Comparative Study-Retrospective Cohort

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Normalization weighted combination scores re-evaluate TNM staging of gastric cancer: a retrospective cohort study based on a multicenter database

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Background: The pathological depth of tumor invasion (pT) and lymph node metastasis (pN) are critical independent prognostic factors for patients with gastric cancer (GC), representing effective methods for evaluating prognosis. In this study, the authors employed a normalization weight combination score to calculate the weight ratio of the pT stage and pN stage. Subsequently, the authors established a novel weighted TN (wTN) staging model based on these T and N weights, evaluating its prognostic capacity.
Methods: This study utilized a training cohort from A Medical University Cancer Hospital and a validation cohort from the SEER database. Least absolute shrinkage and selection operator (LASSO) and Cox regression were employed to screen clinical characteristics. Multivariate linear regression and cluster analysis calculated the weight ratio of T stage and N stage in the training and validation cohorts, respectively, followed by re-staging. Prognostic value was evaluated using C-index, likelihood ratio, Wald, and Score tests for wTN stage and tumor–node–metastasis (TNM) stage. A nomogram model was developed, and accuracy was assessed using receiver operating characteristic curve (ROC), decision curve analysis (DCA), and restricted cubic spline (RCS) analyses.
Results: LASSO was used for initial screening, selecting eight potential features for Cox analysis. Age, tumor size, metastasis lymph nodes (MLNs), and tumor location were confirmed as independent prognostic factors. wTN was calculated in the training and validation cohorts, and nomograms were established with the independent factors. N stage had a higher weight proportion than T stage in both cohorts (0.625/0.375 in training cohort, 0.556/0.444 in validation cohort). wTN outperformed the 8th TNM stage in C-index, likelihood ratio, Wald, and Score tests in the training cohort, with successful validation in the validation cohort. Stratified analysis of distinct pathological types further demonstrates that wTN staging exhibits superior prognostic performance.
Conclusion: The wTN staging model based on T stage and N stage weights has a good prognostic value for GC patients. The same conclusion was obtained in different pathological stratification.

Keywords: gastric cancer, N staging, prognosis, T staging, weighting stage.

Introduction

Gastric cancer (GC) is a highly malignant tumor with significant mortality (about 760 000 deaths annually)[1]. Accurate prognostic staging is crucial due to its high recurrence and metastasis rates[2]. The widely used tumor–node–metastasis (TNM) staging system, developed by the American Joint Commission for Cancer (AJCC), incorporates depth of invasion (pT), the number of metastatic lymph nodes (pN), and the presence of distant metastasis (M0/1) factors to predict prognosis and guide treatment decisions for GC patients[3].

The introduction of the 8th AJCC staging system in 2017 brought significant changes to TNM staging, particularly in stage

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III patients. The refinement of pN3 into pN3a [7–15 metastasis lymph nodes (MLNs)] and pN3b (≥16 MLNs) resulted in reclassification of T1N3b, T2N3b, and T3N3b from stages IIB, IIIA, and IIIB to stages IIIB, IIIB, and IIIC, respectively. Conversely, T4aN2, T4aN3a, T4bN0, and T4bN2 were downgraded from stages IIIB, IIIC, IIIB, and IIIC in the 7th edition to stages IIIA, IIIB, IIIA, and IIIB in the 8th edition[3,4]. While the 8th AJCC staging system improves prognostic prediction for stage III patients, some studies have suggested limitations. Graziosi *et al*.[5] observed a lower 5-year survival rate in stage IIIA compared to stage IIIB patients (25.3% vs. 33%). Fang *et al*.[6] found heterogeneity in prognostic prediction among different cohorts, particularly in stage IIIB patients ($P = 0.002$). Nevertheless, pN stage and pT stage remain important independent prognostic factors for GC patients[7–9]. However, the comparison of the weight impact between these two factors is rarely reported. Therefore, the prognostic significance of weighted TN (wTN) staging based on the prognostic weight of pN and pT staging for GC is still worthy of further exploration. In addition, the predictive performance of wTN and pTNM staging for patients is still unknown.

