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Prognostic value of tumor deposits and positive lymph nodes in colorectal cancer surgery: improved staging for long-term prognosis

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Abstract

Background To evaluate the prognostic value of the presence and number of tumor deposits (TDs) and the combination of TDs and number of positive lymph nodes (PLNs) in patients undergoing colorectal cancer (CRC) surgery, and to modify N staging.

Method The clinical data of 1470 patients with stage I-IV CRC who underwent surgery in Wuhan Union Hospital from February 2014 to May 2018 were collected. The optimal cutoff value for TD + PLNs was obtained using X-tile software, and patients were regrouped accordingly. Cox univariate and multivariate analysis were used to screen the factors affecting the prognosis of patients. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to evaluate the predictive ability of independent prognostic factors for overall survival (OS) and disease-free survival (DFS) of patients.

Result The presence of TD was associated with poor OS (HR = 2.478, 95%CI: 1.794–3.422, $P<0.001$) and DFS (HR = 2.516, 95%CI: 1.874–3.377, $P<0.001$). Combined with TD and PLNs, a total of 128 of 395 N1 patients were reclassified re-staged as N2(TD + PLNs ≥ 3), which had a worse prognosis than those diagnosed with N1. Compared with Tumor Node Metastasis stage and TD number, the multivariate model constructed using independent prognostic factors showed better predictive power for OS (AUC:0.769 vs. 0.681 vs. 0.650) and DFS (AUC:0.757 vs. 0.702 vs. 0.650).

Conclusion TD significantly affects the long-term prognosis of CRC patients. Combining TD and PLNs to redefine the tumor staging of CRC patients can improve the accuracy of long-term prognosis of surgical patients.

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Short abstract
In the retrospective cohort study, for the initial disease stage, patients with tumor deposits had a worse prognosis. Tumor deposit is a predictor of long-term prognosis of colorectal cancer patients. Combining tumor deposits and the number of positive lymph nodes to redefine the tumor staging of colorectal cancer patients can improve the accuracy of long-term prognosis of surgical patients. Compared with Tumor Node Metastasis stage and tumor deposit number, the multivariate model constructed using independent prognostic factors showed better predictive power for OS and DFS.

Keywords Tumor deposition, Colorectal cancer, Tumor N stage, Overall survival, Disease-free survival

Introduction

Colorectal cancer (CRC) is currently the third most common cancer and the second leading cause of death worldwide [1]. There are 1,000,000 new cases and 550,000 deaths annually [2]. According to the 7th edition of the American Joint Committee on Cancer (AJCC) guidelines, patients with stage II CRC (except low-risk patients) and above should be routinely treated with adjuvant therapy after surgery. High-risk factors include: T4, poor histological differentiation (high grade, excluding Microsatellite Instability-High), vascular invasion, nerve invasion, preoperative intestinal obstruction or tumor site perforation, positive or unknown resection margin, insufficient safe margin distance, less than 12 lymph nodes examined, etc [3]. Regardless of whether in the 7th or 8th edition of the staging system, tumor deposition (TD) (+) patients are only classified as N1c when they do not have metastatic lymph nodes. However, the presence of TD indicates that the patient's clinical stage is at least stage III, therefore adjuvant chemotherapy is routine [3, 4].

Tumor depositions (TDs), located in the subserosal, mesenteric or non-peritoneal perirectal, perirectal and mesorectal tissues, also known as tumor nodules, is a common feature of CRC, which is described in 10.2–44.2% of cases [5]. Their first description dates back to 1938, when they were thought to be soft-tissue metastases resulting from vascular tumor infiltration [6]. Starting from the 7th edition of AJCC CRC Staging Manual, TDs were introduced into the "regional lymph nodes" category, as mounting evidence suggested that TDs were a risk factor for recurrence or metastasis [3]. TDs were redefined as discrete tumor nodules within the lymphatic drainage area of the primary cancer without identifiable lymph node, vascular, or neural structures, regardless of their size, shape, and contour. In most cases where TDs are positive, the prognostic value of TD positivity is not reflected in the current N staging, even when concurrent lymph node involvement is present. Although TDs have quantitative value, the current N staging only reports their presence or absence, leading to significant information loss. Studies from France's IDEA [7] and Mayo Clinic [8] show that TDs have a harmful effect in both N1a/b and N2 patients. Therefore, ignoring TDs in the presence of lymph node metastasis means a significant loss of prognostic accuracy. More importantly, as lymph node count now guides treatment decisions on the duration and type of adjuvant chemotherapy, the classification of N1 and N2 will be critical in clinical decision-making. In some large-scale studies [9–11], researchers found that patients with TD (+) only were similar to those with only positive lymph nodes. Therefore, combining TD counts with lymph node numbers may potentially change clinical practice.

In previous studies, exploring the prognostic value of combining TD counts with positive lymph node counts in CRC patients was a major direction, but there is still controversy over the method of restaging and cutoff values [7, 8, 12]. In addition, the Surveillance, Epidemiology, and End Results (SEER) database used in related studies itself has limitations, and there have been few relevant studies on Chinese populations in previous research. Therefore, this study used a large single-center database to evaluate the impact of TD counts on the prognosis of colon cancer patients and revised the N staging by combining TD and positive lymph node numbers. We hypothesized that the revised N staging could more accurately predict the prognosis of colon cancer patients.

Materials and methods

General date

A retrospective analysis was conducted on data from 1,470 patients who underwent curative surgery for CRC at Wuhan Union Hospital from February 2014 to May 2018. The inclusion criteria were: (1) patients aged ≥ 18 years with confirmed CRC by imaging or pathology; (2) patients with a clear pathological diagnosis of TD-positive or negative; (3) patients who underwent primary CRC curative surgery for the first time and whose surgery was pathologically confirmed as radical resection (including complete tumor resection, negative margins of the distant, proximal and rectal mesentery); and (4) patients with complete clinical and pathological data. Exclusion criteria were: (1) patients with multiple metastases or recurrent CRC; (2) incomplete clinical and pathological

data; and (3) patients with other tumors. Ultimately, 1,470 CRC patients who met the inclusion criteria were included in our study (Fig. 1). According to AJCC/Tumor Node Metastasis (TNM) staging system, TDs were defined as discrete tumor nodules found within the lymphatic drainage area of the primary tumor of any shape, contour, or size lacking associated lymph node tissue, vascular structures, or neural structures [3]. Although the 8th edition TNM staging system waspublished on 1 January 2018, because of the controversial definition of TD and the lack of clinical adoption, thepathologists in our study still assessed TDs according tothe 7th edition definition.

Data collection and patient follow-up

We collected the baseline data of patients through the hospital electronic medical record system, such as gender, age, body mass and height index (BMI), family history of cancer, and clinicopathological data, include tumor maximum diameter, tumor location, preoperative obstruction, postoperative radiotherapy, postoperative chemotherapy, vascular invasion, perineural invasion (PNI), differentiation, TNM staging, number of lymph nodes, number of positive lymph nodes, serum tumor markers(STMs) (carcinoembryonic antigen [CEA], carbohydrate antigen [CA]19 – 9, CA72-4, CA125), surgical data: surgical methods, intraoperative management (blood transfusion, primary anastomosis, colostomy, perineum tamponaded hemostatic) and postoperative complications (obstruction, anastomotic fistula, surgical site infection [SSI], thrombosis, cardiovascular disease).

We conducted regular follow-up of patients according to the National Comprehensive Cancer Network (NCCN) guidelines. STMs testing was performed every 3 months during the first 2 years after surgery, and follow-up visits were scheduled every 6 months during 3–5 years. CT scans were performed annually. Patients who failed to attend their scheduled appointments within 1 year of their last visit were considered lost to follow-up. Collected follow-up information included: adjuvant therapy, tumor recurrence, time of recurrence, survival time, and time of death. The latest follow-up date for this study was January 2023. Overall survival (OS) was defined as the time from surgery to death or the date of the last follow-up; disease-free survival (DFS) was defined as the time from surgery to tumor recurrence, metastasis, or the date of the last follow-up. This study was approved by the Ethics Committee of Wuhan Union Hospital (No. 2018-S377).

X-tile analysis

We used X-tile software [13] (version 3.6.1, Yale University School of Medicine, New Haven, CT, USA) to analyze the optimal cutoff value for the total number of TD + the number of positive lymph nodes (PLNs) based on OS in CRC patients, in order to redefine the patients' N staging,

