Original Article

A prognostic nomogram based on desmoplastic reaction/tumor deposit modified lymph node staging in colorectal cancer

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Background: Tumor metastasis within the tumor microenvironment (TME) is a primary driver of tumor progression, with tumor deposit (TD) being one pathway of metastasis. However, the mechanisms underlying TD as a prognostic indicator in colorectal cancer (CRC) remain unclear. The 8th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) stage system does not account for the impact of TD quantity on prognosis in TD-positive patients. This study aims to integrate TD numbers into the existing N-stage system, develop a novel nomogram prediction model (newN), and validate its prognostic significance. Desmoplastic reaction (DR), including immature, intermediate, and mature types, is a critical indicator of TME status and a prognostic factor. While immature DR has been associated with TD presence, the relationship between TD quantity and DR type changes (mature-intermediate-immature) remains unexplored, this study seeks to elucidate this relationship.

Methods: This study enrolled 171 patients with TNM stage II or III pT3 or pT4 colorectal adenocarcinoma who underwent complete tumor resection. DR was evaluated, and TD numbers were recorded. Clinicopathological factors related to TD formation, multiple TD, and DR changes were analyzed to explore their relationships. Kaplan-Meier curves and log-rank tests were used to assess recurrence-free survival (RFS). Univariate and multivariate Cox proportional hazards analyses were performed to identify independent risk factors for overall survival (OS), and a nomogram prediction model was developed. The association between TD, DR, and the TME was investigated, along with the mechanisms underlying TD formation and DR changes.

Results: DR classification and the number of TD-positive cases were assessed using the Gamma test, yielding a statistically significant result (statistic =11.419, P<0.001) and a strong positive correlation (correlation coefficient =0.836) between TD-positive numbers and DR classification. Abnormal carcinoembryonic antigen (CEA) levels, T stage, lymph node (LN) metastasis count, vascular invasion, TD numbers, poor histologic grade, immature DR, newN stage, contrastN stage, and existing N stage were associated with reduced RFS. DR, TD, and newN stage were identified as independent risk factors for CRC prognosis. The C-index values for the newN stage model (0.759), contrastN stage model (0.748), and existing N stage model (0.742) confirmed the superior prognostic accuracy of the newN stage model.

Conclusions: This study confirmed a significant correlation between immature DR and TD, as well as an

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association between DR types and TD quantities. We hypothesize that tumor-cancer-associated fibroblasts (CAFs)-Twist/DR-epithelial-mesenchymal transition (EMT)-tumor budding (TB)-TD interactions within the TME are involved in the mechanism related to TD formation. The revised newN stage system, incorporating TD numbers and the current N stage, provides more accurate OS predictions, highlighting the importance of TD quantity as a critical prognostic factor.

Keywords: Colorectal cancer (CRC); desmoplastic reaction (DR); tumor deposit (TD); N stage; prognosis

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Introduction

Colorectal cancer (CRC) is a prevalent malignant tumor, with its incidence and mortality rates showing an upward trend. The interplay between tumor cell metastasis and the tumor microenvironment (TME) represents the fundamental issue in CRC research. TME plays a pivotal role in various aspects of tumor progression and metastasis, encompassing initial implantation, growth, and immune evasion of tumor cells. Comprising tumor cells, cancer-associated fibroblasts (CAFs), immune cells, vascular endothelial cells, and extracellular matrix (ECM), TME constitutes a dynamic entity (1).

The formation of tumor deposit (TD) is one of the manifestations of tumor metastasis and an important prognostic indicator for CRC. Currently, the origin of TD is not completely clear, but numerous studies have shown that it may be closely related to lymphatic invasion, vascular invasion, and nerve invasion. It is believed that TD has multiple origins (2-4). The TME enables tumor cells to survive and invade in different microenvironments, and then disseminate through lymph, blood supply, direct infiltration, etc. Therefore, we consider that the formation of TD is closely related to the TME. Professor Gabriel introduced the concept of TD in 1935, proposing it as a tumor satellite nodule located within the peritumoral adipose tissue and lacking lymphatic structures. Initially considered to be a hematogenous metastasis, TD was limited to the periphery of the tumor and classified into pT3 stages. TD has been widely recognized mainly due to its prognostic value in CRC patients. The Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) stage criteria have incorporated TD since 1997 for assessing tumor prognosis. However, discrepancies exist in the definition of TD across the fifth, sixth, seventh, and eighth editions of the UICC/AJCC TNM stage criteria. In its fifth edition introduced in 1997, TD was proposed to be classified as lymph node (LN) metastasis when its diameter exceeded 3 mm; whereas TD with a diameter less than or equal to 3mm was considered as discontinuous spread of pT3 tumors (5). This transition from T to N results in certain patients transitioning from stage II to stage III and necessitates a shift in their treatment strategy from observation and follow-up to postoperative chemoradiotherapy. However, this 3 mm rule was soon replaced. In 2002, the sixth edition of the TNM staging system updated the definition of TD again and proposed the edge rule, that is, when it is round and smooth, it is defined as LN metastasis; when it has an irregular and multi-ring shape, it is defined as venous invasion, and TD is considered as a T3 tumor (6). The

Highlight box

Key findings

- This study has confirmed a significant correlation between different types of desmoplastic reaction (DR) and quantities of tumor deposit (TD), suggesting that interactions among within the tumor microenvironment play a crucial role in the mechanism underlying TD formation.

What is known and what is new?

- The current N staging system weakens the prognostic impact of TD and their quantity in TD-positive patients.
- The revised new N stage system more accurate predictions for overall survival compared to the current N stage alone.

What is the implication, and what should change now?

- We propose that the classification of DR should be integrated into routine pathology reports, guiding optimal treatment strategies for patients. Moreover, we should emphasize the significance of considering the quantity of TD as an essential factor in patient prognosis.

7th edition of the UICC/AJCC TNM stage system [2010] provides a more comprehensive definition of TD. TD is characterized as an irregular tumor nodule located in the peri-colorectal adipose tissue, distant from the primary tumor's margin, with no residual LN tissue but situated along the tumor's lymphatic drainage pathway. In this stage system, TD is defined as N1c stage; however, when TD and LN metastases coexist, TD are not considered (7). The concept of TD was further explained in the 8th edition of the TNM stage system in 2017, based on the 7th edition. It was defined as discontinuous macroscopic or microscopic tumor nodules in the peri-colorectal adipose tissue within the lymphatic drainage area of the primary tumor, without LN structure. Furthermore, it clarified that there is no histological evidence of residual LNs or identifiable vascular and neural structures. Additionally, if identifiable vascular structures are present on hematoxylin and eosin (H&E) staining, elastography, and other staining methods, it should be classified as vascular invasion or LN invasion. Similarly, if neural structures are identified, it should be classified as peripheral nerve invasion (8). The studies have demonstrated that patients with TD exhibit significantly elevated rates of local recurrence and metastasis in CRC, leading to reduced postoperative disease-free survival (DFS) and 5-year survival rates. Furthermore, the presence of TD serves as an independent prognostic risk factor for CRC (9-12). In the 7th and 8th editions of the TNM stage system, positive TD without LN involvement is classified as N1c. However, TD is not considered if there is LN metastasis. This is a controversial issue, and its staging of TD positive patients weakens the influence of TD and its number on the prognosis of patients. Therefore, in this study, the number of positive TD was incorporated into the existing N stage to construct a new stage (newN) prediction model and verify its predictability.