This study analyzed the weight ratio of pT and pN stages, re-evaluated the wTN stage using a weight combination score, and compared its predictive performance with the 8th AJCC TNM staging system. The SEER database was used as a validation cohort to enhance the adaptability of wTN staging and provide accurate individualized prediction models for clinicians.

Patients and methods

Patients

GC diagnosis involved gastroscopy and histopathological examination. Preoperative routine examinations included computed tomography (CT) scans, ultrasound, and blood tests. Surgery in the training cohort, performed by experienced surgeons, ensured adequate lymph node removal (≥16) for precise pN staging. After the lymph nodes were removed, they were photographed and individually labeled before being sent to the pathology laboratory for examination. At least two expert pathologists reviewed all pathological findings. All staging was performed according to the 8th AJCC.

A total of 4060 patients who underwent radical gastrectomy with standard D2/D2 + lymph node dissection in the Department of Gastrointestinal Surgery from 20 October 2014 to 15 March 2017 were selected as the training cohort. The clinicopathological data of the patients were saved in the Gastric Cancer information management system. The data included gender, age, tumor diameter, tumor location, pTNM stage, venous invasion, nerve invasion, and pathological examination results. The study was approved by the Ethics Committee of the hospital, and the ethic code for our study is 2018-02-R.

The inclusion criteria were as follows: (1) patients undergoing radical gastrectomy with negative resection margin (R0) and standard D2/D2 + lymph node dissection; (2) regular follow-up for at least 5 years; and (3) at least 16 groups of lymph nodes were dissected during operation. Exclusion criteria included: (1) history of other malignant tumors; (2) patients with preoperative chemotherapy or radiotherapy; (3) the postoperative pathological report showed no tumor; and (4) remnant GC was excluded.

HIGHLIGHTS

- The depth of invasion and the number of lymph node metastases are the most effective ways to evaluate the prognosis of gastric cancer (GC) patients.
- In this study, we calculate the normalization weights of the indicators T and N staging of GC, create a new stage of GC [weighted TN (wTN) staging] and construct a prognostic model based on wTN staging.
- We verified that the prognostic model based on wTN staging had better predictive performance than the 8th edition of American Joint Commission for Cancer (AJCC) tumor–node–metastasis (TNM) staging.

Patients were followed up after discharge through various methods, including telephone, e-mail, and outpatient visits. Follow-up intervals depended on the patient's stage; stage I patients were followed every 12 months, stage II patients every 6 months, and stage III patients every 3–6 months. Overall survival (OS) served as the study endpoint, defined as the time from surgery to death or last follow-up.

Validation cohort selection

The validation cohort consisted of 4514 patients from the SEER database (SEER*Stat software, version 8.4.0.1), spanning from 1 January 2014 to 31 December 2016. Exclusion criteria were applied to remove patients with uncertain age, tumor size, tumor location, number of metastatic lymph nodes, depth of invasion, noncurative resection, and missing information on distant metastasis status.

Weight staging calculation standard

Because all patients with metastases (M1) were labeled as stage IV in the 8th AJCC staging, this study did not include stage IV patients. We referred to the staging method of Li *et al*.[10], and labeled the T stage as 1 = T1, 2 = T2, 3 = T3, 4 = T4a, 5 = T4b according to T and N stages. The N stage was marked as 0 = N0, 1 = N1, 2 = N2, 3 = N3a, 4 = N3b, a total of 25 pairs of combinations. Linear regression was performed according to T stage, N stage, and OS time, and the regression formula was as follows:

$$OS = (c - b_1 \times T - b_2 \times N) \times 100\%,$$

where c is the survival time constant, b_1 and b_2 are the T stage and N stage slopes, respectively. The specific formula is as follows:

$$b_1 = \frac{\Delta OS}{\Delta T},\ b_2 = \frac{\Delta OS}{\Delta N}.$$

The influence ratio of T stage and N stage on OS is given by b_1/b_2, where b_1 represents the effect of T stage on OS and b_2 represents the effect of N stage on OS. To calculate the normalized weight value of T stage and N stage based on their

