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RESEARCH

Evaluating the prognostic significance of tumor deposits in gastric cancer and strategies for their integration into the TNM staging system: a single-center retrospective study

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Abstract

Purpose To propose a new optimal strategy for incorporating tumor deposit (TD) into TNM staging.

Methods Totally, 2730 consecutive gastric cancer (GC) patients were included according to the presence and count of TDs between January 2011 and December 2014. Overall survival (OS) was analyzed using Cox regression and propensity score matching (PSM). The relationship between the number of TDs and GC patients' prognosis was analyzed using restricted cubic spline curves and compared with the prognostic value of lymph node metastases (LNMs). Harrell's C-index (C-index) and the Akaike information criterion (AIC) were employed to assess the prognostic performance of different staging systems.

Results The positive rate of TD was 9.67% (264/2730). The presence of TD was associated with poorer OS before PSM (hazard ratio (HR): 3.31; 95% confidence interval (CI): 2.84, 3.85) and after PSM (HR: 1.62; 95%CI: 1.31, 2.00). The modified TNM staging, equating one TD to four LNMs, achieved superior prognostic performance, surpassing the 8th edition AJCC TNM staging and other modified systems (C-index: 0.751, AIC: 15954.0). In this system, 12.04% (26/216) of TD-positive patients were upstaged from stage II to stage III. These upstaged patients had worse outcomes than the remaining stage II patients (HR: 10.97; 95% CI: 4.55–26.44), while outcomes were similar to those of original stage III patients (HR:1.08; 95%CI: 0.66, 1.78).

Conclusion The presence and increased number of TDs were noted to be associated with GC patients' poor prognosis. Integrating TD count with LNMs could enhance the prognostic accuracy of the TNM staging system.

Keywords Gastric cancer · Tumor deposit · Prognosis · TNM staging

1 Introduction

Gastric cancer (GC) is one of the most common tumors worldwide, and it is the third leading cause of cancer-related deaths [1]. The TNM staging system serves as the cornerstone for clinical diagnosis and personalized treatment of GC [2]. However, clinical findings revealed notable prognostic differences among GC patients at the same stage, even when undergoing identical standard treatments. In recent years, additional predictive factors, including Her-2 status [3], neurovascular invasion [4], and tumor deposit (TD) [5], have emerged as independent prognostic indicators.

TD refers to a tumor nodule located in the drainage area of the primary tumor's lymph node or in the adjacent adipose tissue that is not contiguous with the primary tumor

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and lacks recognizable lymphatic, vascular, or neural structures [6]. TD was first described by Gabriel et al. in 1935 in a study on rectal cancer [7]. Subsequent research has consistently demonstrated that TD is associated with poor prognosis, leading to its inclusion in the TNM staging system for colorectal cancer [8]. Notably, patients without regional lymph node metastases (LNMs) while with TD are categorized as stage N1c [9], resulting in a greater number of patients requiring postoperative adjuvant therapy.

The presence of TD is typically associated with adverse pathological factors in GC and markedly diminishes the survival rates of GC patients [10], while it has not yet been included in the TNM staging system for GC. Several studies have recently proposed methods to integrate TD into TNM staging for GC, while their findings were highly controversial [11, 12]. Some researchers have demonstrated involving TD in N staging [11] or treating them as evidence of plasma membrane invasion in T staging [13, 14]. Others have suggested classifying cases with more than 2 or 3 TD as M1 stage [12]. A major source of this controversy lies in the unresolved question of whether TD or lymph node involvement has a greater impact on prognosis. The UICC/AJCC staging system and Japanese guidelines for GC treatment recommend treating TD as LNM and incorporating them into N staging, while this recommendation is largely empirical [6]. The appropriate inclusion and classification of TD in TNM staging for GC should be determined. Furthermore, advancements in surgical and pathological detection techniques have led to a notable increase in TD detection. The effect of the number of TD on prognosis remains controversial. In addition, TD negatively impacts GC patients' prognosis, and few studies have explored its effects on postoperative adjuvant chemotherapy.

Therefore, the present study aimed to assess the prognostic significance of both the presence and number of TD in patients with resectable GC, and to explore their impact on the efficacy of adjuvant chemotherapy for GC. The study also compared the prognostic significance of a single TD versus a single LNM. Furthermore, a novel optimal strategy for integrating TD into the TNM staging was developed and assessed against previously proposed methods.

2 Materials and methods

2.1 Study population

Data were retrospectively collected from GC patients who underwent radical gastrectomy between January 2011 and December 2014 from a previously established prospective GC cohort at Xijing Hospital [3, 4]. Inclusion criteria were summarized as follows: (1) histologically confirmed gastric adenocarcinoma, (2) radical gastrectomy (R0), and (3) at least D1 + lymph node dissection. Exclusion criteria were summarized as follows: (1) concurrent malignancies, (2) a history of gastrectomy, (3) death within 30 days after surgery, (4) preoperative chemotherapy or radiotherapy, (5) presence of distant metastases or peritoneal dissemination, and (6) loss to follow-up. A total of 2,730 consecutive GC patients meeting these criteria were included in the study (Fig. 1), with follow-up completed through December 2021. This study was approved by the Ethics Committee of Xijing Hospital (Xi'an, China; Approval No. KY20222241-X-1).

2.2 Data collection

Demographic data (age and gender) and pathological characteristics, including tumor size, tumor location, type of gastrectomy, histological subtype, tumor grade, depth of infiltration (T), number of LNMs (N), presence or absence of lymphovascular invasion, perineural invasion, preoperative tumor markers, and the presence and number of TD, were assessed. Tumor size was defined as the maximum diameter. Patients were categorized into TD-positive (TD+) and TD-negative (TD−) groups. The analysis used the updated UICC/AJCC TNM staging system, standardized to version 8.

2.3 Histopathological evaluation

TD was defined as an accumulation of tumor cells located in fibrous or adipose tissue within lymphatic drainage ducts, without identifiable lymph node tissue, vascular structures, or neural structures, and not contiguous with the primary tumor, irrespective of contour, shape, or size. However, if vascular structures were identified and confirmed by hematoxylin and eosin (HE) staining, the deposits were classified as vascular infiltration. Similarly, they were classified as neural infiltration if neural structures were identified [11, 15]. The pathological illustration of TD is presented in Supplementary Fig. S1. Lymphovascular invasion (LVI) was defined as the presence of tumor cells in endothelial-lined spaces, including lymphatic invasion (LI), vascular invasion (VI), or both (LI and VI) [16]. Diagnosis was confirmed using H&E staining and immunohistochemistry, with D2-40 for lymphatic invasion and CD34 for vascular invasion [17]. Perineural invasion (PNI) was defined as the presence of tumor cells in the epineurium, perineurium, or endoneurium of a nerve, or involving at least 33% of the nerve's circumference [18]. S-100 staining was used to confirm nerve invasion [17]. Histological sections of tumor specimens were independently reviewed by two experienced pathologists, and any disagreements were resolved by consulting with a third expert.