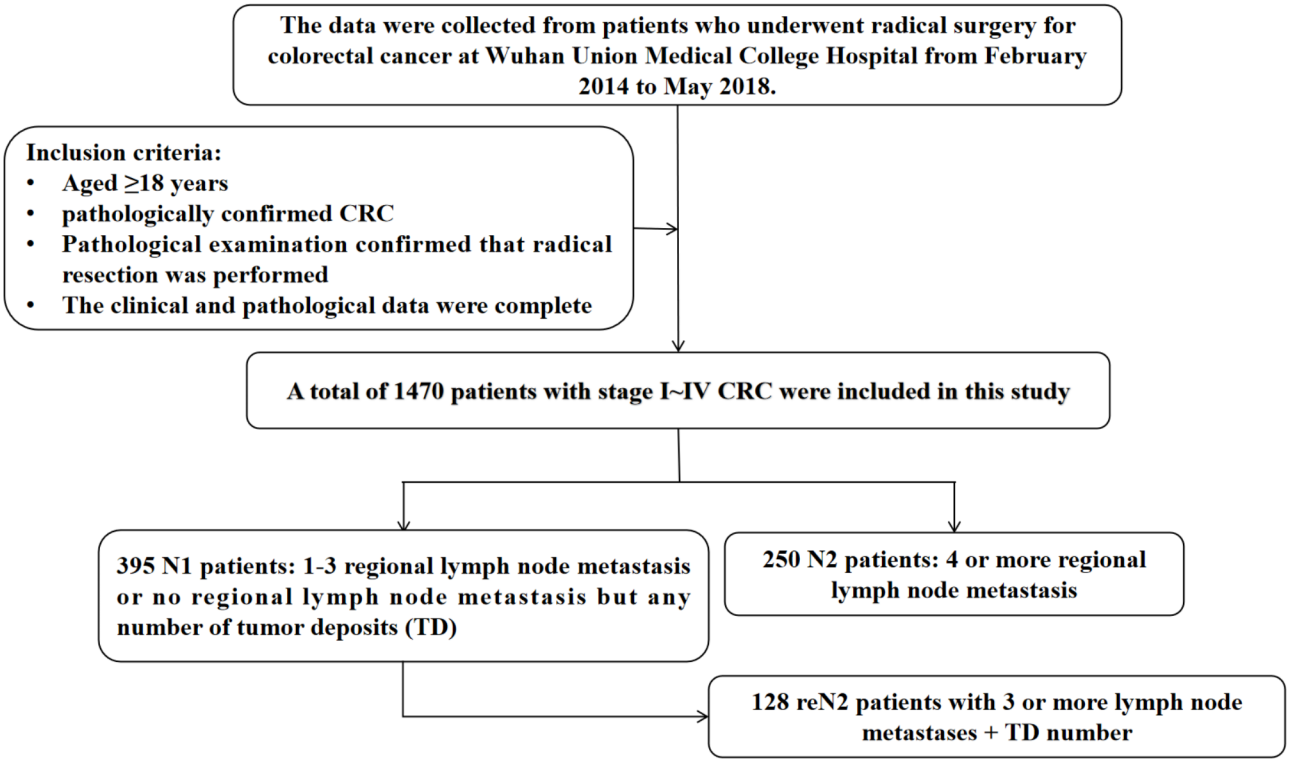

Fig. 1 Procedure for patient screening for inclusion in the study

as follows: re-staged as N0: TD + PLNs = 0, re-staged as N1: TD + PLNs = 1–2, re-staged as N2: TD + PLNs = 3+ (Fig. 2). In addition, we also classified the maximum diameter of the tumor.

Statistical methods

Statistical analysis was performed using SPSS software (version 25.0, Chicago, IL, USA) and GraphPad Prism 9. Count data were expressed as frequencies (percentages), and measurement data were expressed as medians (interquartile ranges). Two-sample comparisons of categorical variables were conducted using the chi-square test, Fisher's exact test, or Mann-Whitney U test, while multiple-group comparisons were conducted using the Kruskal-Wallis test. Kaplan-Meier survival curves were used to evaluate OS and DFS in CRC patients, and intergroup differences were compared using the log-rank test. Cox univariate analysis was conducted on indicators related to survival rate ($P < 0.05$), and indicators with statistical significance were included in multivariate Cox regression analysis to calculate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). A prediction model for patients' long-term survival was established by selecting statistically significant indicators using Cox multivariate analysis, and receiver operating characteristic (ROC) curves were used to evaluate the predictive ability of prognostic factors by calculating the area under the curve (AUC) of different models. $P < 0.05$ was considered statistically significant.

Result

Relationship between TD and demographic and clinicopathological characteristics of patients

Our results showed that 15.78%(232/1470) of the patients were TD positive. Compared to TD (-) patients, TD (+) patients were more likely to have higher BMI ($P = 0.011$), preoperative obstruction ($P = 0.001$), receive neoadjuvant chemotherapy ($P = 0.007$), postoperative radiotherapy ($P = 0.012$), chemotherapy ($P = 0.006$), have vascular invasion ($P < 0.001$) and PNI ($P < 0.001$), T3, T4 ($P < 0.001$), N stage($P < 0.001$),higher CEA ($P < 0.001$), CA19-9 ($P < 0.001$), and CA125 ($P = 0.02$)) in patients with more PLNs ($P < 0.001$) (Table 1). In addition, we compared the differences in various clinicopathological characteristics between different TDs and TD + PLNs total numbers. Compared to patients with TD count of 0, a higher proportion of patients with vascular invasion, PNI, higher tumor stage, higher node stage, higher preoperative STM levels (CEA, CA19-9), and higher number of positive lymph nodes were observed in patients with TD = 1, TD = 2, and TD ≥ 3, and the differences were statistically significant (all $P < 0.05$), but there was no significant difference in TDs among TD (+) patients (Table 2).

When we combined TD count and positive lymph node count and analyzed the optimal cutoff value based on patients' OS, we reclassified patients into three groups: No.=0, No.=1–2, and No.≥3 as N0, re-staged N1, and re-staged N2, respectively. After intergroup comparisons, our results showed that compared to N0 patients, more patients in the re-staged N1 and re-staged N2 groups received chemotherapy after surgery, had vascular invasion and neural invasion, higher tumor stage, higher node stage, higher CEA, CA19-9, and a higher number of positive lymph nodes. Furthermore, compared to patients in the re-staged as N1 group, those in the re-staged as N2 group were more likely to have vascular invasion, a higher tumor stage, higher node stage, and more PLNs (Table 3, all $P < 0.05$). In addition, we also analyzed the relationship between TDs and the perioperative management and postoperative complications of CRC patients underwent surgical. See Supplementary Tables for details.

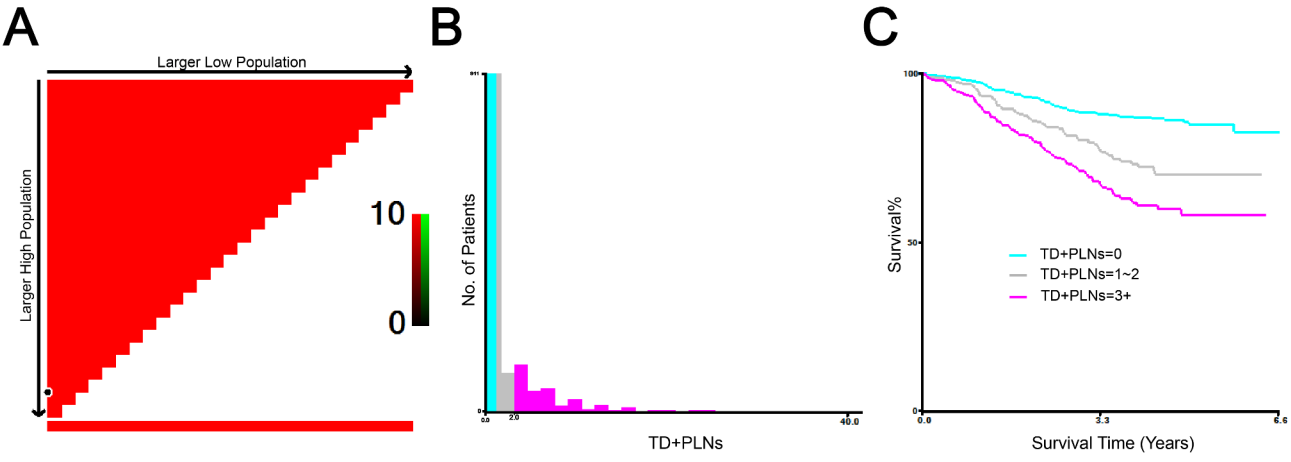

Fig. 2 X-tile analysis of OS according to the number of TD + PLNs. The optimal cut-off values of TD + PLNs is = 0, <3, ≥ 3

Table 1 Characteristics of patients grouped according to the presence or absence of TD

Characteristics	All (*N* = 1470)	TD (-) (*N* = 1238)	TD (+) (*N* = 232)	z/x2	*P*
Age (years)				3.020	0.082
<65	999 (68.00%)	830 (67.00%)	169 (72.80%)		
≥ 65	471 (32.00%)	408 (33.00%)	63 (27.20%)		
BMI				6.437	**0.011**
<25	1185 (80.60%)	1012 (81.70%)	173 (74.60%)		
≥ 25	285 (19.40%)	226 (18.30%)	59 (25.40%)		
Tumor size (cm)				1.174	0.278
≤ 2.70	265 (18.00%)	229 (18.50%)	36 (15.50%)		
>2.70	1205 (82.00%)	1009 (81.50%)	196 (84.50%)		
Obstruction before surgery				10.895	**0.001**
Absent	1272 (86.50%)	1087 (87.80%)	185 (79.70%)		
present	198 (13.50%)	151 (12.20%)	47 (20.30%)		
Sex				0.065	0.799
Male	876 (59.60%)	736 (59.50%)	140 (60.30%)		
Female	594 (40.40%)	502 (40.50%)	92 (39.70%)		
Family history of cancer				0.049	0.825
No	1330 (90.50%)	1121 (90.50%)	209 (90.10%)		
Yes	140 (9.50%)	117 (9.50%)	23 (9.90%)		
Post radiotherapy				6.310	**0.012**
No	1388 (94.40%)	1177 (95.10%)	211 (90.90%)		
Yes	82 (5.60%)	61 (4.90%)	21 (9.10%)		
Chemotherapy				7.461	**0.006**
No	691 (47.00%)	601 (48.50%)	90 (38.80%)		
Yes	779 (53.00%)	637 (51.50%)	142 (61.20%)		
Vascular invasion				56.655	**< 0.001**
Absent	1197 (81.40%)	1049 (84.70%)	148 (63.80%)		
Present	273 (18.60%)	189 (15.30%)	84 (36.20%)		
perineural invasion				87.275	**< 0.001**
Absent	1138 (77.40%)	1013 (81.80%)	125 (53.90%)		
Present	332 (22.60%)	225 (18.20%)	107 (46.10%)		
Histological grade				-3.842	**< 0.001**
Well	217 (14.80%)	195 (15.80%)	22 (9.50%)		
Moderately	1037 (70.50%)	878 (70.90%)	159 (68.50%)		
Poorly	216 (14.70%)	165 (13.30%)	51 (22.00%)		
TNM stage				-14.999	**< 0.001**
I	225 (15.30%)	225 (18.20%)	0 (0.00%)		
II	497 (33.80%)	497 (40.10%)	0 (0.00%)		
III	598 (40.70%)	413 (33.40%)	185 (79.70%)		
IV	150 (10.20%)	103 (8.30%)	47 (20.30%)		
T stage				-7.404	**< 0.001**
T1	95 (6.50%)	94 (7.60%)	1 (0.40%)		
T2	223 (15.20%)	209 (16.90%)	14 (6.00%)		
T3	850 (57.80%)	712 (57.50%)	138 (59.50%)		
T4	302 (20.50%)	223 (18.00%)	79 (34.10%)		
N stage				-17.030	**< 0.001**
N0	772(52.50%)	772(62.40%)	0(0.00%)		
N1	448(30.50%)	305(24.60%)	143(61.60%)		
N2	250(17.00%)	161(13.00%)	89(38.40%)		
M stage				-5.069	**< 0.001**
M0	1334 (90.70%)	1144 (92.40%)	190 (81.90%)		
M1	136 (9.30%)	94 (7.60%)	42 (18.10%)		
Primary tumor location				1.163	0.559
Right colon	359 (24.40%)	307 (24.80%)	52 (22.40%)		