In the TME, CAFs facilitate the synthesis and remodeling of the ECM, which leads to the deposition of reactive stroma known as desmoplastic reaction (DR) (13). The DR can be classified into immature, intermediate, and mature types. Fibrous collagen and hyaluronic acid are predominant components of ECM that serve as pivotal indicators for evaluating DR (1,14). Additionally, DR plays a crucial role in assessing the TME. DR classification has demonstrated its crucial role in prognostic models for predicting DFS, surpassing not only clinical prognostic factors such as TNM stage, T stage, N stage, and tumor grade (15-19), but also other pathological factors like tumor budding (TB) and tumor-stroma ratio (TSR) (20). DR can up-regulate the synthesis of collagen fibers and limit tumor invasion, which is a host reaction. Multilayer dense collagen fibers can effectively restrict tumor invasion. The process of tumor cell metastasis and invasion (including the formation of TD) and DR are a battle between a spear and a shield. CAFs in the TME play a crucial role in the occurrence and development of DR. It has been reported that immature DR is significantly correlated with higher pT stage, LN metastasis, and lymphovascular invasion (16,19), indicating a close relationship among the TME, DR and TD. Further exploration of this relationship and attempts to elucidate the mechanisms controlling it are needed. We present this article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-865/rc).

Methods

Patients

This single-center retrospective cohort study included patients with TNM stage II or III colorectal adenocarcinoma who underwent complete tumor resection at the Affiliated Hospital to Kunming University of Science and Technology (The First People's Hospital of Yunnan Province) between January 2018 and December 2019. All patients were followed up from the date of surgical resection. The primary endpoints of the study were recurrence-free survival (RFS) and overall survival (OS), defined as RFS from the date of index surgery to recurrent disease diagnosis or up to 3 years post-surgery, while OS was calculated from initial surgery until postoperative death due to this disease or up to the fifth postoperative year. This study was approved by the Ethics Committee of The First People's Hospital of Yunnan Province (No. KHLL2024-KY272) and followed the Declaration of Helsinki and its subsequent amendments. Informed consent was waived because the data in this study were from past cases, there was no risk to participants. Patients with pT1 or pT2 tumors were excluded from the study because assessment of DR required tumor invasion to be at least pT3 or pT4 (21). Patients who received neoadjuvant chemotherapy and/or radiotherapy were also excluded. Incomplete clinical data or loss to follow-up were reasons for exclusion, resulting in a total inclusion of 171 patients with TNM stage II or III. The clinicopathological factors, including age, gender, preoperative carcinoembryonic antigen (CEA) level, histological type and grade, T stage, N stage, number of LN

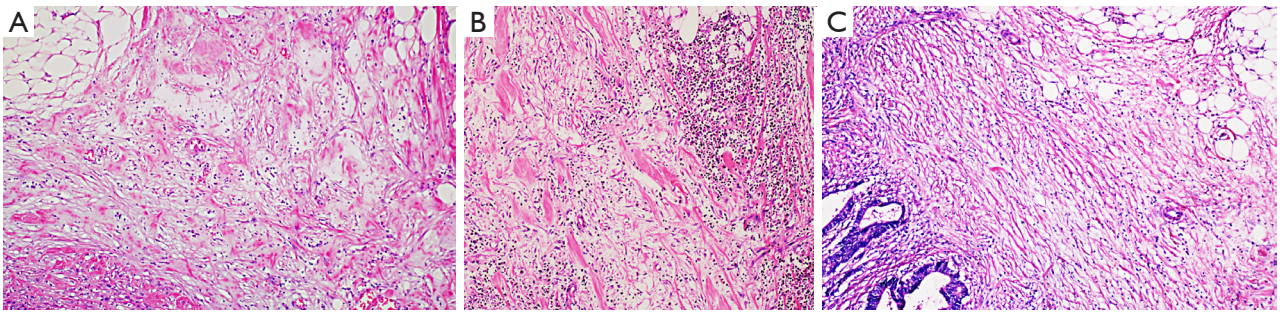

Figure 1 The type of DR following H&E staining, including: (A) immature DR; (B) intermediate DR; (C) mature DR (H&E, ×100). DR, desmoplastic reaction; H&E, hematoxylin and eosin.

metastases, presence or absence of TD and their positive count, vascular invasion, perineural invasion, tumor location and history of postoperative adjuvant chemotherapy were obtained from medical records and pathological reports. Recurrence and survival data were collected through outpatient follow-up visits and telephone interviews.

DR assessment and TD count

Excised slides were stained and independently reviewed by two pathologists. In cases of disagreement between the experts, the slides were discussed and reevaluated together, with all pathological evaluations blinded to clinical information. The classification of DR assessment was performed according to Ueno's method (16,18,22), which divides DR into three types: immature, intermediate, and mature. Initially, low-magnification scanning of H&E slides was performed to identify the location of the extramembranous reactive fibrous area and assess the presence of myxoid matrix and keloid-like collagen. Subsequent high-magnification observation revealed that DR with myxoid changes was classified as immature type. The classification of DR into intermediate or mature type depended on the presence or absence of keloid-like collagen in the fibrotic matrix. In *Figure 1A*, the myxoid matrix is defined as the stroma containing amorphous myxoid material, which typically exhibits basophilic or amphiphilic properties and appears as vacuolated extracellular material located between collagen fibers. The minimum quantity of immature myxoid matrix was determined using a microscope field of 40× objective as the standard. The keloid-like collagen fibers exhibited a dense, low-cellularity collagen structure with a distinct eosinophilic transparency (*Figure 1B*). The mature fibrotic stroma lacked both mucoid matrix and keloid-like collagen, while the cancer nests were enveloped by delicate layers of well-developed collagen fibers (*Figure 1C*). The pathological findings of TD, depicted in *Figure 2*, are observed within the presence of tumor nodules in the peri-colorectal adipose tissue.

Statistical analyses

The statistical analysis was conducted using SPSS 27.0 software. Count data were presented as frequency and constituent ratio, and group comparisons were performed using either the Chi-squared test or Fisher's exact probability method. Univariate binary logistic regression analysis was employed to identify independent risk factors for cancer nodules. Variables with a P value less than 0.05 in the group comparison were included in the multivariate analysis. Survival analysis was carried out using the Kaplan-Meier method (log-rank test), and univariate and multivariate analyses were performed using Cox regression model. Independent risk factors were utilized to construct a nomogram prediction model in R-4.4.1 software. Receiver operating characteristic (ROC) curve was plotted, and area under the curve (AUC) along with C index were calculated to evaluate the predictive performance of the model. Statistical significance was defined as two-sided P values less than 0.05 at a confidence level of 95%.

Results

Patient characteristics

The baseline characteristics of the 171 patients are summarized in *Table 1*. The study included 107 male patients and 64 female patients. The mean age at surgery was 60 years (range, 19 to 87 years). There were a total of

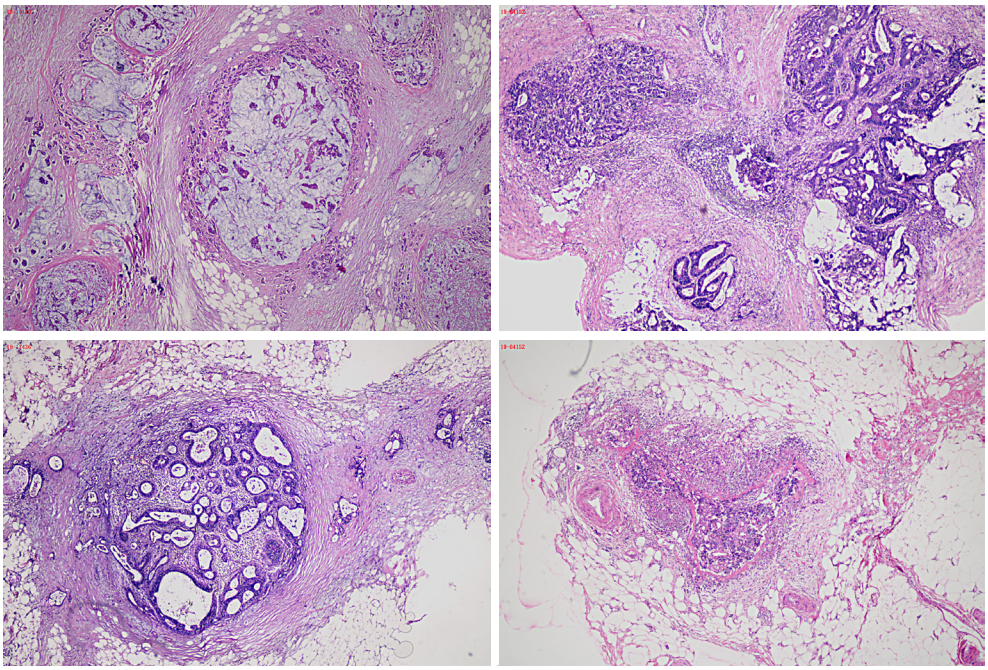

Figure 2 TD was located in the peri-colorectal adipose tissue with no histological evidence of residual lymph nodes or identifiable vascular or neural structures, demonstrates the morphology of TD (H&E, ×40). TD, tumor deposit; H&E, hematoxylin and eosin.