relative influence, the following formula is used:

$$wT = \frac{b_1}{b_1 + b_2} \times 100\%,$$

$$wN = 1 - wT.$$

The TN weight combination score is calculated by multiplying each stage by its corresponding weight, which helps balance the impact of each indicator on the patient. The calculation is performed as follows:

$$wTX_1NX_2 = wT \times X_1 + wN \times X_2,$$

where X_1 represents the T stage and X_2 represents the N stage, wT and wN are the respective weights assigned to the T stage and N stage. For example, if a patient has stage T3N2, the weight combination score can be calculated as follows:

$$wT3N2 = wT \times 3 + wN \times 2.$$

Cluster analysis was performed on the weight combination scores of all patients, resulting in seven cluster groups based on the AJCC standard (IA, IB, IIA, IIB, IIIA, IIIB, and IIIC).

Statistics analysis

Statistical analyses used SPSS software (version 26.0) and R software (version 4.1.2). The *t*-test or χ^2 test analyzed variables. The least absolute shrinkage and selection operator (LASSO) method suitable for high-dimensional data regression was employed to select the most valuable potential predictive features for prognosis from the raw data of the training cohort. Cox regression performed univariate and multivariate analyses. Receiver operating characteristic curve (ROC), decision curve analysis (DCA), and restricted cubic spline (RCS) assessed prediction accuracy and clinical practicability. C-index, likelihood ratio, Wald test, and Score (log-rank) test compared predictive values. Significance was defined as $P < 0.05$. The work has been reported in line with the STROCSS criteria[11] (Supplemental Digital Content 1, http://links.lww.com/JS9/B368).

Table 1

Training cohort and validation cohort patient baseline characteristics.

Characteristics	Training cohort	Validation cohort	*P*
n	4060	4514	
Age, median (IQR)	59 (51, 65)	65 (55, 74)	< 0.001
Tumor size, median (IQR)	45 (30, 60)	43 (25, 65)	0.003
LNRS, median (IQR)	0.053 (0, 0.211)	0.056 (0, 0.306)	< 0.001
Gender, *n* (%)			< 0.001
Male	2982 (73.45%)	2839 (62.89%)	
Female	1078 (26.22%)	1675 (37.11%)	
Tumor site, *n* (%)			< 0.001
L	2915 (71.80%)	1193 (26.43%)	
M	653 (16.08%)	1661 (36.80%)	
U	430 (10.59%)	1319 (29.22%)	
LMU	62 (1.53%)	341 (7.55%)	
pT stage, *n* (%)			< 0.001
T1	902 (22.21%)	963 (21.33%)	
T2	593 (14.61%)	599 (13.37%)	
T3	1245 (30.67%)	1857 (41.14%)	
T4a	1200 (29.56%)	857 (18.99%)	
T4b	120 (2.95%)	238 (5.27%)	
pN stage, *n* (%)			< 0.001
N0	1652 (40.69%)	1639 (36.31%)	
N1	754 (18.57%)	1066 (23.62%)	
N2	745 (18.35%)	800 (17.72%)	
N3a	603 (14.85%)	589 (13.05%)	
N3b	306 (7.54%)	420 (9.30%)	
AJCC TNM, *n* (%)			< 0.001
IA	749 (18.45%)	737 (16.33%)	
IB	411 (10.12%)	417 (9.24%)	
IIA	506 (12.46%)	722 (15.99%)	
IIB	600 (14.78%)	788 (17.46%)	
IIIA	884 (21.77%)	800 (17.72%)	
IIIB	593 (14.61%)	592 (13.11%)	
IIIC	317 (7.81%)	458 (10.15%)	
Histological type, *n* (%)			< 0.001
Adenocarcinoma	2961 (72.93%)	3478 (77.04%)	
Mucinous adenocarcinoma	131 (3.22%)	103 (2.28%)	
Signet-ring cell carcinoma	968 (23.85%)	934 (20.68%)	

AJCC, American Joint Commission for Cancer; IQR, interquartile range; L, Lower; LMU, Whole stomach; LNRS, lymph nodes ratio; M, Middle; TNM, tumor–node–metastasis; U, Upper.