Table 1 (continued)

Characteristics	All (*N* = 1470)	TD (-) (*N* = 1238)	TD (+) (*N* = 232)	z/x2	*P*
Left colon	347 (23.60%)	295 (23.80%)	52 (22.40%)		
Rectum	764 (52.00%)	636 (51.40%)	128 (55.20%)		
ASA				-0.372	0.710
1	20 (1.40%)	17 (1.40%)	3 (1.30%)		
2	1025 (69.70%)	859 (69.40%)	166 (71.60%)		
3	291 (19.80%)	253 (20.40%)	38 (16.40%)		
4	134 (9.10%)	109 (8.80%)	25 (10.80%)		
Previous history of abdominal surgery				0.476	0.490
No	1196 (81.40%)	1011 (81.70%)	185 (79.70%)		
Yes	274 (18.60%)	227 (18.30%)	47 (20.30%)		
Neoadjuvant chemotherapy				7.242	**0.007**
No	1386 (94.30%)	1176 (95.00%)	210 (90.50%)		
Yes	84 (5.70%)	62 (5.00%)	22 (9.50%)		
Preoperative comorbidities					
Any preoperative comorbidities				0.785	0.376
No	1061 (72.20%)	888 (71.70%)	173 (74.60%)		
Yes	409 (27.80%)	350 (28.30%)	59 (25.40%)		
Cardiovascular disease				0.323	0.570
No	1132 (77.00%)	950 (76.70%)	182 (78.40%)		
Yes	338 (23.00%)	288 (23.30%)	50 (21.60%)		
Cerebrovascular disease				0.390	0.532
No	1440 (98.00%)	1211 (97.80%)	229 (98.70%)		
Yes	30 (2.00%)	27 (2.20%)	3 (1.30%)		
COPD				0.019	0.891
No	1430 (97.30%)	1204 (97.30%)	226 (97.40%)		
Yes	40 (2.70%)	34 (2.70%)	6 (2.60%)		
Diabetes				0.983	0.322
No	1358 (92.40%)	1140 (92.10%)	218 (94.00%)		
Yes	112 (7.60%)	98 (7.90%)	14 (6.00%)		
Hematologic disease				0.033	0.857
No	1466 (99.70%)	1234 (99.70%)	232 (100.00%)		
Yes	4 (0.30%)	4 (0.30%)	0 (0.00%)		
CEA (ng/mL)				36.616	**< 0.001**
< 5	901 (61.30%)	800 (64.60%)	101 (43.50%)		
>=5	569 (38.70%)	438 (35.40%)	131 (56.50%)		
CA19-9 (kU/L)				29.516	**< 0.001**
< 37	1215 (82.70%)	1052 (85.00%)	163 (70.30%)		
>=37	255 (17.30%)	186 (15.00%)	69 (29.70%)		
CA72-4 (U/mL)				2.642	0.104
< 6.9	1045 (82.9%)	896 (83.70%)	149 (78.80%)		
>=6.9	215 (17.10%)	175 (16.30%)	40 (21.20%)		
Miss	210	167	43		
CA125 (U/mL)				5.404	**0.020**
< 35	1312 (89.30%)	1115 (90.10%)	197 (84.90%)		
>=35	158 (10.70%)	123 (9.90%)	35 (15.10%)		
LNs		18 (11)	17 (9)	-1.779	0.075
Miss		53	6		
PLNs		0 (1)	2 (6)	-11.369	**< 0.001**
Miss		53	6		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ASA, American Society of Anesthesiologists Physical Status Classification; COPD, chronic obstructive pulmonary disease; CEA, carcino-embryonic antigen; CA19-9; CA72-4; CA125, carbohydrate antigen; LNs, Number of lymph nodes examined; PLNs, Number of positive lymph nodes. Bold was used to highlight values that were statistically significant (< 0.05)

Table 2 Characteristics of patients grouped according to the number of TD

Characteristics	TD = 0 (*N* = 1238)	TD = 1 (*N* = 76)	TD = 2 (*N* = 40)	TD = 3+ (*N* = 116)	*P**	*P***	*P****	*P*****	*P******	*P*******
Age (years)					0.470	0.548	**0.020**	0.350	0.308	0.062
<65	830 (67.00%)	54 (71.10%)	25 (62.50%)	90 (77.60%)						
≥ 65	408 (33.00%)	22 (28.90%)	15 (37.50%)	26 (22.40%)						
BMI					0.542	0.279	**0.008**	0.629	0.252	0.675
<25	1012 (81.70%)	60 (78.90%)	30 (75.00%)	83 (71.60%)						
≥ 25	226 (18.30%)	16 (21.10%)	10 (25.00%)	33 (28.40%)						
Tumor size (cm)					0.554	0.076	0.917	0.208	0.678	0.110
≤ 2.70	229 (18.50%)	12 (15.80%)	3 (7.50%)	21 (18.10%)						
>2.70	1009 (81.50%)	64 (84.20%)	37 (92.50%)	95 (81.90%)						
Obstruction before surgery					**0.025**	**0.016**	0.068	0.629	0.613	0.347
Absent	1087 (87.80%)	60 (78.90%)	30 (75.00%)	95 (81.90%)						
present	151 (12.20%)	16 (21.10%)	10 (25.00%)	21 (18.10%)						
Sex					0.274	0.482	0.370	0.933	0.144	0.280
Male	736 (59.50%)	50 (65.80%)	26 (65.00%)	64 (55.20%)						
Female	502 (40.50%)	26 (34.20%)	14 (35.00%)	52 (44.80%)						
Family history of cancer					0.403	0.242	0.754	0.143	0.370	0.428
No	1121 (90.50%)	71 (93.40%)	34 (85.00%)	104 (89.70%)						
Yes	117 (9.50%)	5 (6.60%)	6 (15.00%)	12 (10.30%)						
Post radiotherapy					**0.009**	0.983	0.088	0.234	0.466	0.460
No	1177 (95.10%)	67 (88.20%)	38 (95.00%)	106 (91.40%)						
Yes	61 (4.90%)	9 (11.80%)	2 (5.00%)	10 (8.60%)						
Chemotherapy					**0.027**	0.092	0.194	0.955	0.353	0.422
No	601 (48.50%)	27 (35.50%)	14 (35.00%)	49 (42.20%)						
Yes	637 (51.50%)	49 (64.50%)	26 (65.00%)	67 (57.80%)						
Vascular invasion					**0.004**	**0.001**	**< 0.001**	0.413	**0.040**	0.422
Absent	1049 (84.70%)	55 (72.40%)	26 (65.00%)	67 (57.80%)						
Present	189 (15.30%)	21 (27.60%)	14 (35.00%)	49 (42.20%)						
perineural invasion					**< 0.001**	**< 0.001**	**< 0.001**	0.070	0.646	**0.021**
Absent	1013 (81.80%)	42 (55.30%)	15 (37.50%)	68 (58.60%)						
Present	225 (18.20%)	34 (44.70%)	25 (62.50%)	48 (41.40%)						
Histological grade					0.222	0.146	**< 0.001**	0.621	0.099	0.353
Well	195 (15.80%)	7 (9.20%)	2 (5.00%)	13 (11.20%)						
Moderately	878 (70.90%)	58 (76.30%)	32 (80.00%)	69 (59.50%)						
Poorly	165 (13.30%)	11 (14.50%)	6 (15.00%)	34 (29.30%)						
TNM stage					**< 0.001**	**< 0.001**	**< 0.001**	0.918	**0.007**	**0.043**
I	225 (18.20%)	0 (0.00%)	0 (0.00%)	0 (0.00%)						
II	497 (40.10%)	0 (0.00%)	0 (0.00%)	0 (0.00%)						
III	413 (33.40%)	67 (88.20%)	35 (87.50%)	83 (71.60%)						
IV	103 (8.30%)	9 (11.80%)	5 (12.50%)	33 (28.40%)						
T stage					**< 0.001**	**0.001**	**< 0.001**	0.997	0.899	0.917
T1	94 (7.60%)	1 (1.30%)	0	0						
T2	209 (16.90%)	6 (7.90%)	2 (5.00%)	6 (5.20%)						
T3	712 (57.50%)	42 (55.30%)	25 (62.50%)	71 (61.20%)						
T4	223 (18.00%)	27 (35.50%)	13 (32.50%)	39 (33.60%)						
N stage					**< 0.001**	**< 0.001**	**< 0.001**	0.693	**0.015**	0.123
N0	772(62.40%)	0(0.00%)	0(0.00%)	0(0.00%)						
N1	305(24.60%)	54(71.10%)	27(67.50%)	62(67.50%)						
N2	161(13.00%)	22(28.90%)	13(32.50%)	54(32.50%)						
M stage					0.354	0.983	**< 0.001**	0.599	**0.007**	**0.011**
M0	1144 (92.40%)	68 (89.50%)	37 (92.50%)	85 (73.30%)						
M1	94 (7.60%)	8 (10.50%)	3 (7.50%)	31 (26.70%)						
Primary tumor location					0.414	0.472	0.184	0.276	0.829	0.175