112 patients in the pT3 group and 59 patients in the pT4 group. Among them, there were 74 TD-positive patients and 97 TD-negative patients. The number of cases with immature DR, intermediate DR, and mature DR was reported as respectively: 85, 46, and 40. At the end of a 3-year follow-up after surgery, recurrence was observed in a total of 62 patients (36.26%), while 109 individuals (63.74%) achieved DFS within this period. Furthermore, 75 subjects (43.86%) deceased during the 5-year postoperative period whereas 96 participants (56.14%) survived.

Clinicopathological features of TD and DR

Relationship between TD and clinicopathological features of CRC patients

The univariate logistic regression analysis in *Table 2* reveals significant correlations between the occurrence of TD in CRC and several factors, including preoperative CEA level (P=0.03), T stage (P=0.007), the number of LN metastasis (P=0.03), and DR (P<0.001). Multivariate logistic regression analysis further confirms that DR (P<0.001), preoperative CEA level (P=0.01), and the number of LN metastasis (P=0.01) independently contribute to the risk of TD in CRC.

Relationship between DR and clinicopathological features of CRC patients

The 3-year recurrence rates for patients with immature DR, intermediate DR and mature DR were 54.1%, 19.6%, and 17.5% respectively. Therefore, in the survival analysis, DR type was divided into two groups: the immature DR group and other types of DR group (19,23). In *Table 3*, there was a significant correlation between immature DR and T stage (P<0.001), presence or absence of TD (P<0.001), as well as the number of positive TD (P<0.001).

The association between multiple TD and clinicopathological features of CRC patients

The 3-year recurrence rate in 97 TD-negative patients was found to be 24.7%. Among the 30 patients with a single cancer nodule, the 3-year recurrence rate was observed to be 30%. On the other hand, among the group of 44 patients with multiple TD, the 3-year recurrence rate significantly increased to 65.9%. Statistical analysis using Chi-squared test (*Table 4*) revealed significant correlations between preoperative CEA level (P=0.03), T stage (P=0.02), number of metastatic LNs (P=0.03), and DR (P<0.001) with respect

Table 1 Baseline clinicopathological characteristics and the distribution of the patients

Variables	Group	Value (N=171), n (%)
RFS	Normal	109 (63.74)
	Relapse	62 (36.26)
OS	Survival	96 (56.14)
	Death	75 (43.86)
Gender	Female	64 (37.43)
	Male	107 (62.57)
Age	<60 years	71 (41.52)
	≥60 years	100 (58.48)
CEA	Normal	97 (56.73)
	Abnormal	74 (43.27)
T stage	T3	112 (65.50)
	T4	59 (34.50)
Number of positive LNs	0	56 (32.75)
	1–3	70 (40.94)
	≥4	45 (26.32)
Perineural invasion	Absent	162 (94.74)
	Present	9 (5.26)
Lymphovascular invasion	Absent	144 (84.21)
	Present	27 (15.79)
TD	Absent	97 (56.73)
	Present	74 (43.27)
Histologic grade	Well	11 (6.43)
	Moderate	131 (76.61)
	Poor	29 (16.96)
Location	Ascending colon	40 (23.39)
	Descending colon	15 (8.77)
	Sigmoid colon	37 (21.64)
	Rectum	79 (46.20)
Number of positive TD	0	97 (56.73)
	1	30 (17.54)
	2	16 (9.36)
	≥3	28 (16.37)
DR	Mature	40 (23.39)
	Intermediate	46 (26.90)
	Immature	85 (49.71)

CEA, carcinoembryonic antigen; DR, desmoplastic reaction; LN, lymph node; OS, overall survival; RFS, recurrence-free survival; TD, tumor deposit.

to the presence of positive TD.

Furthermore, Gamma test results indicated a statistically significant association between the number of positive TD and DR classification (mature-intermediate-immature type) with a statistic value of 11.419 and P<0.001, demonstrating a highly positive correlation coefficient of 0.836 between them. Chi-squared test was performed to compare the number of positive TD and preoperative CEA levels, yielding a Chi-squared value of 9.113 (P=0.03). This indicates that there were statistically significant differences in preoperative CEA levels among the four groups. Further subgroup comparisons revealed statistically significant differences in CEA levels between the negative TD group and the single-positive TD group, while no significant differences were observed between the other groups. After the Gamma test, the number of positive TD and T stage (T3–T4) cases showed statistical significance (χ^2=2.922, P=0.003). It can be concluded that the number of positive TD cases was statistically correlated with the T stage, with a correlation coefficient of 0.375, indicating a low positive correlation. After the Gamma test, the number of positive TD and the number of LN metastases showed a statistical significance (χ^2=2.665, P=0.008). It can be concluded that the number of positive TD was statistically correlated with the number of LN metastases, with a correlation coefficient of 0.288, indicating a low positive correlation.

Therefore, DR, T stage, and the number of LN metastases were significantly correlated with the presence or absence of TD (*Table 2*), and immature DR, pT4, and multiple LN metastases were positively correlated with multiple TD.

Survival analysis

newN stage

To assess the prognostic significance of positive TD, we developed a novel stage system (newN) by integrating the number of positive TD with that of positive LNs. This led to the introduction of N2c and N3 stages, while eliminating the N1c stage, and defining TD positivity as N2b or higher. Consequently, this modification enhanced the status of TD positivity within the existing N stage (*Table 5*).

The correlation between clinicopathological data and RFS in patients with CRC

Table 6 shows the Kaplan-Meier survival curve (log-rank test) data for RFS in patients with CRC. The findings suggest that CEA elevation, T stage, number of LN metastases, Lymphovascular invasion, TD positivity and its

Table 2 The risk factors associated with the formation of TD were investigated through logistic regression analysis

Variables	Univariate analysis					Multivariate analysis				
	β	S.E.	Z	P	OR (95% CI)	β	S.E.	Z	P	OR (95% CI)
Gender	–0.13	0.32	–0.42	0.68	0.88 (0.47–1.64)					
Age	–0.22	0.31	–0.71	0.48	0.80 (0.43–1.48)					
CEA	0.68	0.31	2.16	0.03*	1.97 (1.07–3.66)	1.07	0.42	2.55	0.01*	2.92 (1.28–6.66)
T stage	0.90	0.33	2.72	0.007*	2.45 (1.28–4.67)					
Number of positive LNs	0.44	0.21	2.15	0.03*	1.56 (1.04–2.33)	0.64	0.26	2.42	0.01*	1.90 (1.13–3.19)
Perineural invasion	0.05	0.69	0.07	0.94	1.05 (0.27–4.06)					
Lymphovascular invasion	0.59	0.42	1.39	0.16	1.80 (0.79–4.12)					
Histologic grade	0.13	0.33	0.40	0.69	1.14 (0.60–2.16)					
Location	0.13	0.13	1.00	0.32	1.14 (0.88–1.46)					
DR	2.11	0.33	6.46	<0.001*	8.26 (4.36–15.68)	2.23	0.35	6.41	<0.001*	9.31 (4.71–18.42)
Adjuvant therapy	16.40	758.80	0.02	0.98	13,312,651.74 (0.00–Inf)					

*, P<0.05. CEA, carcinoembryonic antigen; CI, confidence interval; DR, desmoplastic reaction; Inf, infinity; LN, lymph node; OR, odds ratio; S.E., standard error; TD, tumor deposit.

quantity, poor histologic grade, immature DR, newN stage, contrastN stage, and existing N stage exhibit significant associations with reduced RFS.