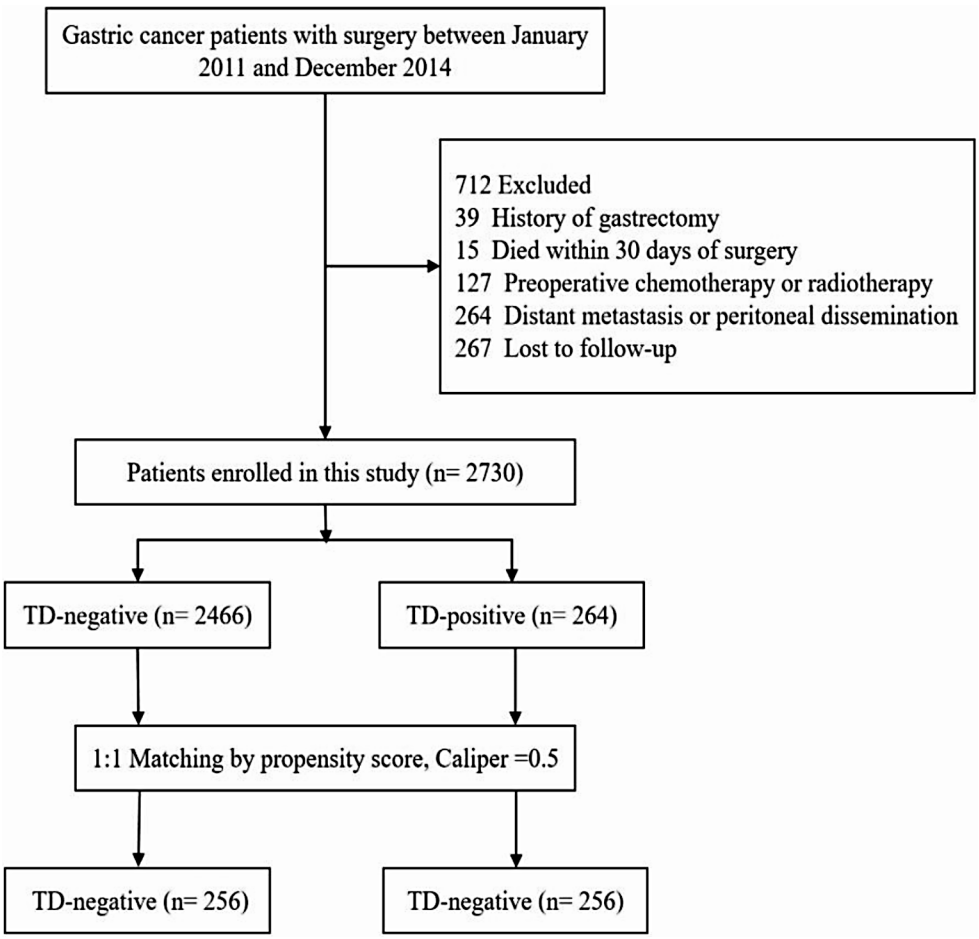

Fig. 1 Flow diagram of patient-selection. TD, tumor deposit

2.4 Statistical analysis

Continuous variables were analyzed using the independent-samples t-test or the Wilcoxon rank-sum test, while categorical variables were evaluated using the Chi-square test or the Fisher's exact test. The Kaplan-Meier method was employed to estimate the 5-year overall survival (OS) rate, and the log-rank test was utilized to compare survival differences between the two groups. Cox regression analysis was conducted on variables identified through univariate analysis to evaluate their correlation in a multivariate model.

Missing data were handled with random forest imputation using the missForest package (version 1.5), utilizing all variables with missing values as predictors. Propensity score matching (PSM) was conducted using the MatchIt package (version 4.5.5) to minimize potential confounding factors. One-to-one PSM between TD-positive and TD-negative patients was undertaken using a greedy matching algorithm, with a caliper width set to 0.05 of the standard deviation of the logit of the propensity score. The PSM process resulted in 256 matched pairs that were well-balanced in baseline clinicopathological characteristics (Table 1). The scores before and after matching between the TD-positive and TD-negative groups are represented as histograms (Supplementary Fig. S2).

The association between the number of TDs and mortality risk was investigated through restricted cubic spline (RCS) analysis. The prognostic predictive value of the TNM staging system and other modified staging systems was assessed using the Harrell's concordance index (C-index) and the Akaike Information Criterion (AIC). Higher C-index values, along with lower AIC values, indicate improved predictive accuracy of the staging system. Additionally, a prognostic nomogram for GC was developed by incorporating each independent risk factor and was subsequently assessed for its predictive performance. The nomogram's calibration was evaluated using a calibration curve.

Statistical analysis was conducted using SPSS 25.0 (IBM, Armonk, NY, USA) and R 4.3.1 (https://www.r-project.org/) software. $P<0.05$ (two-sided) was indicative of statistical significance.

Table 1 Clinicopathological characteristics of gastric cancer patients with or without TD before and after propensity score matching

Factors	Before matching			After matching		
	TD negative N=2466 (%)	TD positive N=264(%)	*P* value	TD negative N=256(%)	TD positive N=256(%)	*P* value
Gender, n (%)			0.873			0.258
Male	1876(76.1)	202(76.5)		188(73.4)	199(77.7)	
Female	590(23.9)	62(23.5)		68(26.6)	57(22.3)	
Age, n (%)			0.004			0.425
≤60 yr	1479(60.0)	134(50.8)		141(55.08)	132(51.56)	
>60 yr	987(40.0)	130(49.2)		115(44.92)	124(48.44)	
Tumor location, n (%)			0.107			0.788
Cardia	668(27.1)	90(34.1)		91 (35.6)	86 (33.6)	
Body	802(32.5)	77(29.2)		69 (27.0)	77 (30.1)	
Pylorus	928(37.6)	89(33.7)		91 (35.5)	86 (33.6)	
Whole	68(2.8)	8(3.0)		5 (2.0)	7 (2.7)	
Tumor size, cm, n (%)			<0.001			
Mean+SD	4.6±2.6	6.0±2.4		5.91±2.72	5.96±2.29	0.812
Tumor differentiation, n (%)			0.03			0.922
Well	875(35.5)	76(28.8)		73 (28.5)	72 (28.1)	
Poor	1591(64.5)	188(71.2)		183 (71.5)	184 (71.9)	
Depth of invasion, n (%)			<0.001			0.623
Tis	4(0.2)	0(0.0)				
T1	537(21.8)	3(1.1)		2 (0.8)	3 (1.2)	
T2	332(13.5)	18(6.8)		22 (8.6)	18 (7.0)	
T3	545(22.1)	33(12.5)		25 (9.8)	33 (12.9)	
T4	1048(42.5)	210(79.6)		207 (80.9)	202 (78.9)	
Lymph node metastasis, n (%)			<0.001			0.904
N0	955(38.7)	23(8.7)		24 (9.4)	23 (9.0)	
N1	405(16.4)	32(12.1)		38 (14.8)	32 (12.5)	
N2	432(17.5)	68(25.8)		68 (26.6)	66 (25.8)	
N3a	452(18.3)	95(36.0)		86 (33.6)	89 (34.8)	
N3b	222(9.0)	46(17.4)		40 (15.6)	46 (18.0)	
pTNM stage, n (%)			<0.001			0.609
Ia	461(18.7)	2(0.8)		1 (0.4)	2 (0.8)	
Ib	203(8.2)	1(0.4)		2 (0.8)	1 (0.4)	
IIa	250(10.1)	7(2.7)		3 (1.2)	7 (2.7)	
IIb	365(14.8)	26(9.9)		36 (14.1)	26 (10.2)	
IIIa	554(22.5)	91(34.5)		94 (36.7)	89 (34.8)	
IIIb	415(16.8)	86(32.6)		74 (28.9)	81 (31.6)	
IIIc	218(8.8)	51(19.3)		46 (18.0)	50 (19.5)	
Lymphovascular invasion, n (%)			<0.001			0.676
Absence	1021(41.4)	59(22.3)		58 (22.7)	62 (24.2)	
Presence	1258(51.0)	189(71.6)		198 (77.3)	194 (75.8)	
Miss	187(7.6)	16(6.1)				
Perineural invasion, n (%)			<0.001			0.77
Absence	466(18.9)	26(9.8)		25 (9.8)	27 (10.5)	
Presence	1750(71.0)	224(84.9)		231 (90.2)	229 (89.5)	
Miss	250(10.1)	14(5.3)				
Surgical scope, n (%)			<0.001			0.812
Proximal	209(8.5)	8(3.0)		6 (2.3)	8 (3.1)	
Distal	1053(42.7)	83(31.4)		78 (30.5)	81 (31.6)	
Whole	1204(48.8)	173(65.5)		172 (67.2)	167 (65.2)	
No. of examined lymph nodes, n (%)			0.002			0.888
≤16	184(7.5)	34(12.9)		29 (11.3%)	28 (10.9)	
>16	2282(92.5)	230(87.1)		227 (88.7%)	228 (89.1)	
Chemotherapy, n (%)			0.030			0.446
No	554(22.5)	44(16.7)		33 (12.9)	39 (15.2)	