Table 2 (continued)

Characteristics	TD = 0 (*N* = 1238)	TD = 1 (*N* = 76)	TD = 2 (*N* = 40)	TD = 3+ (*N* = 116)	*P**	*P***	*P****	*P*****	*P******	*P*******
Right colon	307 (24.80%)	17 (22.40%)	11 (27.50%)	24 (20.70%)						
Left colon	295 (23.80%)	16 (21.10%)	11 (27.50%)	25 (21.60%)						
Rectum	636 (51.40%)	43 (56.60%)	18 (45.00%)	67 (57.80%)						
ASA					0.476	0.572	0.764	0.383	0.687	0.502
1	17 (1.40%)	3 (3.90%)	0	0						
2	859 (69.40%)	53 (69.70%)	27 (67.50%)	86 (74.10%)						
3	253 (20.40%)	12 (15.80%)	9 (22.50%)	17 (14.70%)						
4	109 (8.80%)	8 (10.50%)	4 (10.00%)	13 (11.20%)						
Previous history of abdominal surgery					0.760	0.591	0.281	0.531	0.659	0.318
No	1011 (81.70%)	61 (80.30%)	34 (85.00%)	90 (77.60%)						
Yes	227 (18.30%)	15 (19.70%)	6 (15.00%)	26 (22.40%)						
Neoadjuvant chemotherapy					**0.002**	0.471	**0.041**	0.064	0.426	0.154
No	1176 (95.00%)	66 (86.80%)	39 (97.50%)	105 (90.50%)						
Yes	62 (5.00%)	10 (13.20%)	1 (2.50%)	11 (9.50%)						
Preoperative comorbidities										
Any preoperative comorbidities					0.388	0.915	0.581	0.653	0.734	0.840
No	888 (71.70%)	58 (76.30%)	29 (72.50%)	86 (74.10%)						
Yes	350 (28.30%)	18 (23.70%)	11 (27.50%)	30 (25.90%)						
Cardiovascular disease					0.657	0.798	0.529	0.629	0.952	0.570
No	950 (76.70%)	60 (78.90%)	30 (75.00%)	92 (79.30%)						
Yes	288 (23.30%)	16 (21.10%)	10 (25.00%)	24 (20.70%)						
Cerebrovascular disease					0.612	0.892	0.340	0.643	0.763	0.429
No	1211 (97.80%)	75 (98.70%)	39 (97.50%)	115 (99.10%)						
Yes	27 (2.20%)	1 (1.30%)	1 (2.50%)	1 (0.90%)						
COPD					0.539	0.288	0.919	0.205	0.597	0.306
No	1204 (97.30%)	73 (96.10%)	40 (100.00%)	113 (97.40%)						
Yes	34 (2.70%)	3 (3.90%)	0	3 (2.60%)						
Diabetes					0.208	0.924	0.696	0.414	0.391	0.898
No	1140 (92.10%)	73 (96.10%)	37 (92.50%)	108 (93.10%)						
Yes	98 (7.90%)	3 (3.90%)	3 (7.50%)	8 (6.90%)						
Hematologic disease					0.620	0.719	0.540	1.000	1.000	1.000
No	1234 (99.70%)	76 (100.00%)	40 (100.00%)	116 (100.00%)						
Yes	4 (0.30%)	0	0	0						
CEA (ng/mL)					**0.002**	**< 0.001**	**< 0.001**	0.125	0.730	0.174
< 5	800 (64.60%)	36 (47.40%)	13 (32.50%)	52 (44.80%)						
>=5	438 (35.40%)	40 (52.60%)	27 (67.50%)	64 (55.20%)						
CA19-9 (kU/L)					**0.001**	**0.032**	**< 0.001**	0.870	0.759	0.675
< 37	1052 (85.00%)	54 (71.10%)	29 (72.50%)	80 (69.00%)						
>=37	186 (15.00%)	22 (28.90%)	11 (27.50%)	36 (31.00%)						
CA72-4 (U/mL)					0.373	0.660	0.057	0.397	0.625	0.218
< 6.9	896 (83.70%)	50 (79.40%)	26 (86.70%)	73 (76.00%)						
>=6.9	175 (16.30%)	13 (20.60%)	4 (13.30%)	23 (24.00%)						
Miss	167	13	10	20						
CA125 (U/mL)					0.366	0.989	**0.006**	0.621	0.364	0.230
< 35	1115 (90.10%)	66 (86.80%)	36 (90.00%)	95 (81.90%)						
>=35	123 (9.90%)	10 (13.20%)	4 (10.00%)	21 (18.10%)						
LNs	18 (11)	17 (8)	17 (10)	16 (10)	0.857	0.950	**0.014**	0.974	0.103	0.169
Miss	53	2	0	4						

Table 2 (continued)

Characteristics	TD = 0 (*N* = 1238)	TD = 1 (*N* = 76)	TD = 2 (*N* = 40)	TD = 3+ (*N* = 116)	*P**	*P***	*P****	*P*****	*P******	*P*******
PLNs	0 (1)	2 (4)	2 (5)	3 (7)	**< 0.001**	**< 0.001**	**< 0.001**	0.947	**0.022**	0.063
Miss	53	2	0	4						

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ASA, American Society of Anesthesiologists Physical Status Classification; COPD, chronic obstructive pulmonary disease; CEA, carcino-embryonic antigen; CA19-9; CA72-4; CA125, carbohydrate antigen; LNs, Number of lymph nodes examined; PLNs, Number of positive lymph nodes

Bold was used to highlight values that were statistically significant (< 0.05)

Comparison of long-term prognosis for CRC patients

Compared to TD (-) patients, TD (+) patients was associated with poor OS (HR = 2.478, 95% CI: 1.794–3.422, $P < 0.001$) and DFS (HR = 2.516, 95% CI: 1.874–3.377, $P < 0.001$) (Fig. 3A and D). In the initial N staging, 5-year OS (N1: HR = 2.182, 95% CI: 1.625–2.929, $P < 0.001$; N2: HR = 3.735, 95% CI: 2.632–5.302, $P < 0.001$) and DFS (N1: HR = 1.830, 95% CI: 1.402–2.388, $P < 0.001$; N2: HR = 3.592, 95% CI: 2.631–4.906, $P < 0.001$) of patients in N1 and N2 stages were significantly lower than those of patients in N0 stage. The 5-year OS (HR = 1.731, 95% CI: 1.291–2.320, $P < 0.001$) and DFS (HR = 1.949, 95% CI: 1.487–2.554, $P < 0.001$) of N2 patients were significantly lower than those of N1 patients (Fig. 3B and E). We observed a negative effect of TD (+) on OS and DFS in the N1 group, as the 5-year OS (HR = 1.850, 95% CI: 1.099–3.113, $P = 0.006$) and DFS (HR = 1.992, 95% CI: 1.219–3.254, $P < 0.001$) of TD (+) patients were significantly lower than those of TD (-) patients. However, the presence or absence of TD did not significantly affect the long-term prognosis of CRC patients in the N2 stage ($P > 0.05$) (Fig. 3C and F).

When we re-staged patients by combining TDs and PLNs and analyzed the optimal cut-off value, our results showed that 5-year OS (restaged N1: HR = 2.129, 95% Cl: 1.502–3.017, $P < 0.001$; restaged N2: HR = 3.339, 95% Cl: 2.525–4.415, $P < 0.001$) and DFS (restaged N1: HR = 2.008, 95% Cl: 1.466–2.750, $P < 0.001$; restaged N2: HR = 3.279, 95% Cl: 2.548–4.219, $P < 0.001$) of patients in restaged N1 and restaged N2 stages were significantly lower than those of N0 (no lymph node metastasis and no tumor deposit) stage patients. The 5-year OS (HR = 1.594, 95% Cl: 1.212–2.095, $P = 0.001$) and DFS (HR = 1.655, 95% Cl: 1.290–2.122, $P < 0.001$) of restaged N2 patients were significantly lower than those of restaged N1 patients (Fig. 4A and C). After screening low-risk patients as high-risk patients and restaging as N2, these patients had a worse prognosis than those diagnosed with N1 ($P < 0.001$), but their prognosis was similar to that of patients in the initial N2 stage ($P > 0.05$) (Fig. 4B and D).

Analysis of factors associated with long-term survival

The results of Cox univariate analysis showed that TD, TD + PLNs, age, tumor diameter, preoperative obstruction, postoperative chemotherapy, vascular invasion, PNI, TNM stage, and CEA, CA19-9, CA72-4, CA125, and other factors were all related to OS of CRC patient (all $P < 0.05$). Multivariate analysis revealed that TD + PLNs (re-staged N2: HR = 1.778, 95% CI: 1.046–3.022, $P = 0.033$), age (HR = 1.669, 95% CI: 1.272–2.188, $P < 0.001$), postoperative chemotherapy (HR = 0.542, 95% CI: 0.414–0.710, $P < 0.001$), PNI (HR = 1.822, 95% CI: 1.354–2.451, $P < 0.001$), TNM stage (III: HR = 2.565, 95% CI: 1.187–5.541, $P = 0.017$; IV: HR = 6.999, 95% CI: 3.324–14.736, $P < 0.001$), CEA (HR = 1.507, 95% CI: 1.153–1.970, $P = 0.003$), CA19-9 (HR = 1.476, 95% CI: 1.102–1.976, $P = 0.009$), and preoperative CA125 level (HR = 1.781, 95% CI: 1.252–2.533, $P = 0.001$) were independent prognostic factors for OS in CRC patients (Table 4).

