95	<0.001
Low differentiation	0.600	0.380	2.50	1.82	0.86–3.80	0.118

Abbreviations: BMI, body mass index; CEA, carcinoembryonic antigen; OR, odds ratio; T, tumor; χ^2, chi-square.

Development of a Prognostic Nomogram

A nomogram was developed to predict survival outcomes in early-stage rectal cancer patients based on seven independent risk factors identified through multivariate logistic regression analysis. Each variable was assigned a specific point value on the nomogram's axis. For each patient, the corresponding score was determined by projecting the variable's value vertically onto the scoring scale. The sum of these individual scores yields a total score, which is then mapped to a survival probability on the nomogram's reference axis. Notably, higher total scores correlate with a lower probability of survival (Figure 1).

Calibration of the Nomogram Model

Internal validation of the nomogram was performed using a computer-simulated bootstrap resampling method with 1000 iterations. The corrected concordance index (C-index) was 0.806 (95% CI, 0.768–0.861), indicating excellent discriminative ability of the model. Additionally, the Hosmer–Lemeshow goodness-of-fit test yielded a χ^2 value of 2.865 (P = 0.891), which

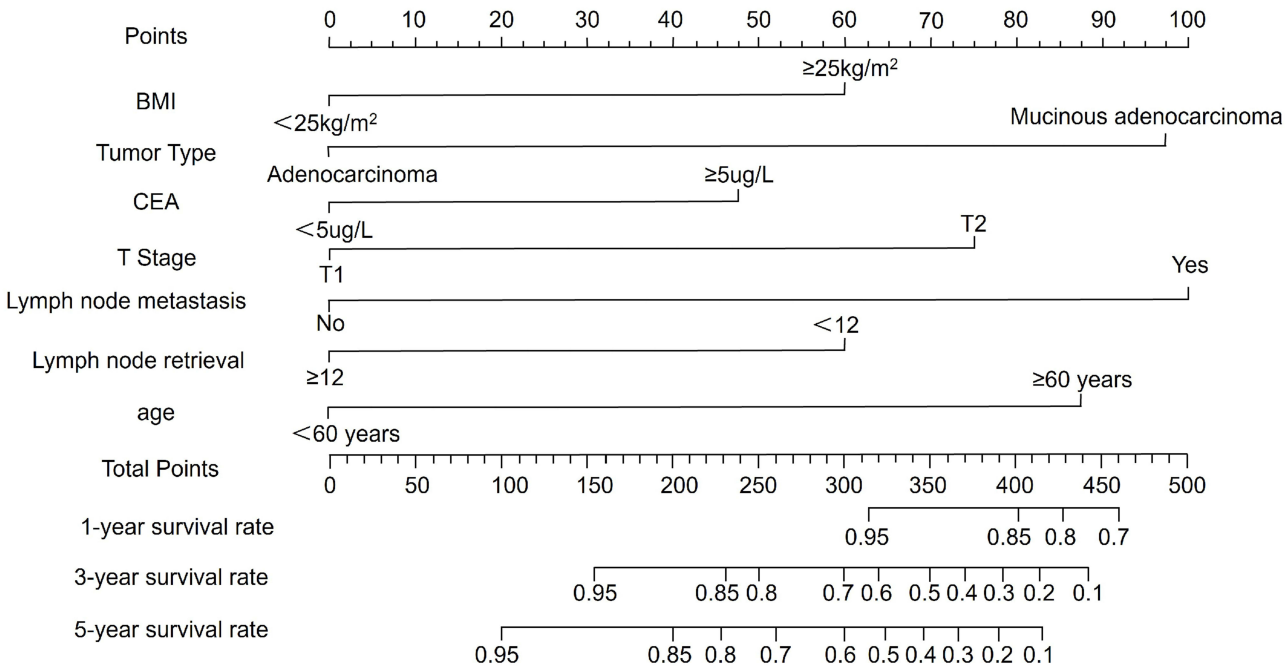

Figure 1 Nomogram for predicting survival outcomes in early-stage rectal cancer patients.