Table 1 (continued)

Factors	Before matching			After matching		
	TD negative N=2466 (%)	TD positive N=264(%)	*P* value	TD negative N=256(%)	TD positive N=256(%)	*P* value
Yes	1903(77.2)	219(83.0)		223 (87.1)	217 (84.8)	
Unknown	9(0.4)	1(0.4)				
CEA, n (%)			<0.001			0.125
<5	1987(80.6)	184(69.7)		200 (78.1)	185 (72.3)	
≥5	419(17.0)	70(26.5)		56 (21.9)	71 (27.7)	
Miss	60(2.4)	10(3.8)				
CA19-9, n (%)			<0.001			0.461
<37	2060(83.5)	191(72.4)		201 (78.5)	194 (75.8)	
≥37	319(12.9)	61(23.1)		55 (21.5)	62 (24.2)	
Miss	87(3.5)	12(4.5)				

TD, tumor deposit; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19−9

3 Results

3.1 Relationship between TD and GC patients' clinicopathological characteristics

A total of 2,730 patients participated in this study, and 1,152 deaths were recorded. The median overall follow-up time was 7.14 years (95% confidence interval (CI): 7.03, 7.25). Participants were categorized into two groups: 264 (9.7%) in the TD-positive group and 2,466 (90.3%) in the TD-negative group. Among 264 TD-positive patients, 105 (39.8%) had a single TD, 111 (42.1%) had two or more, and 48 (18.1%) had missing data regarding the number of TDs. The number of TDs ranged from 1 to 10, with a median of two.

Baseline characteristics, stratified by the presence or absence of TD, are summarized in Table 1. Patients with TD were older than those without TD (age > 60 years: 49.2% vs. 40.0%; $P=0.004$). They also exhibited larger tumors (mean size: 6.0±2.4 cm vs. 4.6±2.6 cm; $P<0.001$), poorer tumor differentiation (71.2% vs. 64.5%; $P=0.030$), higher rates of lymphovascular invasion (71.6% vs. 51.0%; $P<0.001$) and perineural invasion (84.9% vs. 71.0%; $P<0.001$), and more advanced TNM stages (stage III: 86.4% vs. 48.1%; $P<0.001$). Additionally, these patients were more likely to undergo total gastrectomy (65.5% vs. 48.8%; $P<0.001$) and postoperative chemotherapy (83.0% vs. 77.2%; $P=0.030$), had fewer lymph node dissections (>16 nodes: 87.1% vs. 92.5%; $P=0.002$), and presented with elevated preoperative carcinoembryonic antigen (CEA) (26.5% vs. 17.0%; $P<0.001$) and carbohydrate antigen 199 (CA199) (23.1% vs. 12.9%; $P<0.001$) levels.

3.2 Correlation between the presence of TD and GC prognosis

As illustrated in Fig. 2, patients with TD had significantly lower OS compared with those without TD (hazard ratio (HR): 3.31; 95% CI: 2.84, 3.85; $P<0.001$), including in stage II (HR: 3.02; 95% CI: 1.43, 6.38; $P<0.001$) and stage III (HR: 1.90; 95% CI: 1.55, 2.32; $P<0.001$). For stage I patients, those with TD also demonstrated a worse OS rate than those without TD, although the difference was not statistically significant (HR: 3.429; 95% CI: 0.092, 127.9; $P=0.193$) (Fig. S3). Similarly, patients with TD in stages IIB ($P<0.001$), IIIA ($P<0.001$), IIIB ($P=0.003$), and IIIC ($P<0.001$) had worse OS compared with their TD-negative counterparts, while no significant difference was identified in stage IIA ($P=0.140$). The negative impact of TD on OS was also found across different N (N0–N3b) and T (T3–T4) stages (Fig. S4 and Fig. S5; all $P<0.010$).

In a multivariable Cox model, TD was found as an independent predictor of mortality (HR: 1.92; 95%CI:1.63, 2.26; $P<0.001$) (Table 2). Compared with TD-negative group, the TD-positive group had a significantly higher HR in the following subgroups: N0 (HR: 9.04; 95% CI: 3.77, 21.68; *P* for interaction = 0.02), no lymphovascular invasion (HR: 8.85; 95% CI: 4.78, 16.38; *P* for interaction = 0.03), no perineural invasion (HR: 12.36; 95% CI: 4.83, 31.60; *P* for interaction = 0.03), and no postoperative chemotherapy(HR:14.94; 95%CI: 5.79, 38.54; *P* for interaction = 0.02) (Fig. 3).

Following the 1-to-1 PSM, 256 matched pairs with balanced baseline clinicopathological characteristics were generated. The findings were consistent with those of the overall population, demonstrating significantly worse OS in the TD-positive group (HR: 1.62; 95% CI: 1.31, 2.00; $P<0.001$), including stages II and III (all $P<0.050$) (Fig. 2).