Results

Patient characteristics

Table 1 presents baseline characteristics of patients in the training and validation cohorts. Significant differences were observed in age, gender, tumor location, pN stage, pT stage, and TNM stage between the two groups. The training cohort had a younger median age (59 years) compared to the validation cohort (65 years). The validation cohort had a higher proportion of female patients. Tumor locations differed, with the training cohort having more lower location tumors, while the validation cohort had a higher prevalence of upper location tumors. Regarding TNM staging, the training cohort had higher proportions of stages IA, IIIA, and IIIB, while the validation cohort had higher proportions of stages IIA, IIB, and IIIC. Stage IB showed no significant difference between the two groups.

Clinical feature selection and nomogram model construction

Following LASSO screening, the number of clinical features in the training cohort was reduced to eight potential predictive features (age, tumor size, MLNs, γ-GT, albumin, tumor location, HER-2, and Borrmann type) (Fig. 1). Cox proportional hazards model was then used for univariate and multivariate analysis, identifying age, tumor size, MLNs, tumor location, and Borrmann type as independent risk factors affecting patient outcomes (Table 2). A wTN nomogram incorporating these predictors was constructed in both the training and validation cohorts to provide a quantitative method for predicting survival probability in GC patients. However, due to severe collinearity indicated by high variance inflation factor (VIF) values (Borrmann II VIF = 9.47, Borrmann III VIF = 13.94, and Borrmann IV VIF = 7.93), Borrmann type was excluded from the nomogram (Fig. 2).

Multiple linear regressions of T stage, N stage, and OS

Cox analysis confirmed T stage and N stage as independent prognostic factors for GC patients. Multiple linear regression was then conducted. The linear regression equation for the training cohort was $OS = (68.074 - 3.994 \times T - 6.645 \times N) \times 100\%$,

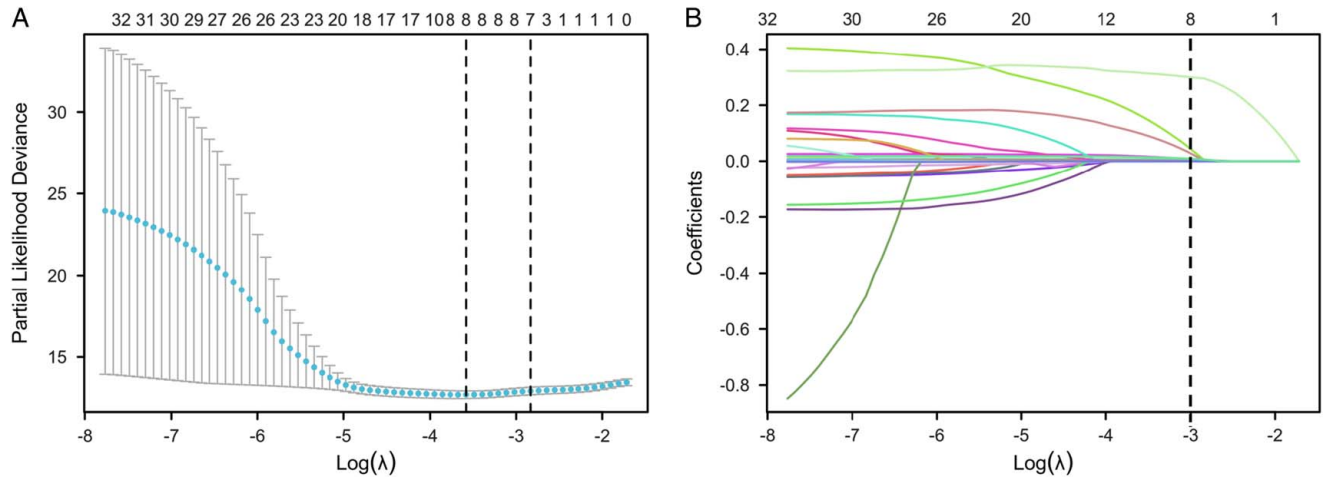

Figure 1. (A, B) LASSO model was used for initial screening of 32 clinical features in the training cohort. (A) Ten-fold cross-validation using LASSO, the left dashed line is the optimal λ value at the optimal value of the model (λ.min), the right dashed line is the model λ value at the range of 1 standard error of the optimal value (λ.1Se). (B) The distribution of LASSO coefficient of 32 basic clinical features, the dashed line is the optimal value of the model. The eight nonzero coefficients resulting from the best λ values are the eight potential predictors. LASSO, least absolute shrinkage and selection operator.