Cox regression analysis was conducted to assess OS in patients with CRC

The results of univariate and multivariate Cox proportional hazards regression analysis for OS in this study are presented in *Table* 7, demonstrating significant associations between pT stage, vascular invasion, TD, DR, and newN stage with OS in the univariate analysis. In the multivariate analysis, DR remained an independent prognostic factor for CRC. Furthermore, TD and newN stage were also identified as prognostic indicators for CRC.

The ROC curve analysis was conducted on TD, DR, newN stage, and N stage in COX regression analysis. The AUC for newN stage was 0.709 [95% confidence interval (CI): 0.6331–0.7853], while the AUC for DR was 0.722 (95% CI: 0.6331–0.7853). Additionally, the AUC for TD was found to be 0.625 (95% CI: 0.5518–0.6986), and that of N stage was determined as 0.659 (95% CI: 0.5789–0.7396). These findings suggest that among the evaluated indicators, DR exhibited relatively superior predictive efficacy regarding postoperative recurrence in patients with CRC (*Figure 3*).

Development and validation of the nomogram

We plotted survival curves for DFS and OS based on both the newN stage and the current N stage, with the results demonstrating statistical significance for both comparisons (P<0.05), as illustrated in *Figures 4*,*5*. Consequently, we constructed a nomogram prediction model based on the N stage. The independent risk factors identified by COX multivariate analysis were utilized to construct the nomogram prediction model, as depicted in *Figures 6*,7. Two distinct nomogram prediction models were developed, one incorporating newN stage and the other incorporating N stage, for predicting the 5-year survival probability of patients. The N stage prediction model exhibited an AUC of 0.749, with a C-index of 0.742. On the other hand, the newN stage prediction model demonstrated an AUC and C-index of 0.778 and 0.759 respectively. To assess calibration, bootstrap resampling method with 1,000 iterations was employed to generate a calibration curve for the newN stage prediction model (*Figure* 7*C*). Notably, this figure highlights that the predictive performance of our novel nomogram based on newN stage surpasses that of the existing N stage prediction model, thereby indicating excellent discrimination and calibration.

Discussion

The findings of this study confirm, for the first time, a highly positive correlation between the increase in

Table 3 The risk factors associated with the development of immature DR were investigated using a Chi-squared test

Variables	Total (n=171), n (%)	Mature/intermediate (n=86), n (%)	Immature (n=85), n (%)	Statistic (χ^2)	P
Gender				0.00	0.95
Female	64 (37.43)	32 (37.21)	32 (37.65)		
Male	107 (62.57)	54 (62.79)	53 (62.35)		
Age				0.71	0.40
<60 years	71 (41.52)	33 (38.37)	38 (44.71)		
≥60 years	100 (58.48)	53 (61.63)	47 (55.29)		
CEA				0.14	0.71
Normal	97 (56.73)	50 (58.14)	47 (55.29)		
Abnormal	74 (43.27)	36 (41.86)	38 (44.71)		
T stage				11.79	<0.001*
T3	112 (65.50)	67 (77.91)	45 (52.94)		
T4	59 (34.50)	19 (22.09)	40 (47.06)		
Number of positive LNs				0.89	0.64
0	56 (32.75)	30 (34.88)	26 (30.59)		
1–3	70 (40.94)	36 (41.86)	34 (40.00)		
≥4	45 (26.32)	20 (23.26)	25 (29.41)		
Perineural invasion				0.49	0.48
Absent	162 (94.74)	83 (96.51)	79 (92.94)		
Present	9 (5.26)	3 (3.49)	6 (7.06)		
Lymphovascular invasion				0.44	0.51
Absent	144 (84.21)	74 (86.05)	70 (82.35)		
Present	27 (15.79)	12 (13.95)	15 (17.65)		
TD				55.88	<0.001*
Absent	97 (56.73)	73 (84.88)	24 (28.24)		
Present	74 (43.27)	13 (15.12)	61 (71.76)		
Histologic grade				2.39	0.30
Well	11 (6.43)	5 (5.81)	6 (7.06)		
Moderate	131 (76.61)	70 (81.40)	61 (71.76)		
Poor	29 (16.96)	11 (12.79)	18 (21.18)		
Location				1.25	0.74
Ascending colon	40 (23.39)	22 (25.58)	18 (21.18)		
Descending colon	15 (8.77)	7 (8.14)	8 (9.41)		
Sigmoid colon	37 (21.64)	16 (18.60)	21 (24.71)		
Rectum	79 (46.20)	41 (47.67)	38 (44.71)		
Number of positive TD				59.08	<0.001*
0	97 (56.73)	73 (84.88)	24 (28.24)		
1	30 (17.54)	9 (10.47)	21 (24.71)		
2	16 (9.36)	1 (1.16)	15 (17.65)		
≥3	28 (16.37)	3 (3.49)	25 (29.41)		

*, P<0.05. χ^2, Chi-squared test; CEA, carcinoembryonic antigen; DR, desmoplastic reaction; LN, lymph node; TD, tumor deposit.

Table 4 The risk factors associated with the development of multiple TD were investigated using a Chi-squared test

Variables	Total (n=171), n (%)	TD =0, n (%)	TD =1, n (%)	TD =2, n (%)	TD ≥3, n (%)	Statistic	P
Gender						2.21	0.53
Female	64 (37.43)	35 (36.08)	9 (30.00)	8 (50.00)	12 (42.86)		
Male	107 (62.57)	62 (63.92)	21 (70.00)	8 (50.00)	16 (57.14)		
Age						2.08	0.57
<60 years	71 (41.52)	38 (39.18)	15 (50.00)	5 (31.25)	13 (46.43)		
≥60 years	100 (58.48)	59 (60.82)	15 (50.00)	11 (68.75)	15 (53.57)		
CEA						9.11	0.03*
Normal	97 (56.73)	62 (63.92)[a]	11 (36.67)[b]	11 (68.75)[a,b]	13 (46.43)[a,b]		
Abnormal	74 (43.27)	35 (36.08)[a]	19 (63.33)[b]	5 (31.25)[a,b]	15 (53.57)[a,b]		
T stage						9.66	0.02*
T3	112 (65.50)	72 (74.23)	19 (63.33)	7 (43.75)	14 (50.00)		
T4	59 (34.50)	25 (25.77)	11 (36.67)	9 (56.25)	14 (50.00)		
Number of positive LNs						14.09	0.03*
0	56 (32.75)	37 (38.14)	9 (30.00)	5 (31.25)	5 (17.86)		
1–3	70 (40.94)	40 (41.24)	15 (50.00)	7 (43.75)	8 (28.57)		
≥4	45 (26.32)	20 (20.62)	6 (20.00)	4 (25.00)	15 (53.57)		
Perineural invasion						–	0.95
Absent	162 (94.74)	92 (94.85)	28 (93.33)	15 (93.75)	27 (96.43)		
Present	9 (5.26)	5 (5.15)	2 (6.67)	1 (6.25)	1 (3.57)		
Lymphovascular invasion						–	0.21
Absent	144 (84.21)	85 (87.63)	26 (86.67)	13 (81.25)	20 (71.43)		
Present	27 (15.79)	12 (12.37)	4 (13.33)	3 (18.75)	8 (28.57)		
Histologic grade						–	0.06
Well	11 (6.43)	5 (5.15)	1 (3.33)	3 (18.75)	2 (7.14)		
Moderate	131 (76.61)	78 (80.41)	22 (73.33)	13 (81.25)	18 (64.29)		
Poor	29 (16.96)	14 (14.43)	7 (23.33)	0 (0.00)	8 (28.57)		
Location						–	0.39[c]
Ascending colon	40 (23.39)	26 (26.80)	4 (13.33)	5 (31.25)	5 (17.86)		
Descending colon	15 (8.77)	8 (8.25)	4 (13.33)	2 (12.50)	1 (3.57)		
Sigmoid colon	37 (21.64)	20 (20.62)	6 (20.00)	1 (6.25)	10 (35.71)		
Rectum	79 (46.20)	43 (44.33)	16 (53.33)	8 (50.00)	12 (42.86)		
DR						64.55	<0.001*
Mature	40 (23.39)	39 (40.21)	1 (3.33)	0 (0.00)	0 (0.00)		
Intermediate	46 (26.90)	34 (35.05)	8 (26.67)	1 (6.25)	3 (10.71)		
Immature	85 (49.71)	24 (24.74)	21 (70.00)	15 (93.75)	25 (89.29)		