3.3 Effects of postoperative chemotherapy on the prognosis of patients with TD

The analysis concentrated primarily on patients with stage II and III GC. Among TD-positive patients, those receiving chemotherapy had significantly better prognoses compared with those without chemotherapy (HR: 0.52; 95% CI: 0.37,

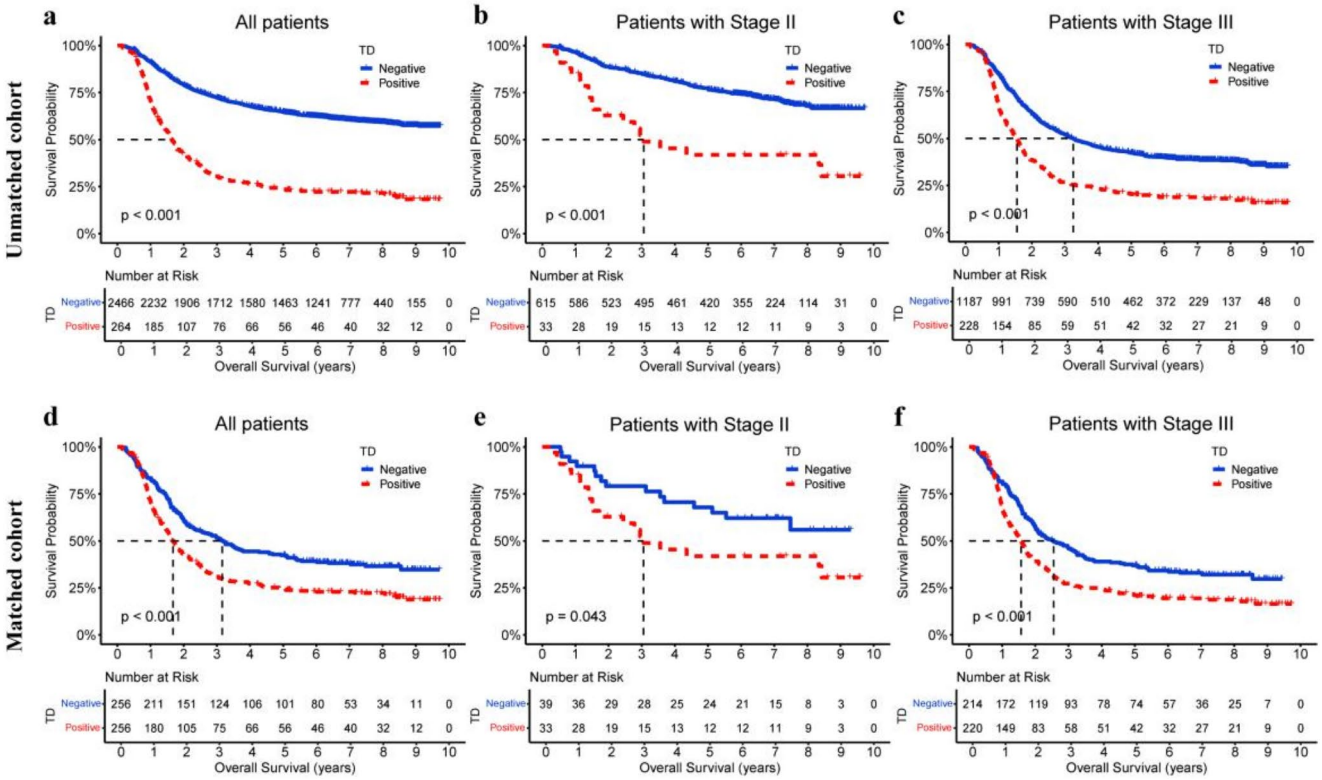

Fig. 2 Kaplan-Meier curves for overall survival comparing TD-negative and TD-positive patients in both unmatched and matched cohorts. **a-c** Unmatched cohort: (**a**) all patients, (**b**) stage II patients, and (**c**) stage III patients. **d-f** Matched cohort: (**d**) all patients, (**e**) stage II patients, and (**f**) stage III patients. TD, tumor deposit

0.74; $P<0.001$). This trend was noted in both stage II (HR: 0.52; 95% CI: 0.19, 1.45; $P=0.210$) and stage III (HR: 0.52; 95% CI: 0.36, 0.76; $P=0.001$) subgroups, although statistical significance was not reached in stage II (Fig. S6). Similarly, chemotherapy improved outcomes for TD-negative patients with GC (HR: 0.62; 95% CI: 0.52, 0.74; $P<0.001$), with significant benefits found in both stage II (HR: 0.52; 95% CI: 0.36, 0.75; $P=0.001$) and stage III (HR: 0.62; 95% CI: 0.51, 0.75; $P<0.001$) subgroups (Fig. S6).

3.4 Correlation between the number of TDs and GC prognosis

The relationship between the number of TDs, LNMs, and patient mortality risk was analyzed using RCS analysis. The results indicated that both TDs and LNMs was associated with a higher risk of mortality, with TDs exerting a more significant impact on the GC patients' prognosis than LNMs. The presence of two TDs quadrupled mortality risk in GC patients, whereas ten LNMs tripled this risk, demonstrating that a single TD has a greater adverse effect on prognosis than a single LNM (Fig. 4a, b). However, the mortality risk associated with TDs plateaued once the number exceeded two, whereas the risk associated with LNMs continued to increase with additional LNMs.

To further validate the impact of the number of TDs on OS and disease-free survival (DFS), patients were categorized into TD-negative, 1-TD, 2-TD, and ≥3-TD groups. Compared with the TD-negative group, the HRs for OS were 2.26 (95% CI: 1.78, 2.88) for 1-TD, 3.97 (95% CI: 2.88, 5.48) for 2-TD, and 4.92 (95% CI: 3.72, 6.52) for ≥3-TD. The 5-year OS rates were 64.7%, 34.6%, 18.9%, and 13.6%, respectively ($P<0.001$) (Fig. 4c), and no significant difference was found between the 2-TD and ≥3-TD groups ($P=0.309$). A similar trend was noted for DFS. The 5-year DFS rates were 62.5%, 34.0%, 19.3%, and 13.6%, respectively ($P<0.001$). HRs for DFS were 2.28 (95% CI: 1.79, 2.89) for 1-TD, 3.85 (95% CI: 2.80, 5.29) for 2-TD, and 4.65 (95% CI: 3.51, 6.16) for ≥3-TD (Fig. 4d).

3.5 External validation of modified staging models and proposal of a new staging strategy

The current primary cohort was utilized to compare the predictive accuracy of six different modified staging models against the 8th edition AJCC TNM staging system. Discriminatory ability was assessed using the C-index and AIC,

Table 2 The univariate and multivariate survival analyses of all patients with gastric cancer

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Gender						
Female vs Male	1.012	0.884–1.158	0.867			
Age						
>60 vs≤60	1.380	1.230–1.550	<0.001	1.359	1.199–1.541	<0.001
Tumor location (vs Cardia)						
Body	0.813	0.701–0.943	0.006	1.050	0.893–1.235	0.553
Pylorus	0.849	0.736–0.979	0.024	1.151	0.986–1.344	0.075
Whole	1.738	1.282–2.356	<0.001	1.616	1.186-2.200	0.002
Tumor differentiation						
Poor vs Well	1.700	1.493–1.935	<0.001	0.989	0.850–1.151	0.889
N-stage (vs N0)						
N1	2.184	1.767–2.708	<0.001	1.437	1.123–1.837	0.004
N2	3.450	2.845–4.183	<0.001	2.024	1.602–2.556	<0.001
N3a	5.873	4.903–7.034	<0.001	3.062	2.427–3.862	<0.001
N3b	9.827	8.039–12.013	<0.001	4.909	3.806–6.333	<0.001
T-stage (vs T1)						
T2	2.606	1.855–3.661	<0.001	1.518	1.024–2.249	0.038
T3	4.717	3.510–6.339	<0.001	2.061	1.428–2.975	0.001
T4	9.984	7.593–13.129	<0.001	3.570	2.501–5.098	<0.001
Lymphovascular invasion						
Yes vs No	2.358	2.069–2.688	<0.001	0.897	0.766–1.050	0.176
Perineural invasion						
Yes vs No	2.643	2.184–3.198	<0.001	1.043	0.834–1.304	0.713
Chemotherapy						
Yes vs No	1.148	0.993–1.327	0.062			
Examined lymph nodes						
>16 vs≤16	1.069	0.861–1.327	0.545			
CEA						
≥5 vs<5	1.930	1.684–2.203	<0.001	1.316	1.139–1.519	<0.001
CA19-9						
≥37 vs<37	2.226	1.930–2.567	<0.001	1.322	1.135–1.539	<0.001
TD						
Yes vs No	3.306	2.839–3.851	<0.001	1.919	1.629–2.262	<0.001