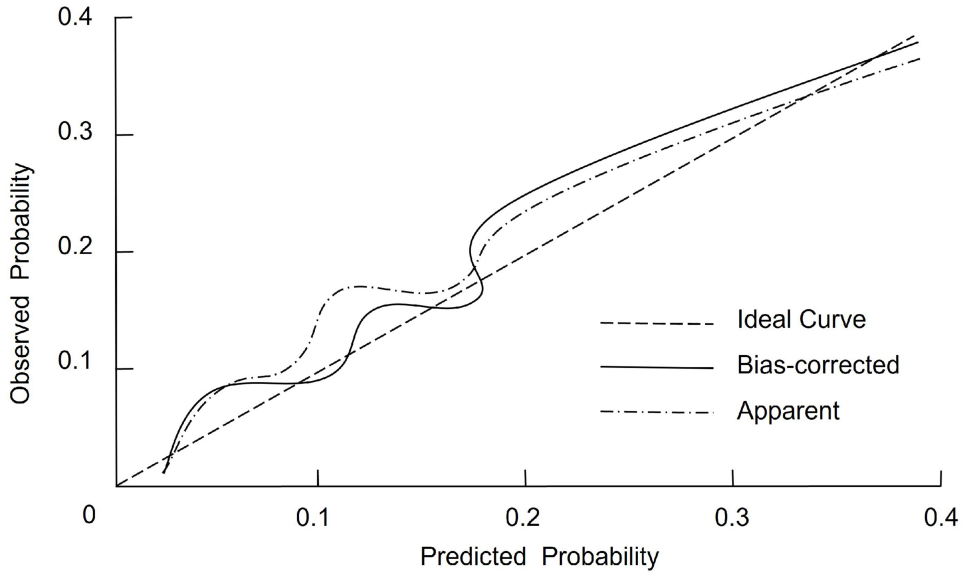

Figure 2 Calibration curve for the nomogram predicting survival outcomes in early-stage rectal cancer patients.

further supports the model's good calibration. Calibration curves demonstrated a close agreement between the predicted and observed probabilities of survival, reinforcing the robustness of the model's predictive accuracy (Figure 2).

Discussion

Early-stage rectal cancer represents a critical window for intervention, yet patient outcomes remain heterogeneous due to diverse clinicopathological factors. In this study, we analyzed key risk factors—including age, BMI, CEA levels, T stage, lymph node status, tumor histology, and lymph node retrieval—to elucidate their impact on overall survival. Our findings underscore that older age, higher BMI, elevated CEA, advanced T stage, lymph node metastasis, mucinous adenocarcinoma, and suboptimal lymph node harvest are independently associated with poorer prognosis. These variables likely

interact through complex biological pathways, such as inflammation, metabolic dysregulation, and tumor microenvironment alterations, which promote aggressive disease behavior and compromise treatment efficacy. Building on these insights, we developed and internally validated a predictive nomogram that demonstrated robust discriminative power (corrected C-index of 0.806) and excellent calibration. This model offers a practical tool for individualized risk assessment, enabling tailored therapeutic strategies and optimizing patient counseling.

Age ≥60 years was identified as a significant prognostic factor, with older patients experiencing poorer survival outcomes. This could be due to age-related declines in physiological reserve, higher comorbidities, and potential differences in tumor biology, all of which may lead to less favorable responses to treatment and greater treatment-related complications.[12] Similarly, a BMI ≥25 kg/m² was associated with worse survival, likely due to obesity-induced chronic inflammation, metabolic dysregulation, and hormone production by adipose tissue, all of which promote tumor growth and impair therapeutic efficacy. Elevated preoperative CEA levels (≥5 μg/L) were also linked to poor prognosis, suggesting more aggressive tumor biology or the presence of micrometastatic disease. CEA's prognostic value can guide decisions regarding adjuvant therapy intensity and surveillance.[13,14] Tumor stage, especially T stage, was another key predictor, with T1 tumors associated with significantly better survival compared to T2 tumors. This aligns with the understanding that deeper tumor invasion increases the risk of local recurrence and metastasis, reflecting the tumor's aggressiveness and genetic alterations.[15] Tumor stage, particularly the T stage, significantly influenced survival outcomes. Patients with T1 stage tumors exhibited a substantially higher 5-year survival rate compared to those with T2 stage disease. This observation aligns with the concept that deeper tumor invasion is associated with a higher likelihood of local recurrence and distant metastasis. The anatomical extent of tumor invasion may also reflect intrinsic differences in tumor aggressiveness and genetic alterations, which can affect the tumor's capacity to metastasize.[16,17] These findings underscore the importance of accurate staging and indicate that even within early-stage rectal cancer, the extent of local invasion is a crucial determinant of prognosis.