$wT = 0.375$, $wN = 0.625$. In the validation cohort, the equation was $OS = (42.137 - 2.700 \times T - 3.386 \times N) \times 100\%$, $wT = 0.444$, $wN = 0.556$. N stage was found to have a more significant impact on patient survival than T stage in both cohorts. Weight combination scores based on wT and wN were assigned to patients, and cluster analysis was performed on these scores, resulting in seven clusters. The wTN stage was then rearranged according to the clustering results, and Figure 3 illustrates the mulberry diagram depicting the specific wTN stages and their migration relative to the AJCC TNM stage in the two cohorts.

Evaluation of the comparative accuracies of the prognostic prediction among wTN stage and AJCC stage

The linear relationship between wTN stage and AJCC stage, as well as their association with 5-year survival rate, were assessed.

Table 2

Results of univariate and multivariate analyses using Cox proportional hazards model.

		Univariate analysis		Multivariate analysis	
Characteristics	**Total (*M*)**	**Hazard ratio (95% CI)**	***P***	**Hazard ratio (95% CI)**	***P***
Age	4060	1.031 (1.024–1.037)	< 0.001	1.030 (1.023–1.037)	< 0.001
Tumor size	4060	1.015 (1.013–1.016)	< 0.001	1.006 (1.003–1.009)	< 0.001
MLNs	4060	1.059 (1.053–1.064)	< 0.001	1.041 (1.034–1.048)	< 0.001
γ-GT	4060	0.998 (0.996–1.000)	0.094	0.999 (0.997–1.001)	0.265
Albumin	4060	0.957 (0.946–0.968)	< 0.001	0.990 (0.978–1.003)	0.147
Primary site	4060		< 0.001		
L	2915	Reference		Reference	
M	653	1.432 (1.216–1.686)	< 0.001	1.248 (1.056–1.477)	0.010
U	430	1.730 (1.443–2.074)	< 0.001	1.389 (1.145–1.683)	< 0.001
LMU	62	3.939 (2.826–5.491)	< 0.001	1.307 (0.885–1.931)	0.178
HER-2	4060		0.078		
0	2166	Reference		Reference	
1 +	1086	0.910 (0.780–1.062)	0.233	0.926 (0.791–1.083)	0.334
2 +	527	0.966 (0.793–1.178)	0.736	0.928 (0.759–1.135)	0.467
3 +	281	1.278 (1.014–1.612)	0.038	1.229 (0.971–1.554)	0.086
Borrmann types	4060		< 0.001		
Borrmann 0	440	Reference		Reference	
Borrmann I	219	4.143 (2.453–6.995)	< 0.001	2.866 (1.612–5.093)	< 0.001
Borrmann II	1127	3.671 (2.339–5.761)	< 0.001	2.716 (1.647–4.481)	< 0.001
Borrmann III	1951	7.138 (4.618–11.033)	< 0.001	4.755 (2.916–7.755)	< 0.001
Borrmann IV	250	13.303 (8.361–21.165)	< 0.001	4.670 (2.677–8.145)	< 0.001
Borrmann V	73	8.495 (4.755–15.176)	< 0.001	4.152 (2.206–7.813)	< 0.001

γ-GT, Gamma-Glutamyl Transferase; HER-2, Human epidermal growth factor receptor-2; L, Lower; LMU, Whole stomach; M, Middle; MLNs, metastasis lymph nodes; U, Upper.