TD, tumor deposit; 95%CI, 95% confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19−9

where higher C-index values and lower AIC values indicated superior performance. Among the models, integrating TDs into N staging demonstrated superior predictive ability compared with the system that classified TD as part of T4a (Table 3).

Given the significant impact of a single TD on GC prognosis compared with a single LNM, this study tested equivalencies of one TD to two, three, four, and five LNMs within the TNM staging. The model equating one TD to four LNMs exhibited the best prognostic performance, surpassing the 8th edition AJCC TNM system and other modified models (C-index: 0.751, AIC: 15954.0).

3.6 The prognostic effect of including TD in TNM staging

After excluding 48 TD-positive patients with missing TD count data, a modified staging system incorporating one TD as equivalent to four LNMs was applied. Among TD-positive patients, 68.0% (147/216) experienced stage upgrades, representing 5.5% (147/2,682) of the entire cohort. The highest rate of stage migration was identified in stage IIIa (10.22%) (Fig. 5a). Additionally, 75.5% (163/216) of TD-positive patients had upgrades in N stage, accounting for 6.0% (163/2,682) of all patients, and N2 exhibited the highest migration rate (12.6%) (Fig. 5b).

Notably, 12.04% (26/216) of TD-positive patients were upstaged from stage II to stage III. These upstaged patients exhibited significantly worse OS compared with other stage II patients (HR: 10.97; 95% CI: 4.55, 26.44; $P<0.0001$),

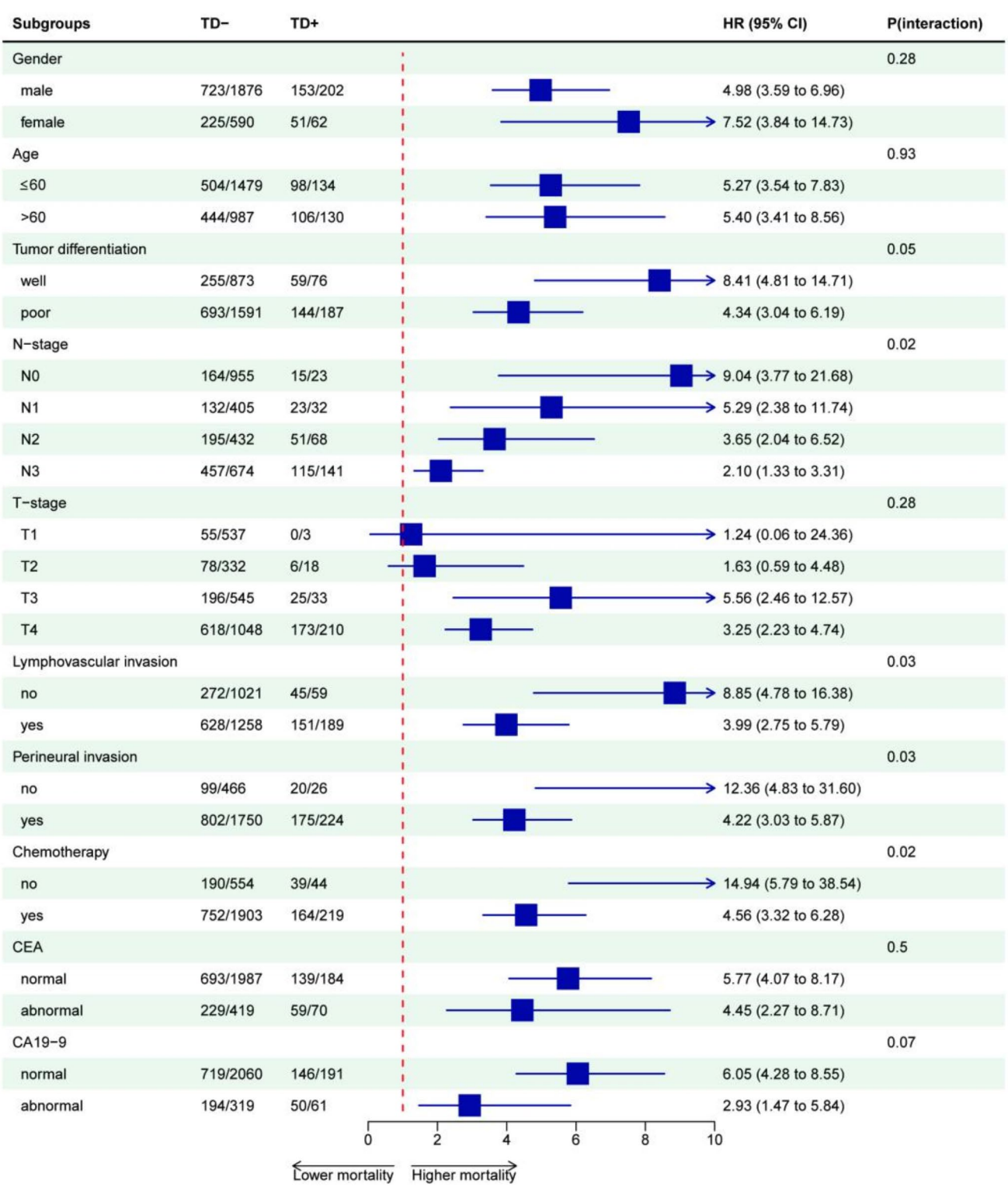

Fig. 3 Forest plot illustrating the independent clinical risk factors for TD presence in patients with gastric cancer. TD, tumor deposit; HR, hazard ratio; 95%CI, 95% confidence interval; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199