*, P<0.05. χ^2, Chi-squared test; –, Fisher exact; [a,b], pairwise comparisons among the four groups were performed using the z-test based on Chi-squared statistics, and pairwise comparisons are corrected by Bonferroni. Subgroups were defined by letters "a" and "b", where the same letter indicates no statistically significant difference between subgroups, while different letters indicate a statistically significant difference; [c], simulated P value. CEA, carcinoembryonic antigen; DR, desmoplastic reaction; LN, lymph node; TD, tumor deposit.

Table 5 The distribution of patients in both the newN stage and the currently established N stage

AJCC 8th pN stage	newN stage					
	N0 (LN0)	N1 (LN1–3)	N2a (LN4–6)	N2b (LN7–9/TD1–4, TD + LN ≤9)	N2c (LN >9/TD1–4, TD + LN >9/TD ≥5, TD + LN ≤9)	N3 (TD ≥5, TD + LN >9)
N0 (LN0)	37	0	0	0	0	0
N1a (LN1)	0	13	0	10	0	0
N1b (LN2–3)	0	27	0	16	1	3
N1c (TD+, LN–)	0	0	0	17	1	1
N2a (LN4–6)	0	0	15	13	0	5
N2b (LN ≥7)	0	0	0	3	5	4

AJCC, American Joint Committee on Cancer; LN, lymph node; newN stage, new N stage; TD, tumor deposit.

Table 6 The Kaplan-Meier survival curve (log-rank test) data for RFS in patients with colorectal cancer

Variables	P	HR (95% CI)
CEA	0.03*	1.746 (1.058–2.881)
T stage	0.003*	2.093 (1.271–3.446)
Number of positive LNs	0.001*	–
Lymphovascular invasion	0.002*	2.347 (1.327–4.152)
TD	<0.001*	2.521 (1.511–4.205)
Histologic grade	<0.001*	–
Number of positive TD	<0.001*	–
DR	<0.001*	–
newN stage	<0.001*	–
contrastN stage	<0.001*	–
N stage	<0.001*	–

*, P<0.05. CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; LN, lymph node; newN stage, new N stage; DR, desmoplastic reaction; TD, tumor deposit.

the number of TD and the type of DR (mature type-intermediate type-immature type). Additionally, it reveals that patients with multiple TD have a worse prognosis compared to those with single TD. Previous studies have also shown a significant correlation between TD and immature DR in CRC (23), which is consistent with our findings in this study. We further demonstrate that TD is closely associated with immature DR in the primary lesion, as well as with factors such as the number of LN metastases around the primary lesion and preoperative CEA level. This study found that immature DR, changes in T stage, and an increased number of LN metastases were more likely to lead to the formation and increase of TD. However, changes in preoperative CEA levels did not show the same effect. We believe that preoperative CEA levels can be used as an indicator to evaluate the degree of malignancy, but their sensitivity and specificity are not high. In this study, the CEA levels of 97 tumor patients (56.73%) were within the normal range. Due to individual differences among patients, CEA levels may also be affected by inflammatory diseases, benign diseases, and other factors, resulting in preoperative CEA levels not fully reflecting the malignant degree of tumors. The crucial role of the TME in CRC progression and invasion has gained increasing recognition (24,25), with extracellular matrix components influencing CRC progression (14,26-29). Postoperative pathological examination often reveals higher number of TD in patients with immature DR, highlighting the indispensable contribution of TME changes to TD formation.

Given its significant attention as a prognostic indicator, the DR classification proposed by Ueno *et al.* (22,30) has emerged as a pivotal feature for predicting disease-specific mortality in stage II CRC (20,31). In this study, there was a notable correlation between immature DR and pT4, with the DR classification exhibiting superior prognostic significance compared to conventional clinicopathological factors such as TD, newN stage, and existing N stage. These findings align with previous reports on CRC (18,20,23). The DR assessment refers to the fibrotic cancer stroma located outside the muscularis propria, which represents the distal extent of tumor invasion and is typically surrounded by adipose tissue. Additionally, it allows for observation of the tumor invasion layer (pT). Upon traversing the muscularis propria, tumor cells elicit a fibrointerstitial

Table 7 Univariate and multivariate cox regression analysis for OS in CRC

Variables	Univariate					Multivariate				
	β	S.E.	Z	P	HR (95% CI)	β	S.E.	Z	P	HR (95% CI)
Age (*vs*. <60 years)										
≥60 years	−0.34	0.23	−1.45	0.15	0.71 (0.45–1.12)					
CEA (*vs*. abnormal)										
Normal	−0.42	0.23	−1.81	0.07	0.66 (0.42–1.04)					
T stage (*vs*. T3)										
T4	0.67	0.23	2.86	0.004*	1.95 (1.23–3.07)					
newN stage (*vs*. N0)										
N1	0.35	0.43	0.81	0.42	1.42 (0.61–3.32)	0.38	0.43	0.88	0.38	1.46 (0.62–3.43)
N2a	0.45	0.56	0.81	0.42	1.57 (0.53–4.70)	0.56	0.56	1.00	0.32	1.75 (0.58–5.25)
N2b	0.92	0.38	2.42	0.01*	2.51 (1.19–5.32)	1.76	0.58	3.02	0.003*	5.81 (1.85–18.23)
N2c	1.71	0.53	3.24	0.001*	5.55 (1.97–15.64)	2.49	0.67	3.72	<0.001*	12.11 (3.25–45.08)
N3	2.79	0.45	6.24	<0.001*	16.22 (6.76–38.90)	3.65	0.69	5.33	<0.001*	38.56 (10.07–147.72)
Perineural invasion (*vs*. absent)										
Present	0.32	0.46	0.69	0.49	1.38 (0.55–3.41)					
Lymphovascular invasion (*vs*. absent)										
Present	0.66	0.28	2.32	0.02*	1.93 (1.11–3.35)					
TD (*vs*. absent)										
Present	0.82	0.23	3.50	<0.001*	2.27 (1.43–3.59)	−1.75	0.51	−3.42	<0.001*	0.17 (0.06–0.47)
Histologic grade (*vs*. well)										
Moderate	−0.38	0.43	−0.88	0.38	0.68 (0.29–1.59)					
Poor	0.43	0.47	0.91	0.37	1.53 (0.61–3.87)					
Location (*vs*. ascending colon)										
Descending colon	−0.39	0.50	−0.77	0.44	0.68 (0.25–1.81)					
Sigmoid colon	−0.20	0.34	−0.59	0.56	0.82 (0.42–1.59)					
Rectum	−0.12	0.29	−0.42	0.67	0.89 (0.51–1.55)					
DR (*vs*. mature/intermediate)										
Immature	1.43	0.27	5.37	<0.001*	4.19 (2.48–7.06)	1.51	0.33	4.59	<0.001*	4.52 (2.37–8.61)
Adjuvant therapy (*vs*. TNM II stage without therapy)										
TNM II stage with therapy	−0.58	0.80	−0.72	0.47	0.56 (0.12–2.70)					
TNM III stage with therapy	0.45	0.72	0.63	0.53	1.57 (0.38–6.40)					
Gender (*vs*. female)										
Male	−0.54	0.23	−2.31	0.02	0.58 (0.37–0.92)	−0.65	0.24	−2.71	0.007*	0.52 (0.33–0.84)