Lymph node metastasis was a key predictor of poor survival, with node-positive patients demonstrating significantly worse outcomes.[18–20] Lymphatic spread indicates tumor dissemination and a higher risk of systemic recurrence, highlighting the need for extensive adjuvant treatment. Moreover, the retrieval of fewer than 12 lymph nodes was independently associated with poorer survival, emphasizing the importance of thorough lymphadenectomy.[21] Histological subtype also influenced prognosis, with mucinous adenocarcinoma linked to worse outcomes compared to conventional adenocarcinoma. Mucinous tumors, characterized by microsatellite instability and distinct gene expression patterns, may be more resistant to standard therapies, suggesting the need for alternative or more aggressive treatments.[22] These prognostic factors likely interact through complex biological pathways, including inflammation, hormonal dysregulation, and tumor microenvironment alterations, all of which influence tumor behavior and treatment response.[23–25] Elevated CEA levels and advanced T stage reflect more aggressive tumor biology, while lymph node metastasis and inadequate lymph node retrieval suggest suboptimal local disease control. The distinct biology of mucinous adenocarcinoma further underscores the need for tailored therapies for this subtype.

The development of a prognostic nomogram based on these independent risk factors offers a practical tool for individualized risk assessment in early-stage rectal cancer. By assigning weighted scores to each variable, the nomogram allows clinicians to estimate a patient's survival probability, thereby facilitating personalized treatment planning and patient counseling. Notably, the model demonstrated robust discriminative ability with a corrected C-index of 0.806, and calibration assessments further confirmed that the predicted survival probabilities closely matched the observed outcomes. Compared to existing clinical models, our nomogram offers several advantages. Firstly, it incorporates a comprehensive set of independent risk factors, including clinical, pathological, and demographic variables, which may not be considered together in traditional staging systems. This enables a more nuanced assessment of prognosis, especially in cases where traditional TNM staging may fail to capture the complexity of individual risk profiles. Secondly, the model's ability to stratify patients into distinct risk categories allows for tailored treatment strategies. For example, high-risk patients may benefit from more aggressive treatment regimens or enrollment in clinical trials for novel therapeutic approaches, while low-risk patients could follow less intensive follow-up protocols. By offering personalized risk stratification, our model enhances clinical decision-making and may help to optimize resource allocation by directing intensive treatments and surveillance to those most likely to benefit.

Although surgery remains the cornerstone of curative treatment for early-stage rectal cancer, non-surgical approaches—such as total neoadjuvant therapy (TNT), organ preservation protocols, and "watch-and-wait" after clinical complete response

—are increasingly adopted in selected patients. Our nomogram can inform these decisions by stratifying patients according to individualized risk. Patients with low predicted risk (eg, age <60 years, BMI <25 kg/m², CEA <5 μg/L, T1 stage, node-negative, conventional histology, ≥12 nodes retrieved) may be ideal candidates for less intensive neoadjuvant regimens or non-operative management, given their favorable prognosis and low likelihood of residual disease. Conversely, high-risk patients (eg, age ≥60 years, BMI ≥25 kg/m², elevated CEA, T2 stage, nodal involvement, mucinous subtype, suboptimal lymphadenectomy) could benefit from intensified preoperative chemoradiotherapy or consolidation chemotherapy to maximize tumor downstaging and reduce recurrence risk. By predicting long-term outcomes before treatment initiation, the model supports shared decision-making on the intensity and sequence of multimodal therapy, potentially allowing safe de-escalation in low-risk individuals and therapeutic escalation in those at higher risk of adverse events.

This study has several limitations that warrant consideration. Firstly, the retrospective design may introduce inherent selection bias, and despite rigorous inclusion criteria, some confounding variables might have influenced the results. Secondly, the analysis was conducted at a single institution with a relatively limited sample size, which could affect the generalizability of the findings. Additionally, while the nomogram demonstrated strong internal validity, external validation in larger, multi-center cohorts is necessary to confirm its broader applicability. Future research should focus on prospective studies with larger, diverse populations to validate and refine the predictive model. Incorporating molecular and genetic biomarkers could further enhance risk stratification and provide deeper insights into tumor biology. Moreover, exploring the impact of emerging therapeutic strategies in relation to the identified prognostic factors may offer opportunities to tailor treatment and improve clinical outcomes for early-stage rectal cancer patients.

Conclusions

Our study identified key prognostic factors in early-stage rectal cancer, including age, BMI, CEA levels, T stage, lymph node metastasis, tumor histology, and lymph node retrieval. The predictive nomogram developed demonstrated robust discriminative ability and calibration, providing a practical tool for individualized risk assessment and treatment planning, thereby potentially improving patient outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of TCM-Integrated Hospital of Southern Medical University. All study procedures complied with ethical standards set by institutional and national research committees, aligning with the 1964 Helsinki Declaration and subsequent updates. Informed consent was secured from all participants or their legal guardians.

Consent for Publication

Informed consent for participation and publication was obtained from all subjects or their legal guardians.

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Disclosure

The authors declare that they have no competing interests in this work.

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