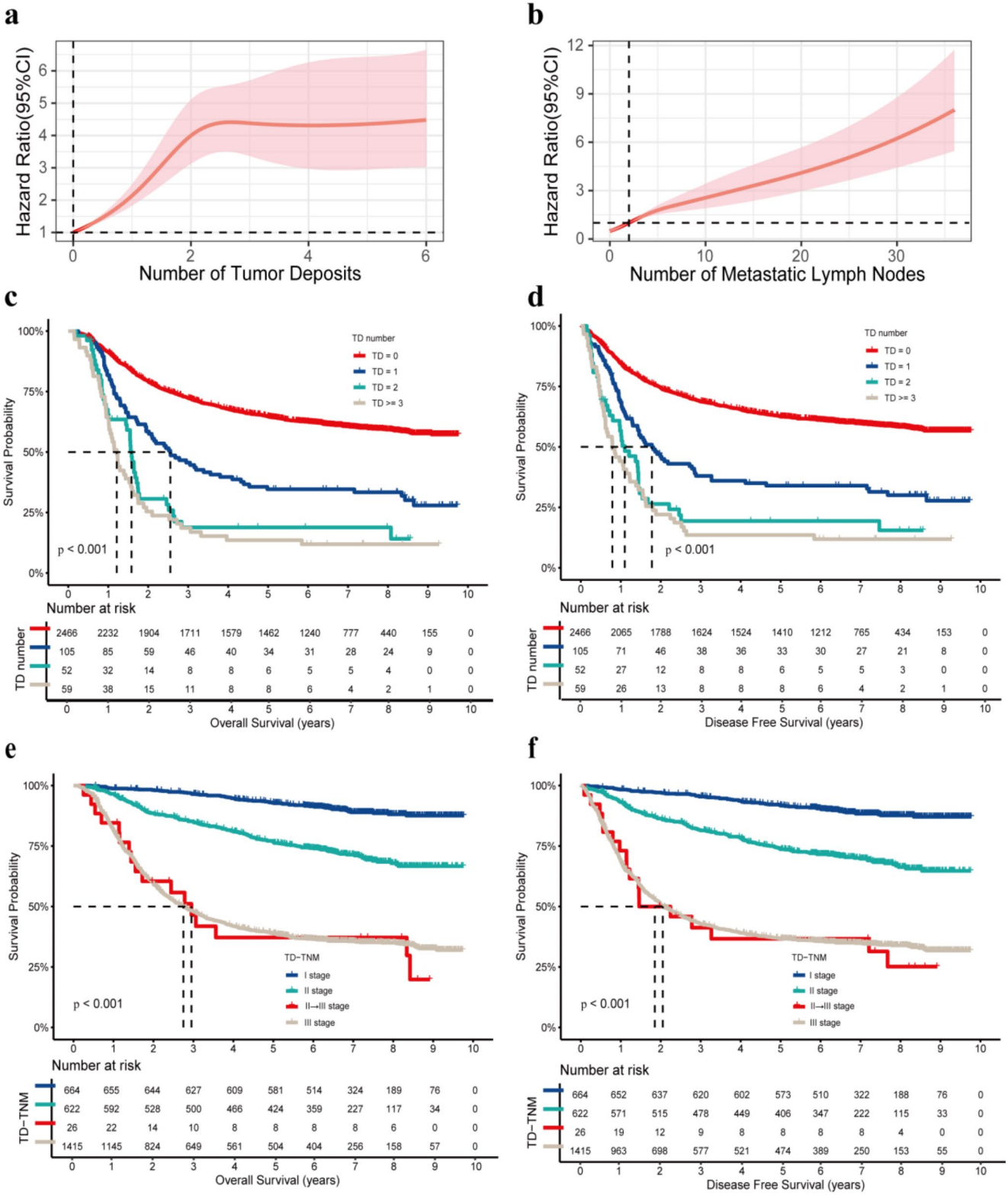

Fig. 4 Effects of TD and LNM on gastric cancer patients' prognosis. **a-b** Restricted cubic spline regression analysis of overall survival in the number of TDs (**a**) and LNMs (**b**), and the shaded area represents the 95% confidence interval (CI); **c-d** Overall survival (**c**) and disease-free survival (**d**) according to the number of TDs; **e-f** Overall survival (**e**) and disease-free survival (**f**) according to the modified TNM staging system. TD, tumor deposit; LNM, lymph node metastasis

Table 3 Comparison of the performance of the TNM staging system and other revised staging systems for gastric cancer

Year	Authors	Description	C-index	95%CI	AIC
2018	Chen H. et al	Presence of TDs upstage N stage except for N3b	0.749	0.736–0.762	15975.0
2020	Gu L. et al.	Presence of TDs upstage TNM stage except for IIIC	0.749	0.736–0.761	15975.4
2012	Sun Z. et al.	Presence of TDs as T4a	0.743	0.730–0.756	16009.7
2017	Anup S. et al.				
2019	Liang Y. et al.	Presence of TDs upstage N category as follows: N0→mN2; N1→mN2; N2→mN3a. Others unmentioned remained unchanged.	0.750	0.738–0.763	16596.4
2013	Lee H.S. et al.	1 TD as 1 positive LN	0.748	0.735–0.760	15978.6
2017	AJCC	8th GC's TNM stage	0.744	0.731–0.756	16641.0
Modified TNM staging systems		1 TD as 2 positive LN	0.750	0.737–0.763	15965.3
		1 TD as 3 positive LN	0.750	0.737–0.763	15964.2
		1 TD as 4 positive LN	0.751	0.738–0.764	15954.0
		1 TD as 5 positive LN	0.751	0.738–0.764	15956.4

95%CI, 95% confidence interval; AIC, Akaike information criterion

a

		Revised TNM Staging, No.(%)							
		Ia	Ib	IIa	IIb	IIIa	IIIb	IIIc	Total
AJCC 8th TNM Staging	Ia	461(99.56)			2(0.43)				463
	Ib		203(99.51)			1(0.49)			204
	IIa			250(97.28)	4(1.56)	3(1.16)			257
	IIb				365(94.07)	15(3.87)	5(1.29)	3(0.77)	388
	IIIa					571(89.78)	52(8.18)	13(2.04)	636
	IIIb						432(89.81)	49(10.19)	481
	IIIc							253(100)	253
	Total	461	203	250	371	590	489	318	2682

b

		Revised pN Staging, No.(%)					
		N0	N1	N2	N3a	N3b	Total
AJCC 8th pN Staging	N0	955(97.85)		12(1.23)	7(0.72)	2(0.20)	976
	N1		405(93.53)	18(4.16)	7(1.62)	3(0.69)	433
	N2			432(87.45)	50(10.12)	12(2.43)	494
	N3a				474(90.11)	52(9.89)	526
	N3b					253(100)	253
	Total	955	405	462	538	322	2682

Fig. 5 After incorporating 1 TD as 4 LNM into gastric cancer TNM staging, **a** Changes in TNM stage distribution; **b** Changes in N stage distribution

while similar OS to original stage III patients (HR: 1.08; 95% CI: 0.66, 1.78; $P=0.761$) (Fig. 4e). Similarly, their DFS was poorer than stage II patients (HR: 3.39; 95% CI: 2.09, 5.50; $P<0.001$), while was comparable to stage III patients (HR: 1.08; 95% CI: 0.668, 1.73; $P=0.740$) (Fig. 4f).

3.7 Development and validation of a prognostic nomogram

A prognostic nomogram was developed based on multivariate analysis results and the equivalence of one TD to four LNMs (Fig. S7a). The nomogram demonstrated superior predictive performance, with a C-index of 0.765 and an AUC of 0.806, outperforming individual risk factors (Fig. S7c). Furthermore, calibration curves indicated excellent agreement between predicted outcomes and observed results (Fig. S7b).