*, P<0.05. CI, confidence interval; CEA, carcinoembryonic antigen; CRC, colorectal cancer; DR, desmoplastic reaction; HR, hazard ratio; newN stage, new N stage; OS, overall survival; S.E., standard error; TD, tumor deposit.

response from the host as a means to restrict further tumor progression. Notably, we observed that most instances of DR assessment occur at pT3 level. However, if tumor cells breach this barrier, it indicates infiltration or breakthrough at pT4 level followed by epithelial-mesenchymal transition (EMT), resulting in LN metastasis and subsequent formation of distant metastases. The correlation between pT4 and immature DR is statistically significant. Due to its composition of myxoid matrix and keloid-like collagen fibers, the presence of immature DR impairs its ability to effectively contain tumor growth. Consequently, tumor cells within immature DR exhibit an increased propensity for local invasion and metastasis, resulting in significantly reduced RFS and OS rates among patients. Therefore, we propose that the classification of DR should be incorporated into routine pathology reports as a valuable prognostic indicator to guide optimal treatment strategies for patients.

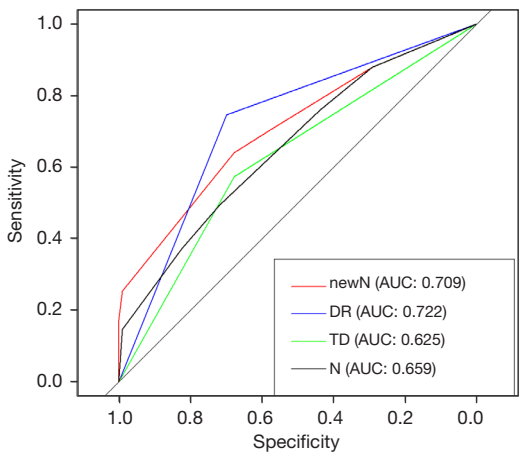

Figure 3 The ROC curve was employed to assess the factors associated with OS in patients diagnosed with colorectal cancer. AUC, area under the curve; DR, desmoplastic reaction; newN, new N; OS, overall survival; ROC, receiver operating characteristic; TD, tumor deposit.

The 8th edition of TNM stage emphasizes the importance of TD number in the stage and prognosis of CRC (8), but it does not correlate TD number with TNM stage. Currently, there exists a general consensus that TD is influenced by multiple factors, leading to ongoing debates regarding its placement within the TNM stage classification system. Scholars have expressed divergent opinions on whether TD should be categorized under T, N, or M stages. In this study, TD formation was correlated with the number of LN metastases; therefore, we included the number of TD in the revised N stage. Mirkin *et al.* (32) reported no statistically significant difference in survival rates between the TD(+) LN(–) group and LN(+)TD(–) group at T1–4 stage, suggesting that TD should be considered as metastatic LNs and included in the N stage. Pricolo *et al.* (10) proposed introducing the definition of "N2c" as [LN(+)TD(+) or LN(–), TD ≥3], and redefining "N1c" as [LN(–), TD ≤2] to reflect distinct prognoses and enable individualized treatment for patients with stage III colon cancer who are positive for TD. Some scholars (33) incorporated the number of TD into the number of LN and introduced "N3" (TD + LN ≥10) to indicate high-risk factors for stage III CRC, this stage method was adopted in our study to construct a predictive model (contrastN), resulting in a calculated C index =0.748. The number of TD and the

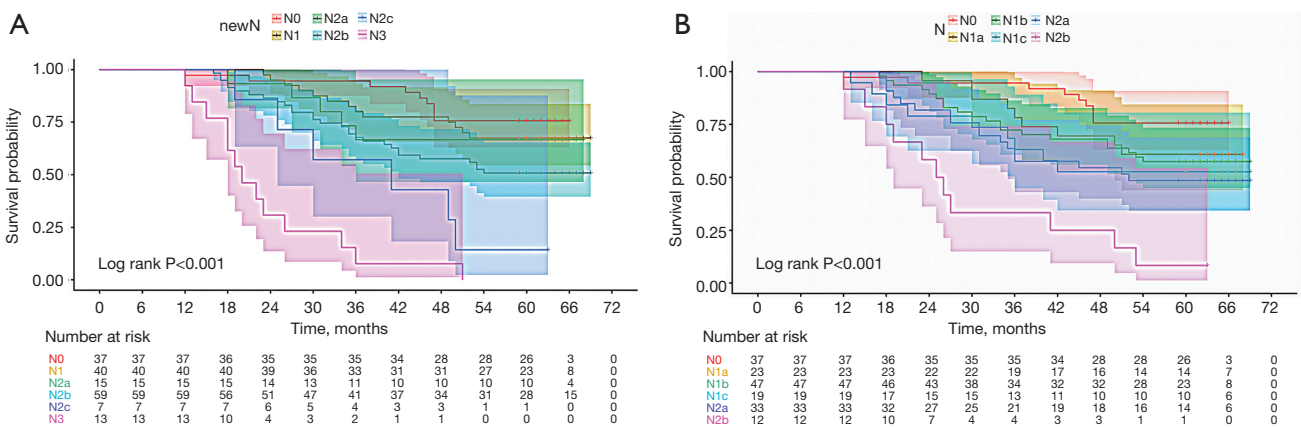

Figure 4 The Kaplan-Meier curves show the overall survival rate of the new and current N stages, with the time unit measured in months. (A) newN stage; (B) current N stage. newN stage, new N stage.

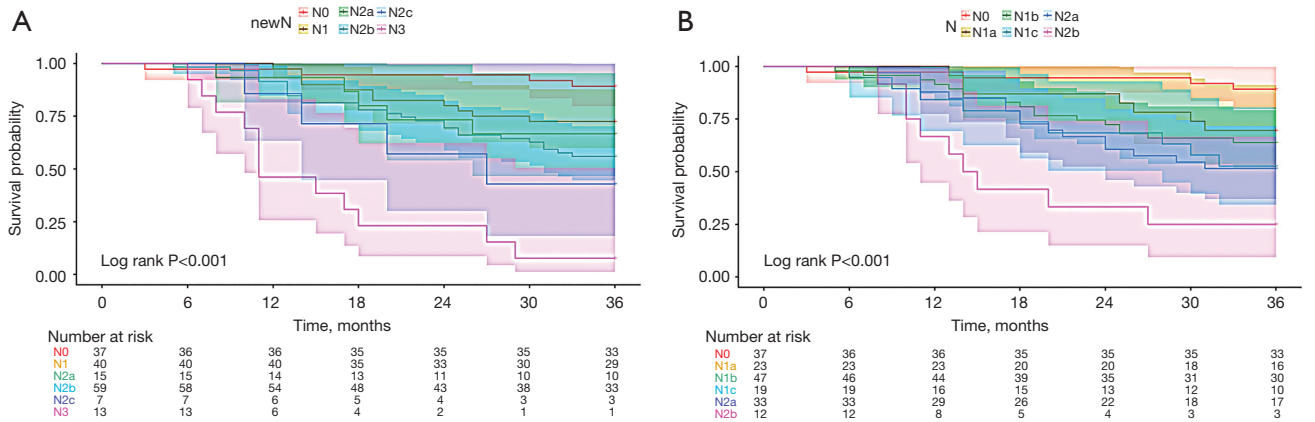

Figure 5 The Kaplan-Meier curves show the recurrence-free survival rate of the new and current N stages, with the time unit measured in months. (A) newN stage; (B) current N stage. newN stage, new N stage.