For DFS, TDs, TD + PLNs, age, tumor maximum diameter, preoperative obstruction, vascular invasion, PNI, differentiation degree, TNM stage, preoperative comorbidities (cardiovascular and cerebrovascular diseases), and preoperative levels of CEA, CA19-9, and CA125 were significantly associated with patient prognosis (all $P < 0.05$). Multivariate analysis revealed that TD + PLNs (re-staged N2: HR = 1.637, 95% CI: 1.063–2.521, $P = 0.025$), age (HR = 1.548, 95% CI: 1.237–1.936, $P < 0.001$), PNI (HR = 1.690, 95% CI: 1.328–2.151, $P < 0.001$), TNM stage (II: HR = 1.915, 95% CI: 1.103–3.323, $P = 0.021$; III: HR = 2.370, 95% CI: 1.248–4.501, $P = 0.008$; IV: HR = 7.955, 95% CI: 4.280-14.785, $P < 0.001$), preoperative CEA level (HR = 1.305, 95% CI: 1.046–1.629, $P = 0.019$), and preoperative CA125 level (HR = 1.430, 95% CI: 1.054–1.939, $P = 0.021$) were independent prognostic factors for patient prognosis (Table 5).

Analysis of predictive model for long-term prognosis of patients

After redefining patient staging, a predictive model for patient's OS was constructed based on the results of Cox multivariate analysis, including TD + PLNs, age, postoperative chemotherapy, PNI, TNM stage, preoperative CEA level, preoperative CA19-9 level, and preoperative CA125 level. The area under the curve (AUC) of the model was 0.769 (95% CI: 0.739–0.798, $P < 0.001$, Fig. 5A). For DFS, the predictive model included TD + PLNs, age, PNI, TNM stage, preoperative CEA level, and preoperative CA125 level, and the AUC of the model was 0.757 (95% CI: 0.729–0.785, $P < 0.001$, Fig. 5B).

Table 3 Characteristics of patients grouped according to the number of TD + PLNs

Characteristics	No.=0 (*N* = 780)	No.=1–2 (*N* = 288)	No.=3+ (*N* = 402)	*P**	*P***	*P****
Age (years)				0.369	0.279	0.953
<65	519(66.50%)	200(69.40%)	280(69.70%)			
≥ 65	261(33.50%)	88(30.60%)	122(30.30%)			
BMI				0.796	0.527	0.465
<25	631(80.90%)	235(81.60%)	319(79.40%)			
≥ 25	149(19.10%)	53(18.40%)	83(20.60%)			
Tumor size (cm)				0.015	**< 0.001**	0.089
≤ 2.70	175(22.40%)	45(15.60%)	45(11.20%)			
>2.70	605(77.60%)	243(84.40%)	357(88.80%)			
Obstruction before surgery				0.234	0.185	0.998
Absent	685 (87.80%)	245 (85.10%)	342 (85.10%)			
present	95 (12.20%)	43 (14.90%)	60 (14.90%)			
Sex				0.544	0.635	0.870
Male	471 (60.40%)	168 (58.30%)	237 (59.00%)			
Female	309 (39.60%)	120 (41.70%)	165 (41.00%)			
Family history of cancer				0.688	0.114	0.384
No	713 (91.40%)	261 (90.60%)	356 (88.60%)			
Yes	67 (8.60%)	27 (9.40%)	46 (11.40%)			
Post radiotherapy				0.194	0.128	0.951
No	744 (95.40%)	269 (93.40%)	375 (93.30%)			
Yes	36 (4.60%)	19 (6.60%)	27 (6.70%)			
Chemotherapy				**0.005**	**< 0.001**	0.633
No	406 (52.10%)	122 (42.40%)	163 (40.50%)			
Yes	374 (47.90%)	166 (57.60%)	239 (59.50%)			
Vascular invasion				**< 0.001**	**< 0.001**	**< 0.001**
Absent	713 (91.40%)	231 (80.20%)	253 (62.90%)			
Present	67 (8.60%)	57 (19.80%)	149 (37.10%)			
Perineural invasion				**< 0.001**	**< 0.001**	0.076
Absent	685 (87.80%)	200 (69.40%)	253 (62.90%)			
Present	95 (12.20%)	88 (30.60%)	149 (37.10%)			
Histological grade				0.229	**< 0.001**	**0.013**
Well	126 (16.20%)	35 (12.20%)	56 (13.90%)			
Moderately	566 (72.60%)	220 (76.40%)	251 (62.40%)			
Poorly	88 (11.30%)	33 (11.50%)	95 (23.60%)			
TNM stage				**< 0.001**	**< 0.001**	**0.007**
I	223(28.60%)	2(0.70%)	0(0.00%)			
II	483(61.90%)	7(2.40%)	7(1.70%)			
III	31(4.00%)	246(85.40%)	321(79.90%)			
IV	43(5.50%)	33(11.50%)	74(18.40%)			
T stage				**< 0.001**	**< 0.001**	**0.005**
T1	86 (11.00%)	5 (1.70%)	4 (1.00%)			
T2	174 (22.30%)	27 (9.40%)	22 (5.50%)			
T3	408 (52.30%)	190 (66.00%)	252 (62.70%)			
T4	112 (14.40%)	66 (22.90%)	124 (30.80%)			
N stage				**< 0.001**	**< 0.001**	**< 0.001**
N0	750(96.20%)	13(4.50%)	9(2.20%)			
N1	22(2.80%)	273(94.80%)	153(38.10%)			
N2	8(1.00%)	2(0.70%)	240(59.70%)			
M stage				**0.001**	**< 0.001**	**0.016**
M0	742 (95.10%)	258 (89.60%)	334 (83.10%)			
M1	38 (4.90%)	30 (10.40%)	68 (16.90%)			
Primary tumor location				0.378	0.233	0.084
Right colon	192 (24.60%)	80 (27.80%)	87 (21.60%)			

Table 3 (continued)

Characteristics	No.=0 (*N* = 780)	No.=1–2 (*N* = 288)	No.=3+ (*N* = 402)	*P**	*P***	*P****
Left colon	186 (23.80%)	66 (22.90%)	95 (23.60%)			
Rectum	402 (51.50%)	142 (49.30%)	220 (54.70%)			
ASA				0.979	0.178	0.297
1	10 (1.30%)	5 (1.70%)	5 (1.20%)			
2	535 (68.60%)	196 (68.10%)	294 (73.10%)			
3	166 (21.30%)	60 (20.80%)	65 (16.20%)			
4	69 (8.80%)	27 (9.40%)	38 (9.50%)			
Previous history of abdominal surgery				0.460	0.506	0.899
No	641 (82.20%)	231 (80.20%)	324 (80.60%)			
Yes	139 (17.80%)	57 (19.80%)	78 (19.40%)			
Neoadjuvant chemotherapy				0.229	0.396	0.080
No	736 (94.40%)	266 (92.40%)	384 (95.50%)			
Yes	44 (5.60%)	22 (7.60%)	18 (4.50%)			
Preoperative comorbidities						
Any preoperative comorbidities				0.794	0.420	0.681
No	557 (71.40%)	208 (72.20%)	296 (73.60%)			
Yes	223 (28.60%)	80 (27.80%)	106 (26.40%)			
Cardiovascular disease				0.694	0.480	0.832
No	595 (76.30%)	223 (77.40%)	314 (78.10%)			
Yes	185 (23.70%)	65 (22.60%)	88 (21.90%)			
Cerebrovascular disease				0.507	0.601	0.869
No	766 (98.20%)	281 (97.60%)	393 (97.80%)			
Yes	14 (1.80%)	7 (2.40%)	9 (2.20%)			
COPD				0.142	0.158	0.809
No	753 (96.50%)	283 (98.30%)	394 (98.00%)			
Yes	27 (3.50%)	5 (1.70%)	8 (2.00%)			
Diabetes				0.892	0.249	0.287
No	717 (91.90%)	264 (91.70%)	377 (93.80%)			
Yes	63 (8.10%)	24 (8.30%)	25 (6.20%)			
Hematologic disease				0.929	0.213	0.237
No	777 (99.60%)	287 (99.70%)	402 (100.00%)			
Yes	3 (0.40%)	1 (0.30%)	0 (0.00%)			
CEA (ng/mL)				**< 0.001**	**< 0.001**	0.555
< 5	534 (68.50%)	157 (54.50%)	210 (52.20%)			
>=5	246 (31.50%)	131 (45.50%)	192 (47.80%)			
CA19-9 (kU/L)				**< 0.001**	**< 0.001**	0.069
< 37	693 (88.80%)	228 (79.20%)	294 (73.10%)			
>=37	87 (11.20%)	60 (20.80%)	108 (26.90%)			
CA72-4				0.602	**< 0.001**	**0.019**
< 6.9	579 (85.80%)	200 (84.40%)	266 (76.40%)			
>=6.9	96 (14.20%)	37 (15.60%)	82 (23.60%)			
Miss	105	51	54			
CA125 (U/mL)				0.158	0.065	0.834
< 35	708 (90.80%)	253 (87.80%)	351 (87.30%)			
>=35	72 (9.20%)	35 (12.20%)	51 (12.70%)			
LNs	17 (11)	18 (12)	18 (9)	0.227	0.208	0.990
Miss	53	2	4			
PLNs	0 (0)	1 (1)	5 (4)	**< 0.001**	**< 0.001**	**< 0.001**
Miss	53	2	4			

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ASA, American Society of Anesthesiologists Physical Status Classification; COPD, chronic obstructive pulmonary disease; CEA, carcino-embryonic antigen; CA19-9; CA72-4; CA125, carbohydrate antigen; LNs, Number of lymph nodes examined; PLNs, Number of positive lymph nodes

Bold was used to highlight values that were statistically significant (< 0.05)