4 Discussion

In this study, data from 2,730 GC patients who underwent radical gastrectomy were retrospectively analyzed. The results revealed that both the presence and an increased number of TD were associated with poor prognosis in GC. Postoperative adjuvant chemotherapy significantly improved TD-positive patients' prognosis; however, their outcomes remained inferior to those of TD-negative patients. Notably, the adverse impact of a single TD on prognosis exceeded that of a single LNM. Incorporating one TD as equivalent to four LNMs in the TNM staging system improved the accuracy of prognostic predictions for GC.

The presence of TD is an important prognostic factor for GC patients. A systematic review reported TD positivity rates in GC patients ranging from 10.6 to 36.7% [19], and higher rates were found in advanced tumor stages. In the present study, the TD detection rate was 9.67%, which was slightly lower than previously reported rates. This discrepancy could be attributed to the exclusion of stage IV patients. The findings indicated that TD was associated with older age, larger tumor size, poor tumor differentiation, advanced TNM stage, and the presence of lymphovascular and perineural invasion, emerging consistent with previous studies [10, 19, 20]. Additionally, TD-positive patients exhibited the increased preoperative CA199 and CEA levels, suggesting greater tumor aggressiveness.

The present study further revealed that the presence of TD decreased the 5-year OS rate in GC patients, a trend observed consistently both before and after matching analyses and across various clinical subgroups. This finding aligns with previously reported result [11, 19, 21]. Notably, TD had a more remarkable adverse effect on the prognosis of patients without lymph node involvement (N0) or neurovascular invasion, appearing consistent with colorectal cancer-related study, suggesting that TD has a greater negative prognostic impact on earlier N stages [22]. In the present study, the TD positivity rate among early-stage (stage I) GC patients was only 0.448%, being in line with that of previous research [10]. This low prevalence limited the ability to draw definitive conclusions, and only a trend indicated that TD could worsen early-stage GC patients' prognosis. Future research should concentrate on larger cohorts that include a substantial proportion of early-stage GC patients, particularly in regions with robust early tumor screening programs, to enable more comprehensive analysis of TD's prognostic impact on early-stage GC patients.

The effect of TD on the prognosis of GC patients receiving adjuvant chemotherapy and the potential for chemotherapy to improve outcomes in TD-positive patients remain critical concerns. This study demonstrated that adjuvant chemotherapy improved survival rates in both TD-positive and TD-negative GC patients. However, the presence of TD remained an adverse prognostic indicator regardless of chemotherapy, appearing consistent with prior findings [10, 11]. These results highlight the importance of prioritizing postoperative adjuvant therapy for TD-positive patients, adopting more aggressive treatment strategies to enhance outcomes, and closely monitoring disease progression in this high-risk group.

LNM serves as a critical indicator for assessing GC patients' prognosis. With advancements in pathological detection techniques, the detection rate of TDs has also increased. For the first time, this study employed RCS analysis to compare the relative impact of a single TD versus a single LNM on GC prognosis. The analysis revealed that a single TD could exert a significantly more adverse effect on patient outcomes than a single LNM. The prognostic impact of the number of TDs on GC has been explored in several studies. While Anup et al. and Zhou et al. reported no significant association between TD count and prognosis [13, 23], other studies confirmed that an increasing number of TDs were correlated with a declining 5-year OS rate, although the relationship was nonlinear [10, 14, 20, 21, 24]. In the present study, a similar nonlinear relationship was identified: an increasing number of TDs were associated with worsening prognosis. However, no significant decline in 5-year OS was identified when the number of TDs exceeded two, nor did the risk of mortality increase further with additional TDs. Conversely, the mortality risk continued to elevate with an increasing number of LNMs. Thus, assessing the number of TDs is crucial for accurately prognosticating and strategizing treatment for GC patients.

The inclusion of TD in the TNM staging system has consistently attracted clinicians' attention. Several prior studies

have attempted to integrate TD into the TNM staging for GC. Studies proposed incorporating TD into T staging, recommending that TD-positive patients be classified as T4a [13, 14]. The majority of studies have supported integrating TD into N staging, although the methods of inclusion varied [11, 21, 25]. Some studies proposed direct incorporation of TD into the TNM staging system. For instance, Gu et al. recommended upgrading the stage for TD-positive patients by one grade, except for stage IIIC [26]. Wang et al. suggested classifying TD within the N3 or M1 stages, depending on TD counts [12], although some studies considered this approach inappropriate [10, 14]. Determining the most effective method for integrating TD into the TNM staging system remains an area requiring further investigation. Using our dataset, various approaches to incorporate TD into the TNM staging system were assessed based on two metrics: the C-index and AIC. The findings indicated that TD integration is more suitable within the N stage. Specifically, equating one TD to four LNMs in the TNM staging system improved the accuracy of prognostic predictions for GC. This approach also surpassed the predictive performance of the current TNM staging system and previously proposed modifications. Under the revised staging methodology, patients reclassified from stage II to stage III exhibited worse prognoses compared to other stage II patients, while had outcomes comparable to those originally classified as stage III. This reclassification implies that a greater number of patients may require postoperative adjuvant therapy, emphasizing the critical role of TD in prognosis and treatment guidance for GC patients. Furthermore, a nomogram was developed by integrating the revised N stage with other clinical and prognostic factors, achieving superior predictive efficacy for patient outcomes. This study lays a critical foundation for incorporating TD into the TNM staging system for GC, enhancing prognostic accuracy and guiding postoperative adjuvant therapy.

Our study encounters several limitations. Primarily, it is a single-center retrospective study lacking external validation. Selection bias might influence the findings; however, PSM was employed to minimize the effects of potential confounders and selection bias. Furthermore, GC in China is predominantly diagnosed at advanced stages, with relatively few patients identified in the early stages of the disease. This limited representation of early-stage patients in the study could restrict the ability to accurately assess the influence of TD on early-stage GC patients' prognosis. The influence of TD on early-stage cancer patients' prognosis warrants further investigation. Additionally, a study showed that different TD classifications impact prognosis differently [27]. Combining TD classification and count may improve prognostic accuracy, but exploring the better way to incorporate both into the TNM system remains challenging. We look forward to more in-depth research in the future. As a clinical study, these findings reflect the necessity of additional research to explore the origins, mechanisms, and implications of TD in tumor metastasis.

5 Conclusions

TD is a crucial factor in determining the TNM staging of GC and serves as a predictor of prognosis to guide postoperative adjuvant therapy. The presence and increased number of TD are linked to poor prognosis in GC. Notably, the negative impact of a single TD on prognosis surpasses that of a single LNM. Although postoperative adjuvant chemotherapy markedly improves the prognosis of patients with TD, their prognosis remains inferior to that of patients without TD. This study proposed a novel staging strategy, integrating one TD as equivalent to four LNMs in the TNM staging system to enhance the precision of prognostic predictions.

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

Declarations

Ethical approval This study was approved by the Ethics Committee of Xijing Hospital (approval number: KY20222241-X-1).

Competing interests The authors declare no competing interests.