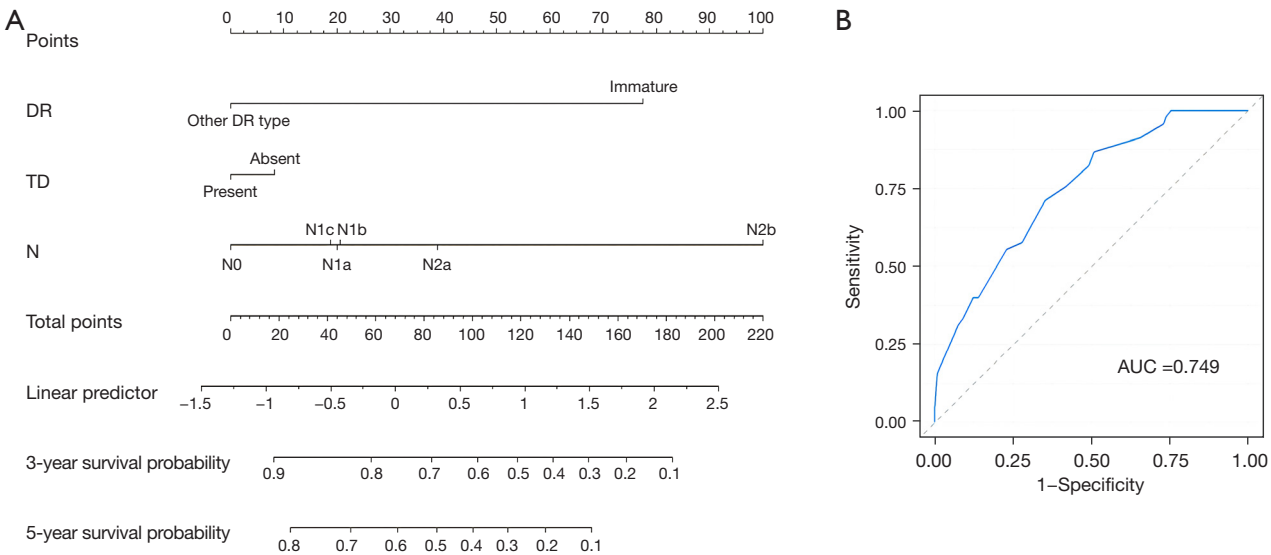

Figure 6 N stage nomogram prediction model and its ROC curve. (A) Nomogram for predicting the survival rate of colorectal cancer patients, incorporating DR, TD, and N stage variables; (B) ROC curve analysis of the predictive model for N stage. AUC, area under the curve; DR, desmoplastic reaction; ROC, receiver operating characteristic; TD, tumor deposit.

number of metastatic LNs were integrated in this study to form a newN stage. "N3" represents TD ≥5 and TD + LN >9, while "N2c" includes LN >9, TD ≤4 but TD + LN >9, and TD ≥5 but TD + LN ≤9. A significant correlation was observed between the existing N stage and the newN stage (Spearman's rho =0.725, P<0.001). The C index values for the prediction models based on the newN stage model, contrastN stage model, and existing N stage model were found to be 0.759, 0.748, and 0.742 respectively. Notably, our newN stage model exhibited superior predictive performance compared to both the contrastN stage model and existing N stage systems by achieving higher AUC values and C-index scores.

Both immature DR and TD are important prognostic indicators for patients with CRC, but the formation mechanisms of both are not clear, we believe that the TME is inseparable from them. The TME has an important impact on tumor behavior, including metastatic potential, by inducing EMT. The Twist family functions as transcription factors that induce EMT. Studies have demonstrated that

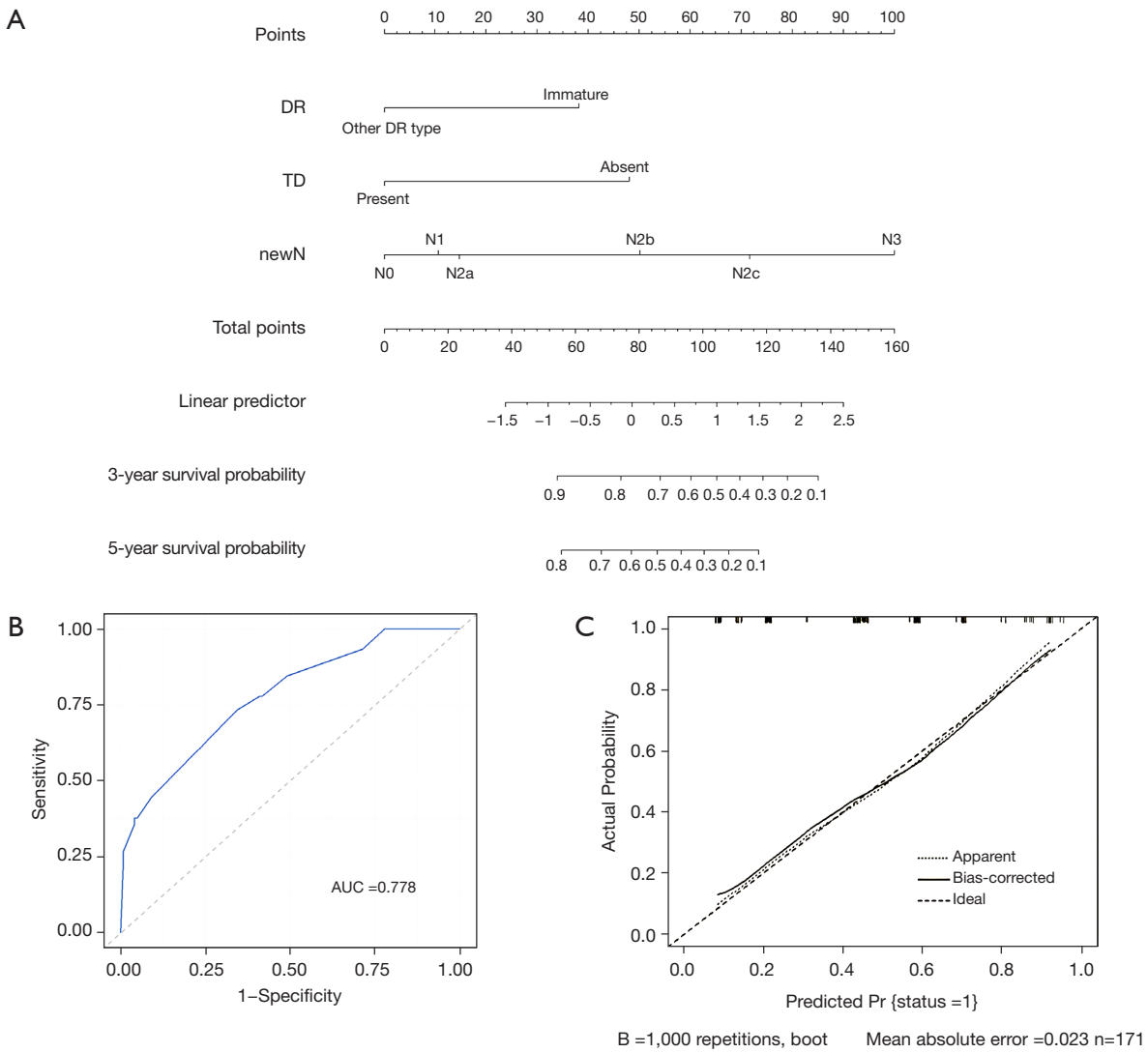

Figure 7 newN stage nomogram prediction model and ROC curve and Bootstrap sampling correction curve. (A) Nomogram for predicting the survival rate of colorectal cancer patients, incorporating DR, TD, and newN stage variables; (B) ROC curve analysis of the predictive model for newN stage; (C) the calibration curve of the newN stage prediction model. AUC, area under the curve; DR, desmoplastic reaction; newN stage, new N stage; ROC, receiver operating characteristic; TD, tumor deposit.