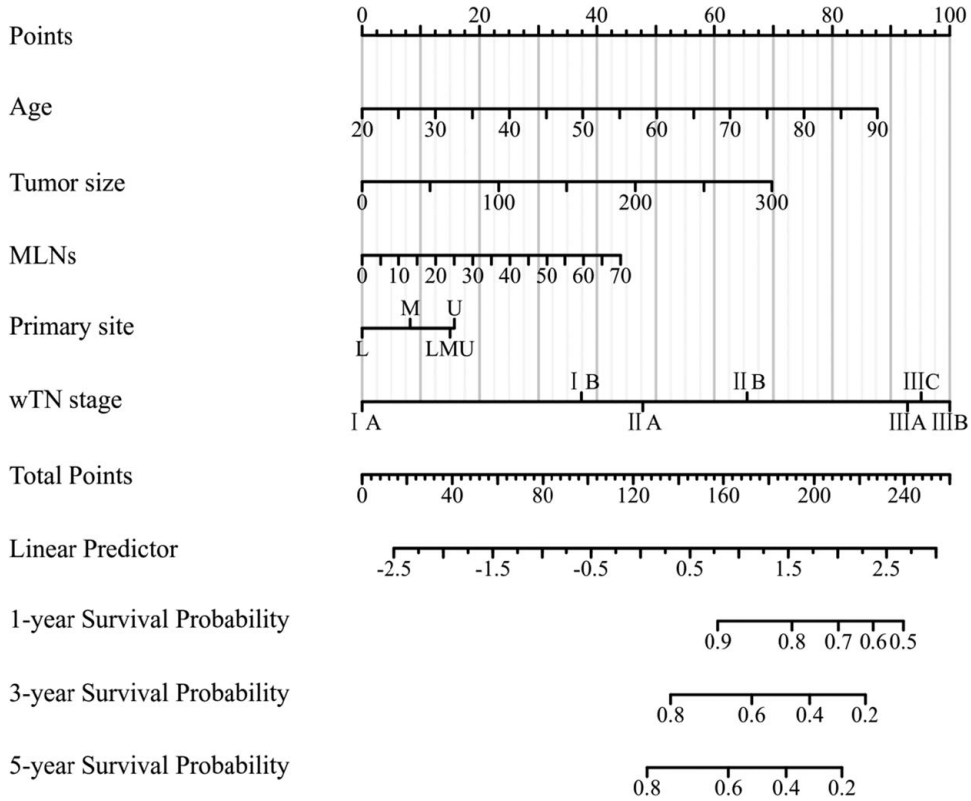

Figure 2. Four important clinical predictive features generated by Cox analysis (including age, tumor size, MLNs, and tumor location) and wTN stage were used to form a nomograph for gastric cancer patients and predict the survival status of individual patients at 1, 3, and 5 years. MLNs, metastasis lymph nodes; wTN, weighted TN.

In the training cohort, wTN stage exhibited higher R^2 and R_a^2 values (0.840 for R^2 and 0.833 for R_a^2) compared to AJCC stage (0.764 for R^2 and 0.753 for R_a^2). Similarly, in the validation cohort, wTN stage showed better linear relationship ($R^2 = 0.942$, $R_a^2 = 0.940$) than AJCC stage ($R^2 = 0.855$, $R_a^2 = 0.849$), indicating superior stratification ability (Fig. 4). C-index analysis revealed that wTN staging had a higher prognostic accuracy (C-index = 0.729) compared to AJCC staging (C-index = 0.714) in the training cohort. Likelihood ratio, Wald test, and log-rank test also demonstrated the superiority of wTN stage over AJCC stage (all $P < 0.001$). In the validation cohort, the C-index of wTN-SEER stage (0.688) was higher than that of AJCC-SEER stage (0.685), and wTN-SEER staging was superior to AJCC-SEER staging in likelihood ratio, Wald test, and log-rank test (all $P < 0.001$) (Table 3).