References

1. E.C. Smyth, M. Nilsson, H.I. Grabsch, N.C. van Grieken, F. Lordick, Gastric cancer. Lancet. **396**, 635–648 (2020)
2. J.A. Ajani, T.A. D'Amico, D.J. Bentrem, J. Chao, D. Cooke, C. Corvera, P. Das, P.C. Enzinger, T. Enzler, P. Fanta et al., Gastric Cancer, Version 2.2022, NCCN Clinical Practice guidelines in Oncology. J. Natl. Compr. Canc Netw. **20**(2), 167–192 (2022)
3. X. Gao, L. Zhao, N. Zhang, W. Han, K. Liu, J. Yan, L. Chen, Y. Pan, R. Li, W. Li et al., Impact of HER2 on prognosis and benefit from adjuvant chemotherapy in stage II/III gastric cancer patients: a multicenter observational study. Int. J. Surg. **109**(5), 1330–1341 (2023)
4. X. Gao, G. Li, J. Deng, L. Zhao, W. Han, N. Zhang, Y. Gao, L. Lu, S. Wang, J. Yu et al., Association of survival with adjuvant chemotherapy in patients with stage IB gastric cancer: a multicentre, observational, cohort study. Lancet Reg. Health West. Pac. **45**, 101031 (2024)
5. R. Yao, X. Gao, J. Yu, S. Wang, X. Wang, K. Uehara, Y. Nie, Tumor deposits in colorectal and gastric cancers. Med. Plus. **1**(2), 100025 (2024)
6. Japanese classification of gastric carcinoma, 3rd English edition. Gastric Cancer. **14**(2), 101–112 (2011)
7. W. Gabriel, C. Dukes, H. Bussey, Lymphatic spread in cancer of therectum. Br. J. Surg. **23**(90), 395–413 (1935)
8. L.L. Tong, P. Gao, Z.N. Wang, Y.X. Song, Y.Y. Xu, Z. Sun, C.Z. Xing, H.M. Xu, Is the seventh edition of the UICC/AJCC TNM staging system reasonable for patients with tumor deposits in colorectal cancer? Ann. Surg. **255**(2), 208–213 (2012)
9. S.B. Edge, C.C. Compton, The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann. Surg. Oncol. **17**(6), 1471–1474 (2010)
10. X. Song, K. Liu, X. Liao, Y. Zhu, B. Peng, W. Zhang, L. Zhao, X. Chen, K. Yang, J. Hu, Clinical significance of tumor deposits in gastric cancer after radical gastrectomy: a propensity score matching study. World J. Surg. Oncol. **21**(1), 325 (2023)
11. H.S. Lee, H.E. Lee, H.K. Yang, W.H. Kim, Perigastric tumor deposits in primary gastric cancer: implications for patient prognosis and staging. Ann. Surg. Oncol. **20**(5), 1604–1613 (2013)
12. W. Wang, Y. Li, Y. Zhang, X. Yuan, D. Xu, Y. Guan, X. Feng, Y. Chen, X. Sun, W. Li et al., Incorporation of extranodal metastasis of gastric carcinoma into the 7th edition UICC TNM staging system. Plos One **6**(6), e19557 (2011)
13. S. Anup, J. Lu, C.H. Zheng, P. Li, J.W. Xie, J.B. Wang, J.X. Lin, Q.Y. Chen, L.L. Cao, M. Lin et al., Prognostic significance of perigastric tumor deposits in patients with primary gastric cancer. Bmc Surg. **17**(1), 84 (2017)
14. Z. Sun, Z.N. Wang, Y.Y. Xu, G.L. Zhu, B.J. Huang, Y. Xu, F.N. Liu, Z. Zhu, H.M. Xu, Prognostic significance of tumor deposits in gastric cancer patients who underwent radical surgery. Surgery. **151**(6), 871–881 (2012)
15. M.B. Amin, F.L. Greene, S.B. Edge, C.C. Compton, J.E. Gershenwald, R.K. Brookland, L. Meyer, D.M. Gress, D.R. Byrd, D.P. Winchester, The Eighth Edition AJCC Cancer staging Manual: continuing to build a bridge from a population-based to a more personalized approach to cancer staging. Ca Cancer J. Clin. **67**(2), 93–99 (2017)
16. B.H. Min, S.J. Byeon, J.H. Lee, K.M. Kim, J.Y. An, M.G. Choi, J.H. Lee, T.S. Sohn, J.M. Bae, Lymphovascular invasion and lymph node metastasis rates in papillary adenocarcinoma of the stomach: implications for endoscopic resection. Gastric Cancer. **21**(4), 680–688 (2018)
17. J. Li, Y. Jiang, C. Chen, W. Tan, P. Li, G. Chen, Q. Peng, W. Yin, Integrin beta4 is an effective and efficient marker in synchronously highlighting Lymphatic and Blood Vascular Invasion, and Perineural Aggression in Malignancy. Am. J. Surg. Pathol. **44**(5), 681–690 (2020)
18. C. Liebig, G. Ayala, J.A. Wilks, D.H. Berger, D. Albo, Perineural invasion in cancer: a review of the literature. Cancer. **115**(15), 3379–3391 (2009)
19. M.C. Graham, N. Knijn, M. Verheij, I.D. Nagtegaal, R.S. van der Post, Tumour deposits are a significant prognostic factor in gastric cancer - a systematic review and meta-analysis. Histopathology. **74**(6), 809–816 (2019)
20. R. Xu, Y. Zhang, J. Zhao, K. Chen, Z. Wang, Prognostic value of tumor deposits in lymph node-negative gastric cancer: a propensity score matching study. Eur. J. Surg. Oncol. **49**(4), 845–852 (2023)
21. Y. Liang, L. Wu, L. Liu, X. Ding, X. Wang, H. Liu, J. Meng, R. Xu, D. He, H. Liang, Impact of extranodal tumor deposits on prognosis and N stage in gastric cancer. Surgery. **166**(3), 305–313 (2019)
22. E. Mayo, A.A. Llanos, X. Yi, S.Z. Duan, L. Zhang, Prognostic value of tumour deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study. Histopathology. **69**(2), 230–238 (2016)
23. M. Zhou, W. Yang, W. Zou, J. Yang, C. Zhou, Z. Zhang, Y. Wang, J. Zhang, Y. Wang, G. Li et al., Prognostic significance of tumor deposits in radically resected gastric cancer: a retrospective study of a cohort of 1915 Chinese individuals. World J. Surg. Oncol. **20**(1), 304 (2022)
24. T. Etoh, M. Sasako, K. Ishikawa, H. Katai, T. Sano, T. Shimoda, Extranodal metastasis is an indicator of poor prognosis in patients with gastric carcinoma. Br. J. Surg. **93**(3), 369–373 (2006)
25. G. Puppa, P. Maisonneuve, A. Sonzogni, M. Masullo, P. Capelli, M. Chilosi, F. Menestrina, G. Viale, G. Pelosi, Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. Mod. Pathol. **20**(8), 843–855 (2007)
26. L. Gu, P. Chen, H. Su, X. Li, H. Zhu, X. Wang, P.A. Khadaroo, D. Mao, M. Chen, Clinical significance of Tumor deposits in gastric Cancer: a retrospective and propensity score-matched study at two institutions. J. Gastrointest. Surg. **24**(11), 2482–2490 (2020)
27. M. Hayashi, M. Abe, T. Fujita, H. Matsushita, Prognostic effect of categorized tumor deposits in gastric cancer: a single-center retrospective study. Surgery. **175**(2), 373–379 (2024)