Twist expression promotes TD formation, establishing a mechanistic relationship: Twist-EMT-TD (34), with Twist being produced by both tumor cells and CAFs. Twist expression in CAFs is upregulated through the transforming growth factor-β (TGF-β)/SMAD3 pathway (35). Induction of EMT involves multiple signaling pathways, including TGF-β, Wnt, receptor tyrosine kinases (RTK), etc., which ultimately activate transcription factors such as SNAIL1, SLUG, Twist 1/2, and ZEB1/2 (36). These factors downregulate the expression of epithelial markers like E-cadherin, claudin, occludin, and ZO-1 while eliminating key features essential for maintaining epithelial integrity such as nonmotility and tight junctions (37). TB is closely related to EMT, which is defined as small clusters of undifferentiated tumor cells (consisting of 1–4 cells) at the leading edge of tumor invasion under high-power microscopy (38). TB is considered to be the histological manifestation of EMT at the tumor-host interface in CRC (39). The study found that patients with a higher TB grade in stage III CRC were more likely to develop TD (40), once

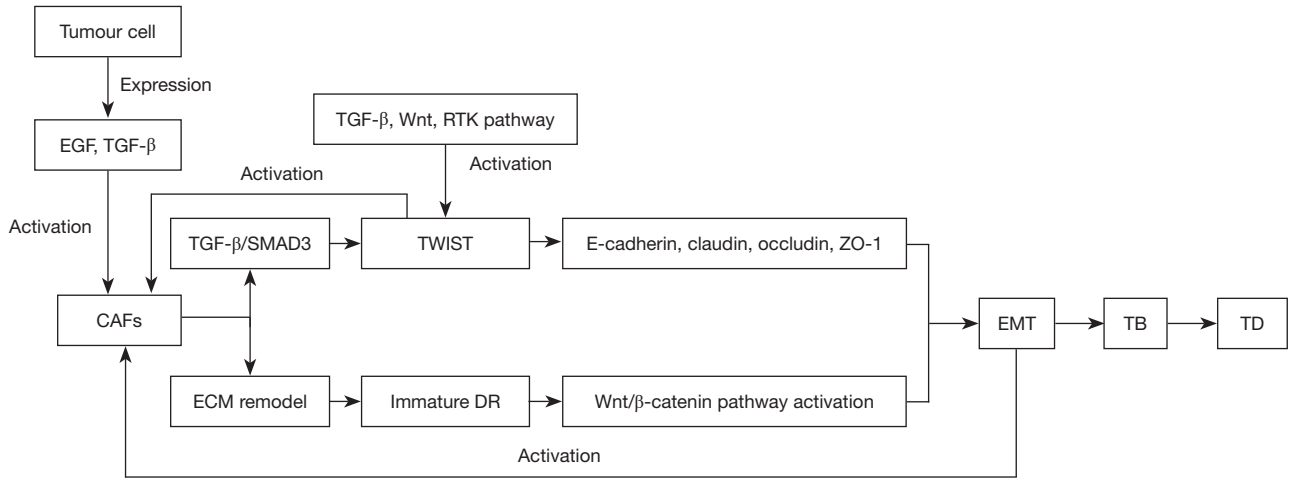

Figure 8 Mechanism of TD formation. Tumor cell-secreted TGF-β induces fibroblast activation and their transformation into CAFs, and CAFs exhibit the expression of TWIST transcription factor, which is activated by various pathways including TGF-β, Wnt, and RTK signaling. This activation downregulates several epithelial markers to facilitate the formation of EMT-TB-TD; EGF derived from tumor cells leads to immature CAFs, which reconstitute ECM to form immature DR, and activate Wnt/β-catenin signaling pathway to promote the formation of EMT-TB-TD. CAFs, cancer-associated fibroblasts; DR, desmoplastic reaction; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; RTK, receptor tyrosine kinases; TB, tumor budding; TD, tumor deposit; TGF-β, transforming growth factor-β; ZO-1, zonula occludens-1.

again demonstrating the involvement of the TME in TD formation. The mechanism we propose involves tumors-CAFs-Twist-EMT-TB-TD formation.

Studies have demonstrated that tumor-derived growth factors, including epidermal growth factor (EGF), fibroblast growth factor (FGF), and TGF, play a regulatory role in the maturation of CAFs and exert an influence on tumor growth patterns. Epidermal growth factor receptor (EGFR) expression is observed at low levels in immature CAFs. Immature CAFs contribute to the formation of a loosely organized fibrous matrix, referred to as immature DR, characterized by myxoid material, keloid-like collagen deposition, and an abundance of immature CAFs. This microenvironment facilitates tumor infiltration and TB formation (41). CAFs determine the type of ECM, and changes in ECM components are crucial for tumor occurrence and development. Fibrous collagen and hyaluronic acid are the main constituents of the ECM (1,14). The excessive deposition of type I collagen is the fundamental hallmark of keloid-like collagen in immature DR (22). The myxoid matrix component is histologically characterized by a dense distribution of myofibroblasts and excessive synthesis of nonfibrous ECM components, including increased production and degradation of hyaluronic acid, both contributing to tumor progression (14,27,42). Nuclear accumulation of β-catenin serves as compelling evidence for the activation of the Wnt/β-catenin signaling pathway, which is closely associated with promoting loss of epithelial differentiation and induction of EMT in tumor cells (43,44). Tumor cells located proximal to or within the myofibroblast region exhibit enhanced nuclear localization of β-catenin, indicating the regulation of Wnt signaling pathway by the TME (45). Therefore, myxoid matrix and scar-like collagen can be regarded as histological features intricately linked to EMT-mediated tumor cell metastasis. These two stromal components represent transient phenotypes that exclusively manifest at the invasive front. CAFs produce diverse ECM constituents that act as catalysts to further facilitate TB formation, thereby inducing dedifferentiation in tumor cells and orchestrating dynamic processes at the interface between tumors and their host necessary for metastasis (15,16), actively participating in TD formation. Furthermore, our study revealed a significant correlation between immature DR and TD formation, thereby establishing a mechanistic relationship involving tumor-CAFs-Twist/DR-EMT-TB-TD formation (*Figure 8*).

There are several limitations to this study. Firstly, it is a retrospective analysis conducted at a single institution, which inevitably introduces selection bias. Therefore,

large-scale multi-center studies are warranted to further validate the findings. Secondly, due to inevitable inter-observer differences in evaluating DR and TD, additional pathologists are required for evaluation. The formation of TD and the change of DR are interconnected processes influenced by complex and multiple factors. This study has provided preliminary insights into the mechanisms underlying the development of immature DR and TD, thus contributing to the theoretical basis in this field. It has been demonstrated that both DR and TD exhibit close associations with the TME, serving as key factors in tumor progression. These findings offer supplementary prognostic information and potential therapeutic targets for patients with CRC.

Conclusions

The present study has confirmed a significant correlation between the type of DR and the number of TD. We hypothesized that TD formation within the TME involves relevant mechanisms, including tumor-CAFs-Twist/DR-EMT-TB-TD. The updated version of the newN stage system incorporates both the presence of TD and current N stage, providing a more accurate prediction of OS compared to solely relying on N stage. Therefore, this emphasizes the importance of considering the number of TD as a crucial factor in patient prognosis.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2024-865/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board of The First People's Hospital of Yunnan Province (No. KHLL2024-KY272) and the requirement for individual consent for this retrospective analysis was waived because the data in this study were from past cases, there was no risk to participants.

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