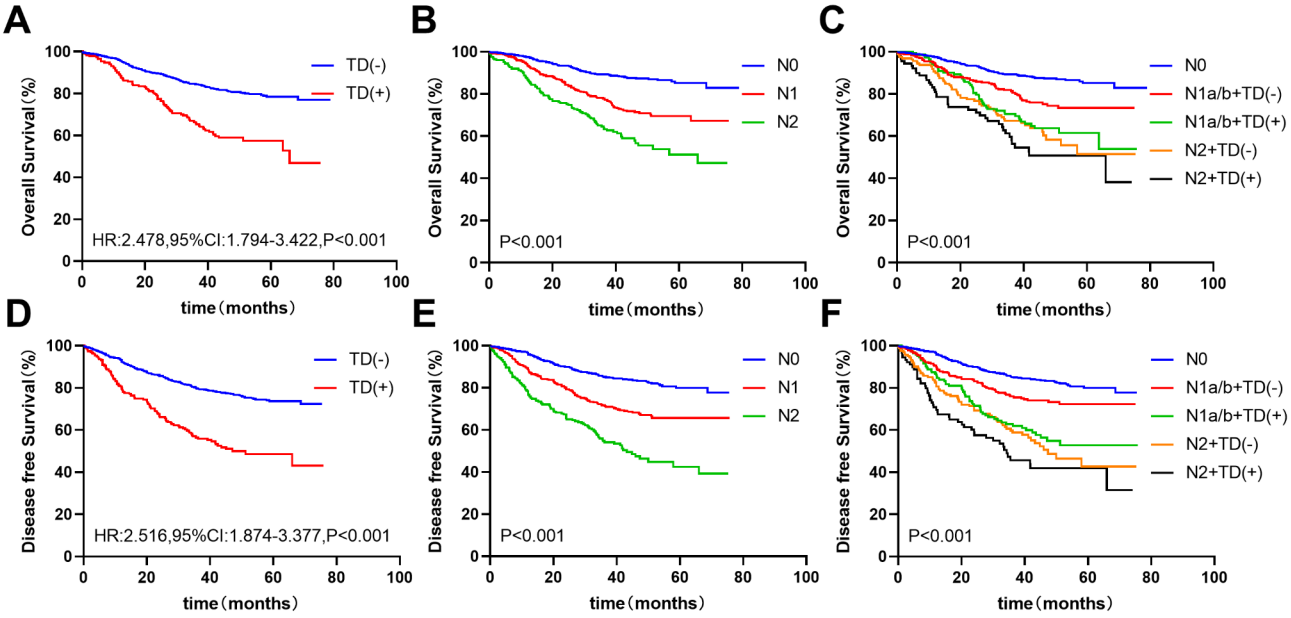

Fig. 3 Kaplan-Meier (K-M) survival curves of overall survival (OS) and disease-free survival (DFS) colorectal cancer (CRC) patients in different groups. K-M survival curves of OS in CRC patients for TD (+) and TD (-) (**A**); K-M survival curves of OS in CRC patients for the initial N stage (**B**); K-M survival curve of OS in CRC patients grouped based on TD status combined with N stage (**C**); K-M survival curves of DFS in CRC patients for TD (+) and TD (-) (**D**); K-M survival curves of DFS in CRC patients for the initial N stage (**E**); K-M survival curve of DFS in CRC patients grouped based on TD status combined with N stage (**F**)

Compared with traditional TNM staging (OS: 0.681, 95% CI: 0.648–0.714, $P<0.001$; DFS: 0.650, 95% CI: 0.616–0.686, $P<0.001$) and TD + PLNs (OS: 0.702, 95% CI: 0.672–0.733, $P<0.001$; DFS: 0.650, 95% CI: 0.618–0.683, $P<0.001$), the newly constructed predictive models showed better prediction performance for OS and DFS.

Discussion

15.7% of patients with stage I-IV CRC had TD. Patients with TD (+) showed significantly worse prognosis, and those with TD but without lymph node metastasis had similar or even worse outcomes than those classified as N1 (lymph node metastasis < 4 or no lymph node metastasis but with TD). For patients with positive lymph nodes, TD was a factor associated with poor survival outcomes. Some studies have found that the number of TDs has a linear effect on patient prognosis, and combining the number of TDs with the number of positive lymph nodes can improve the prognostic accuracy of TNM staging [8]. We redefined staging by combining the number of TDs with the number of positive lymph nodes using X-tile software and found that patients originally classified as N1 but reclassified as re-staged N2 (TD + lymph node metastasis ≥ 3) had worse prognosis than those still classified as N1 but similar to those classified as N2 (> 4 lymph node metastases). Therefore, redefining tumor staging in CRC patients based on the total number of TDs and positive lymph nodes can improve the accuracy of long-term prognosis prediction and help guide clinical diagnosis and treatment. In addition, compared to using TNM staging alone or the total number of TDs and positive lymph nodes, a model combining both with clinical features shows better ability to predict long-term survival.

To date, the pathogenesis of TDs is not clear, early studies found that TDs contain various structures, and one study [14]showed that venous invasion, lymphatic invasion, perineural invasion, and sustained growth accounted for 26%, 4%, 9%, and 12% of TDs, respectively, while in 49% of cases, no morphologically unique structures associated with deposits were found. The current hypothesis is that TDs may be due to invasion by some structure, followed by subsequent destruction. Therefore, TDs reflect different possible invasion pathways of tumors along lymphatic, venous, or neural axes. However, these axes usually run parallel, explaining the presence of multiple structures in larger TDs. Since the seventh edition of the AJCC CRC staging manual, tumor deposits (TDs) have been introduced into the "regional lymph nodes" category. Jin et al. [15]. reported that patients with pN1c who had more than three TDs had a shorter survival time (the median survival is 16.5 months for TD ≥ 4, and 32.5 months for TD < 4, 16.5 months versus 32.5 months, $p=0.025$). These results were confirmed in an analysis of the NCDB database. In our study, the survival rate of patients with pN1c and ≥ 3 TDs was lower than that of patients with 1 or 2 TDs (5-year OS of 51.4% vs. 60.6%), but similar to that of patients with pN2 (48.9%) or 1–3 LNM and TDs (currently classified

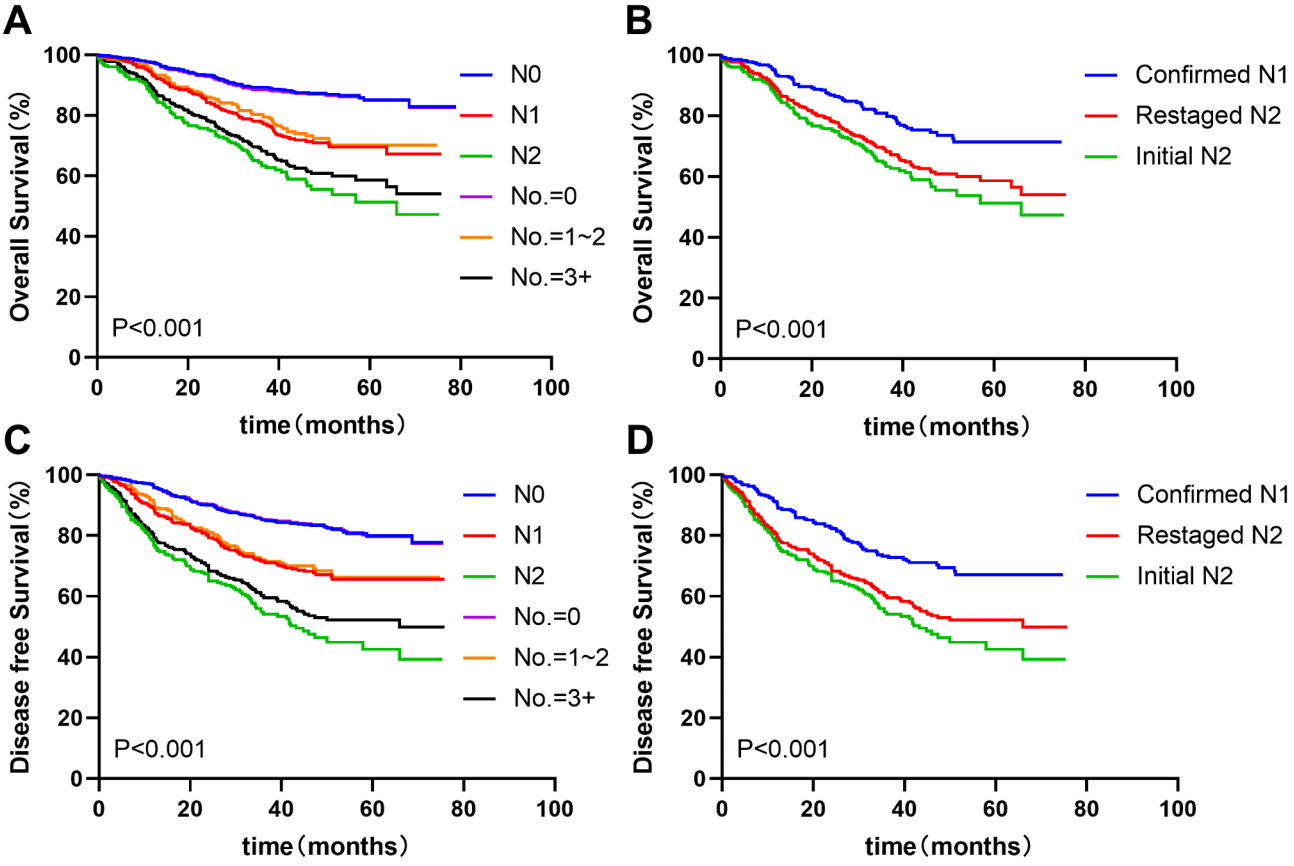

Fig. 4 Comparison of Kaplan-Meier (K-M) survival curves for colorectal cancer (CRC) patients before and after grouping. Comparison of K-M survival curves of overall survival (OS) in CRC patients for the initial N stage and regrouped based on total TD and PLNs(**A**); Comparison of K-M survival curves of OS in CRC patients for the initial N stage and restaged N stage based on TD + PLNs(**B**); Comparison of K-M survival curves of disease-free survival (DFS) in CRC patients for the initial N stage and restaged N stage based on TD + PLNs(**C**); Comparison of K-M survival curves of DFS in CRC patients for the initial N stage and restaged N stage based on TD + PLNs(**D**)

as pN1a/b; 50.7%). Shi et al. [16]. analyzed 29,017 stage III CRC patients with known numbers of TDs in the SEER database. The 5-year tumor-specific survival rates of patients without TDs, with 1–2 TDs, and with ≥ 3 TDs were 76.3%, 68.9%, and 53.6%, respectively ($p < 0.001$). These results are consistent with several cohort studies [17, 18] and the results of the CALGB/SWOG 80,702 phase III trial [12]. In the latter, increasing of TDs were significantly associated with increased HRs for DFS and OS: the higher the number of TDs, the worse the survival prognosis. Increasingly, more studies have shown that combining theTDs with PLNs can improve the prognostic accuracy of TNM staging [5, 18–20].