Evaluation and validation of the wTN nomograms

ROC analysis was conducted to evaluate the prognostic value of wTN stage and AJCC stage. In the training cohort, the AUC for wTN stage was 0.746, and for AJCC stage, it was 0.745. In the validation cohort, the AUC for wTN-SEER stage was 0.733, and for AJCC-SEER stage, it was 0.733. Time-dependent ROC analysis showed that the AUC values of wTN stage were consistently higher than those of AJCC stage at 1, 3, and 5 years, with the best predictive ability observed at 3 years (wTN stage AUC = 0.777, AJCC stage AUC = 0.775) in the training cohort. In the validation cohort, wTN-SEER stage had higher AUC values than AJCC-SEER stage at 1 and 3 years, with equal performance at 5 years. Both stages demonstrated the best predictive power at 3 years (wTN-SEER AUC = 0.749, AJCC-SEER AUC = 0.748) (Fig. 5). DCA plots indicated that wTN stage outperformed AJCC stage in clinical application at all time points (1, 3, and 5 years) in both the training and validation cohorts (Fig. 6). RCS analysis revealed a positive correlation trend between wTN stage and TNM stage with respect to patient mortality risk (Fig. 7). In both the training cohort and the validation cohort, wTN stage and TNM stage showed a positive correlation trend with HR. wTN stage exhibited a better fitting ability to the real world, while the relationship between the stages and mortality risk was nonlinear in the training cohort (nonlinear $P < 0.001$), but linear in the validation cohort (nonlinear $P > 0.05$) (Fig. 7).

Adaptability of wTN staging to different pathological types

We conducted an in-depth assessment of wTN's applicability across diverse pathological types to gauge its impact on GC patient prognosis. Initially, Kaplan–Meier survival analysis unveiled that signet-ring cell carcinoma patients exhibited notably worse prognoses compared to adenocarcinoma or mucinous adenocarcinoma in both the training and validation cohorts (Fig. S1, Supplemental Digital Content 2, http://links.lww.com/JS9/B369). Subsequently, employing DCA and time–ROC analyses at 1-year, 3-year, and 5-year intervals, we found that across varying pathological types, the training cohort consistently demonstrated improved wTN staging outcomes over AJCC staging (Fig. S2,

A

	N0	N1	N2	N3a	N3b
T1	IA	IB	IIA	IIB	IIIB
T2	IB	IIA	IIB	IIIA	IIIB
T3	IIA	IIB	IIIA	IIIB	IIIC
T4a	IIB	IIIA	IIIA	IIIB	IIIC
T4b	IIIA	IIIB	IIIB	IIIC	IIIC

B

	N0	N1	N2	N3a	N3b
T1	IA	IB	IIA	IIB	IIIA
T2	IB	IIA	IIB	IIIA	IIIB
T3	IB	IIB	IIIA	IIIB	IIIB
T4a	IIA	IIB	IIIA	IIIB	IIIC
T4b	IIB	IIIA	IIIB	IIIC	IIIC

C

	N0	N1	N2	N3a	N3b
T1	IA	IB	IB	IIA	IIB
T2	IA	IB	IIA	IIB	IIIA
T3	IB	IIA	IIB	IIIA	IIIB
T4a	IIA	IIB	IIIA	IIIB	IIIC
T4b	IIB	IIIA	IIIB	IIIC	IIIC