The impact of TDs combined with the number of positive lymph nodes on the prognosis of CRC patients has been studied in previous studies, but there is no standard for the specific cut-off value selection. JF Delattre [7] and R. Cohen [8] found that patients reclassified as re-staged N2 based on TD + PLNs < 4 had a worse prognosis than those with TD + PLNs ≥ 4. Our results showed that patients with a TD + PLNs of less than 3 were re-staged as N1, and those with a TD + PLNs of more than 3 were re-staged as N2. Patients who were initially staged as N1 but were re-staged as N2 had a worse prognosis than those who remained N1 but had a prognosis similar to that of N2, both of which are similar to the results of previous studies.

Tumor invasion and metastasis lead to poor prognosis and shortened survival time in CRC patients, and PNI is a marker of poor prognosis and a precursor of decreased survival in many tumors, indicating that patients have a poorer prognosis [21, 22]. In digestive malignancies, PNI is considered one of the local spread mechanisms of tumors and plays an important role in determining prognosis [23]. Increasingly, more studies [24–27] have shown that PNI is an independent prognostic factor for stage I-IV CRC patients, consistent with the results of this study. However, there are few reports on the impact of PNI on the prognosis of TD (+) patients, which may be a direction for future research.

Adjuvant therapy, including postoperative chemotherapy, has long been shown to prolong OS and DFS in

Table 4 Univariate and multivariate analyses of the prognostic factors for overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Tumor deposits				
No	Ref.		Ref.	
Yes	2.482 (1.937–3.181)	**< 0.001**	0.943 (0.682–1.304)	0.723
TD + PLNs				
0(N0)	Ref.		Ref.	
1–2(reN1)	2.13 (1.566–2.896)	**< 0.001**	1.18 (0.687–2.028)	0.548
3+(reN2)	3.379 (2.605–4.384)	**< 0.001**	1.778 (1.046–3.022)	**0.033**
Age (years)				
<65	Ref.		Ref.	
≥ 65	1.960 (1.564–2.456)	**< 0.001**	1.669 (1.272–2.188)	**< 0.001**
BMI				
<25	Ref.			
≥ 25	0.933 (0.701–1.242)	0.633		
Tumor size (cm)				
≤ 2.70	Ref.		Ref.	
>2.70	1.602 (1.145–2.242)	**0.006**	0.925 (0.636–1.347)	0.686
Obstruction before surgery				
Absent	Ref.		Ref.	
present	2.546 (1.956–3.315)	**< 0.001**	1.372 (0.975–1.932)	0.070
Sex				
Male	Ref.			
Female	0.837 (0.663–1.057)	0.135		
Family history of cancer				
No	Ref.			
Yes	0.852 (0.566–1.283)	0.444		
Post radiotherapy				
No	Ref.			
Yes	0.967 (0.585–1.601)	0.898		
Chemotherapy				
No	Ref.		Ref.	
Yes	0.659 (0.525–0.827)	**< 0.001**	0.542 (0.414–0.710)	**< 0.001**
Vascular invasion				
Absent	Ref.		Ref.	
Present	2.141 (1.665–2.753)	**< 0.001**	0.946 (0.689-1.300)	0.733
Perineural invasion				
Absent	Ref.		Ref.	
Present	2.409 (1.899–3.055)	**< 0.001**	1.822 (1.354–2.451)	**< 0.001**
Histological grade				
Well	Ref.			
Moderately	0.952 (0.685–1.323)	0.770		
Poorly	1.432 (0.967–2.122)	0.073		
TNM stage				
I	Ref.		Ref.	
II	1.991 (1.135–3.494)	**0.016**	1.699 (0.885–3.261)	0.111
III	4.611 (2.715–7.833)	**< 0.001**	2.565 (1.187–5.541)	**0.017**
IV	9.751 (5.575–17.053)	**< 0.001**	6.999 (3.324–14.736)	**< 0.001**
Primary tumor location				
Right colon	Ref.			
Left colon	1.165 (0.858–1.581)	0.328		
Rectum	0.78 (0.592–1.027)	0.077		
ASA				
1	Ref.			

Table 4 (continued)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
2	0.806 (0.299–2.168)	0.669		
3	0.98 (0.357–2.694)	0.970		
4	1.695 (0.608–4.721)	0.313		
Previous history of abdominal surgery				
No	Ref.			
Yes	1.013 (0.76–1.351)	0.929		
Neoadjuvant chemotherapy				
No	Ref.			
Yes	1.307 (0.83–2.058)	0.247		
Preoperative comorbidities				
Any preoperative comorbidities				
No	Ref.		Ref.	
Yes	1.52 (1.202–1.922)	**< 0.001**	1.432 (0.846–2.425)	0.181
Cardiovascular disease				
No	Ref.		Ref.	
Yes	1.499 (1.172–1.917)	**0.001**	0.992 (0.578–1.702)	0.977
Cerebrovascular disease				
No	Ref.		Ref.	
Yes	1.912 (1.047–3.491)	**0.035**	1.411 (0.739–2.693)	0.297
COPD				
No	Ref.			
Yes	1.727 (0.991–3.011)	0.054		
Diabetes				
No	Ref.			
Yes	1.185 (0.798–1.76)	0.399		
Hematological diseases				
No	Ref.			
Yes	1.216 (0.171–8.661)	0.845		
CEA (ng/mL)				
Normal	Ref.		Ref.	
High	2.466 (1.964–3.096)	**< 0.001**	1.507 (1.153–1.970)	**0.003**
CA19-9 (kU/L)				
Normal	Ref.		Ref.	
High	2.357 (1.841–3.017)	**< 0.001**	1.476 (1.102–1.976)	**0.009**
CA72-4 (U/mL)				
Normal	Ref.		Ref.	
High	1.465 (1.092–1.964)	**0.011**	1.252 (0.922-1.700)	0.151
CA125 (U/mL)				
Normal	Ref.		Ref.	
High	2.938 (2.229–3.873)	**< 0.001**	1.781 (1.252–2.533)	**0.001**

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ASA, American Society of Anesthesiologists Physical Status Classification; COPD, chronic obstructive pulmonary disease; CEA, carcino-embryonic antigen; CA19-9; CA72-4; CA125, carbohydrate antigen; LNs, Number of lymph nodes examined; PLNs, Number of positive lymph nodes

Bold was used to highlight values that were statistically significant (< 0.05)

CRC patients. Patients of different ages [28] and different tumor stages [29] can benefit from postoperative adjuvant therapy. Therefore, for patients with stage II (except low-risk patients) and above colon cancer, postoperative adjuvant therapy should be routinely performed. Our study also showed that postoperative chemotherapy significantly affects the OS of patients. Compared with colon cancer patients who did not receive postoperative chemotherapy, those who received postoperative chemotherapy had significantly better OS, but postoperative chemotherapy did not have a significant impact on patient DFS. In addition, studies [16, 30] have also indicated that adjuvant chemotherapy can significantly improve OS and CSS in patients with solitary TDs in colon cancer.

Table 5 Univariate and multivariate analyses of the prognostic factors for disease-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Tumor deposits				
No	Ref.		Ref.	
Yes	2.522 (2.016–3.156)	**< 0.001**	1.096 (0.839–1.433)	0.500
TD + PLNs				
0(N0)	Ref.		Ref.	
1–2(reN1)	1.994 (1.511–2.631)	**< 0.001**	1.176 (0.757–1.828)	0.470
3+(reN2)	3.309 (2.625–4.171)	**< 0.001**	1.637 (1.063–2.521)	**0.025**
Age (years)				
<65	Ref.		Ref.	
≥ 65	1.525 (1.241–1.875)	**< 0.001**	1.548 (1.237–1.936)	**< 0.001**
BMI				
<25	Ref.			
≥ 25	0.985 (0.764–1.27)	0.905		
Tumor size (cm)				
≤ 2.70	Ref.		Ref.	
>2.70	1.49 (1.112–1.997)	**0.008**	1.113 (0.817–1.515)	0.498
Obstruction before surgery				
Absent	Ref.		Ref.	
present	1.839 (1.422–2.379)	**< 0.001**	1.164 (0.872–1.554)	0.303
Sex				
Male	Ref.			
Female	0.95 (0.773–1.167)	0.625		
Family history of cancer				
No	Ref.			
Yes	1.055 (0.752–1.482)	0.755		
Post radiotherapy				
No	Ref.			
Yes	0.965 (0.615–1.514)	0.877		
Chemotherapy				
No	Ref.			
Yes	0.936 (0.765–1.145)	0.518		
Vascular invasion				
Absent	Ref.		Ref.	
Present	2.304 (1.844–2.88)	**< 0.001**	1.137 (0.874–1.478)	0.338
perineural invasion				
Absent	Ref.		Ref.	
Present	2.541 (2.054–3.143)	**< 0.001**	1.690 (1.328–2.151)	**< 0.001**
Histological grade				
Well	Ref.		Ref.	
Moderately	1.086 (0.8-1.474)	0.596	0.847 (0.620–1.156)	0.296
Poorly	1.569 (1.09–2.258)	**0.015**	0.959 (0.659–1.397)	0.829
TNM stage				
I	Ref.		Ref.	
II	2.515 (1.474–4.291)	**0.001**	1.915 (1.103–3.323)	**0.021**
III	5.032 (3.016–8.394)	**< 0.001**	2.370 (1.248–4.501)	**0.008**
IV	15.665 (9.226–26.6)	**< 0.001**	7.955 (4.280-14.785)	**< 0.001**
Primary tumor location				
Right colon	Ref.			
Left colon	1.207 (0.911-1.6)	0.189		
Rectum	0.891 (0.693–1.145)	0.366		
ASA				
1	Ref.			

Table 5 (continued)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
2	1.029 (0.383–2.763)	0.955		
3	1.164 (0.426–3.182)	0.767		
4	1.812 (0.653–5.025)	0.254		
Previous history of abdominal surgery				
No	Ref.			
Yes	0.852 (0.649–1.119)	0.250		
Neoadjuvant chemotherapy				
No	Ref.			
Yes	1.321 (0.88–1.982)	0.179		
Preoperative comorbidities				
Any preoperative comorbidities				
No	Ref.		Ref.	
Yes	1.386 (1.12–1.716)	**0.003**	1.176 (0.742–1.863)	0.489
Cardiovascular disease				
No	Ref.		Ref.	
Yes	1.403 (1.122–1.755)	**0.003**	1.035 (0.638–1.679)	0.890
Cerebrovascular disease				
No	Ref.			
Yes	1.334 (0.711-2.5)	0.369		
COPD				
No	Ref.			
Yes	1.357 (0.78–2.36)	0.279		
Diabetes				
No	Ref.			
Yes	0.963 (0.655–1.416)	0.849		
Hematological diseases				
No	Ref.			
Yes	2.082 (0.519–8.361)	0.301		
CEA (ng/mL)				
Normal	Ref.		Ref.	
High	2.038 (1.665–2.495)	**< 0.001**	1.305 (1.046–1.629)	**0.019**
CA19-9 (kU/L)				
Normal	Ref.		Ref.	
High	2.006 (1.594–2.523)	**< 0.001**	1.257 (0.983–1.609)	0.068
CA72-4 (U/mL)				
Normal	Ref.			
High	1.298 (0.987–1.708)	0.062		
CA125 (U/mL)				
Normal	Ref.		Ref.	
High	2.156 (1.644–2.827)	**< 0.001**	1.430 (1.054–1.939)	**0.021**

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ASA, American Society of Anesthesiologists Physical Status Classification; COPD, chronic obstructive pulmonary disease; CEA, carcino-embryonic antigen; CA19-9; CA72-4; CA125, carbohydrate antigen; LNs, Number of lymph nodes examined; PLNs, Number of positive lymph nodes

Bold was used to highlight values that were statistically significant (< 0.05)

Tumor markers such as CEA, CA19-9, and CA125 have been widely used in clinical practice due to their great convenience and acceptability [31]. Preoperative levels of CEA, CA19-9, and CA125 have also been shown to be valuable in the prognosis of surgical patients with CRC in many studies [24, 29, 31]. However, due to factors such as non-uniform abnormal values and detection errors, the impact of preoperative tumor marker levels on the specific prognosis of patients is still controversial. The study showed that preoperative CEA and CA125 levels were independent prognostic factors for tumor recurrence and survival, and preoperative CA19-9 level was an independent prognostic factor for OS, which is consistent with previous research reports.

Using traditional TNM staging or a single index alone to predict patient prognosis is often not precise enough.

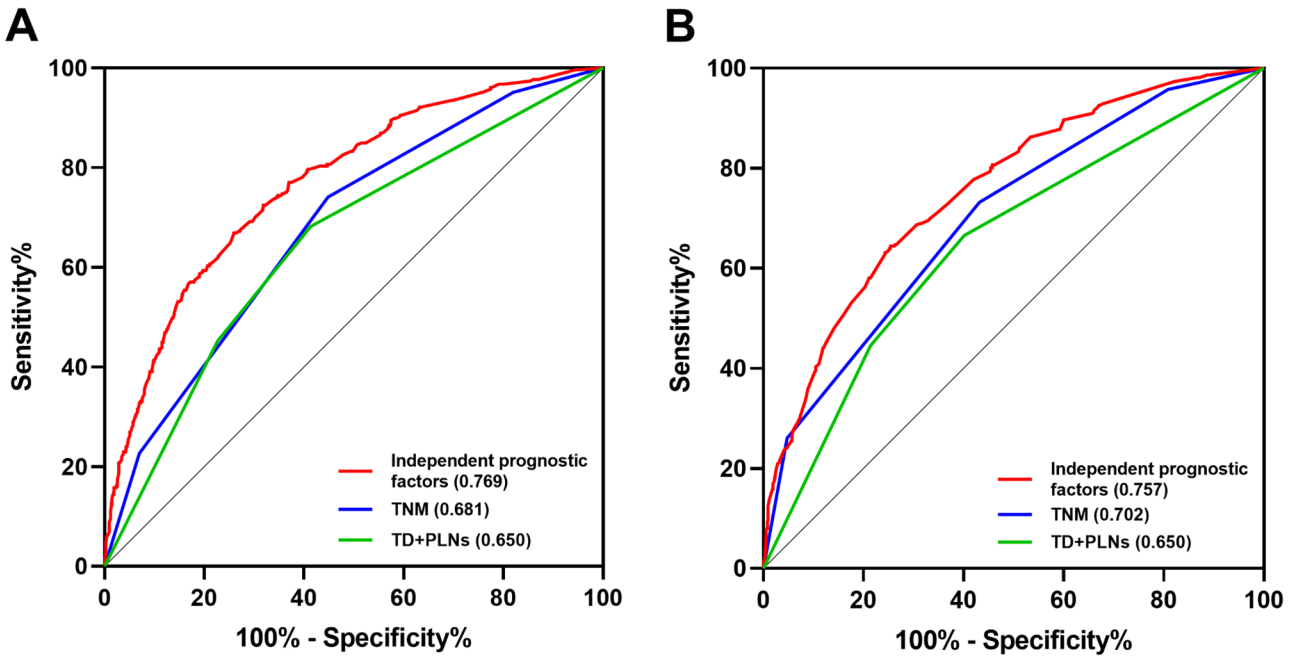

Fig. 5 Receiver operating characteristic (ROC) cuve of different prediction models.ROC curves of different prediction models for overall survival (**A**); ROC curves of different prediction models for disease-free survival (**B**)

In this study, the AUCs of the OS and DFS prediction models constructed using only TNM staging and only TD + PLNs were 0.681 and 0.650, and 0.702 and 0.650, respectively. The AUCs of the multivariate models constructed based on significant indicators from Cox multivariate analysis for patient OS and DFS were both greater than 0.75, indicating that these models had good predictive ability. This also suggests that the indicators used in constructing the models can significantly impact the prognosis of CRC patients. Therefore, compared with traditional TNM staging or single index-based prognosis assessment, the predictive models we developed have greater advantages.

This study also has limitations. First, as a retrospective study conducted at a single center, the results may be limited by bias. Second, due to the inevitable variability in TD detection among observers, our results should be validated by various cohorts collected from other centers. Because even well-designed multicenter randomized controlled trials lack standardization for the presence and counting of TDs in pathological analysis, and given the impact of TDs on prognosis, we advocate for a clear, systematic, and standardized description of the presence and number of TDs in pathological reports. Third, this study assumes that all single TDs have the same prognostic weight, regardless of their size, location, and shape, among other characteristics. In particular, the position of TDs relative to adjacent lymphovascular structures, which was not reported in our pathological reports, may be clinically and pathologically relevant. Finally, due to a lack of data, this study did not capture more details about chemotherapy, such as specific regimens.

Conclusion

In summary, regardless of the number of positive lymph nodes, TDs have significant predictive value for the prognosis of colon cancer patients as a quantitative value. Compared with current staging, an N staging system revised using the combined count of TDs and positive lymph nodes can more accurately predict survival.

Abbreviations

TD(s)	Tumor Deposit(s)
PLNs	Positive Lymph Nodes
CRC	Colorectal Cancer
ROC	The Receiver Operating Characteristic
AUC	The Area Under the Curve
OS	Overall Survival
DFS	Disease-Free Survival
AJCC	The American Joint Committee on Cancer
SEER	The Surveillance, Epidemiology, and End Results
TNM	Tumor Node Metastasis
BMI	Body Mass and Height Index
PNI	Erineural Invasion
STMs	Serum Tumor Markers
CEA	Carcinoembryonic Antigen
CA 19 – 9, CA72-4, CA125	Carbohydrate Antigen
SSI	Surgical Site Infection
NCCN	The National Comprehensive Cancer Network
HRs	Hazard Ratios
Cis	Confidence Intervals

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Author contributions
Y.C. and L.Q. contributed to the design of the study. L.Q., Y.H. and X.W. participated in data acquisition. Y.H. and N.H. participated in data analysis and interpretation. M.H., Y.H., J.X., and N.H. prepared the first draft of the manuscript. All authors contributed to, and approved, the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
The study was approved by the Ethics Committee of Wuhan Union Hospital (No. 2018-S377). Due to the retrospective design of the study, the Ethics Committee of Wuhan Union Hospital confirmed that informed consent from participants was not necessary, and all methods were carried out in accordance with relevant guidelines and regulations.

Competing interests
The authors declare no competing interests.

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