D

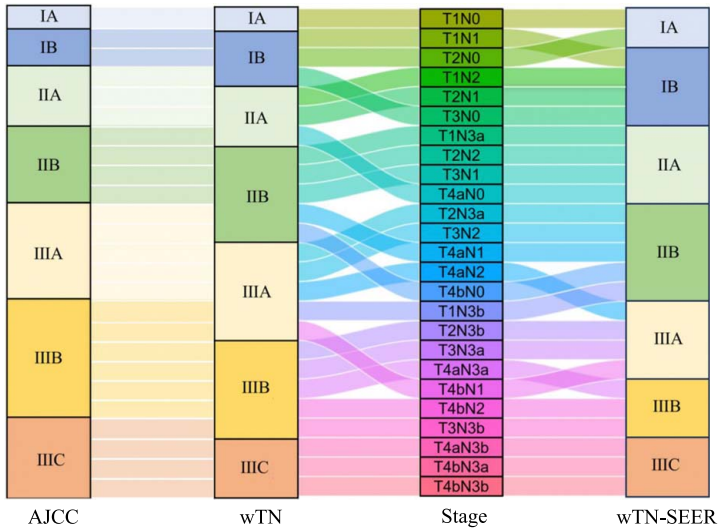

Figure 3. (A–D) Specific staging content and staging metastasis of the 8th edition AJCC staging system and wTN staging system. (A) 8th AJCC staging system. (B) wTN staging of the training cohort. (C) wTN-SEER staging of validation cohort. (D) Mulberry plot of metastasis changes in AJCC stage, wTN stage in training cohort, and WTN-SEER stage in validation cohort. AJCC, American Joint Commission for Cancer; wTN, weighted TN.

Supplemental Digital Content 3, http://links.lww.com/JS9/B370). Further ROC analysis on the training cohort indicated higher AUC values for wTN staging across all three pathological groups compared to AJCC stages (0.750 vs. 0.749, 0.699 vs. 0.691, and 0.744 vs. 0.742) (Fig. S3, Supplemental Digital Content 4, http://links.lww.com/JS9/B371). Moreover, the time–ROC outcomes indicated that, across different pathological types, both wTN and AJCC stages displayed their highest AUC values at the 3-year mark, with the AUC of wTN stage exceeding that of AJCC stage (Fig. S3, Supplemental Digital Content 4, http://links.lww.com/JS9/B371).

Directly evaluating the two-cohorts stage system, we employed C-index, likelihood ratio, Wald test, and Score (log-rank) test for the three distinct pathological types. In the training cohort, for adenocarcinoma, wTN staging surpassed AJCC stage in terms of C-index (0.732 vs. 0.731), likelihood ratio (79.65 vs. 77.61, $P < 0.001$), Wald test (61.55 vs. 58.29, $P < 0.001$), and Score (log-rank) test (83.27 vs. 79.78, $P < 0.001$). For mucinous adenocarcinoma, the C-index (0.708 vs. 0.693), likelihood ratio (49.43 vs. 47.35, $P < 0.05$), and Score (log-rank) test (65.95 vs. 61.63, $P < 0.05$) were superior in wTN staging, although the Wald test yielded no specificity (the P values were 0.126 and 0.621, respectively). Similarly, for signet-ring cell carcinoma, wTN staging outperformed AJCC stage in terms of C-index (0.726 vs. 0.724), likelihood ratio (49.53 vs. 48.35, $P < 0.001$), Wald test (41.43 vs. 41.08, $P < 0.001$), and Score (log-rank) test (59.54 vs. 55.15, $P < 0.001$) (Table S1, Supplemental Digital Content 5, http://links.lww.com/JS9/B372). These conclusions were consistently validated within the verification queue (Fig. S4, Supplemental Digital Content 6, http://links.lww.com/JS9/B373; Fig. S5, Supplemental Digital Content 7, http://links.lww.com/JS9/B374; Table S1, Supplemental Digital Content 5, http://links.lww.com/JS9/B372).

Discussion

This retrospective study introduces the wTN staging based on the TN weight combination score, which outperforms the AJCC TNM staging in prognostic value. The SEER dataset was added for further validation. LASSO is used to address collinearity, and a nomogram incorporating wTN stage and clinical characteristics is developed for individual prognosis prediction.

The AJCC guideline has been widely utilized by medical professionals worldwide, providing practical guidance for the diagnosis and treatment of GC[12,13]. The refinement of pN3 in the 8th AJCC guidelines improved TNM staging for stage III patients[12,14], but further studies revealed limitations in predicting patient prognosis. Graziosi *et al.*[5] found that the 5-year survival rate of stage IIIA was lower than stage IIIB, and the survival rate of stage IIIB decreased over time compared to stages IIIA and IV (25.3% vs. 33%); when survival was prolonged, the survival rate of stage IIIB was lower than that of stage IIIA and stage IV. Studies by Fang *et al.*[6] and Lu *et al.*[15] highlighted poor

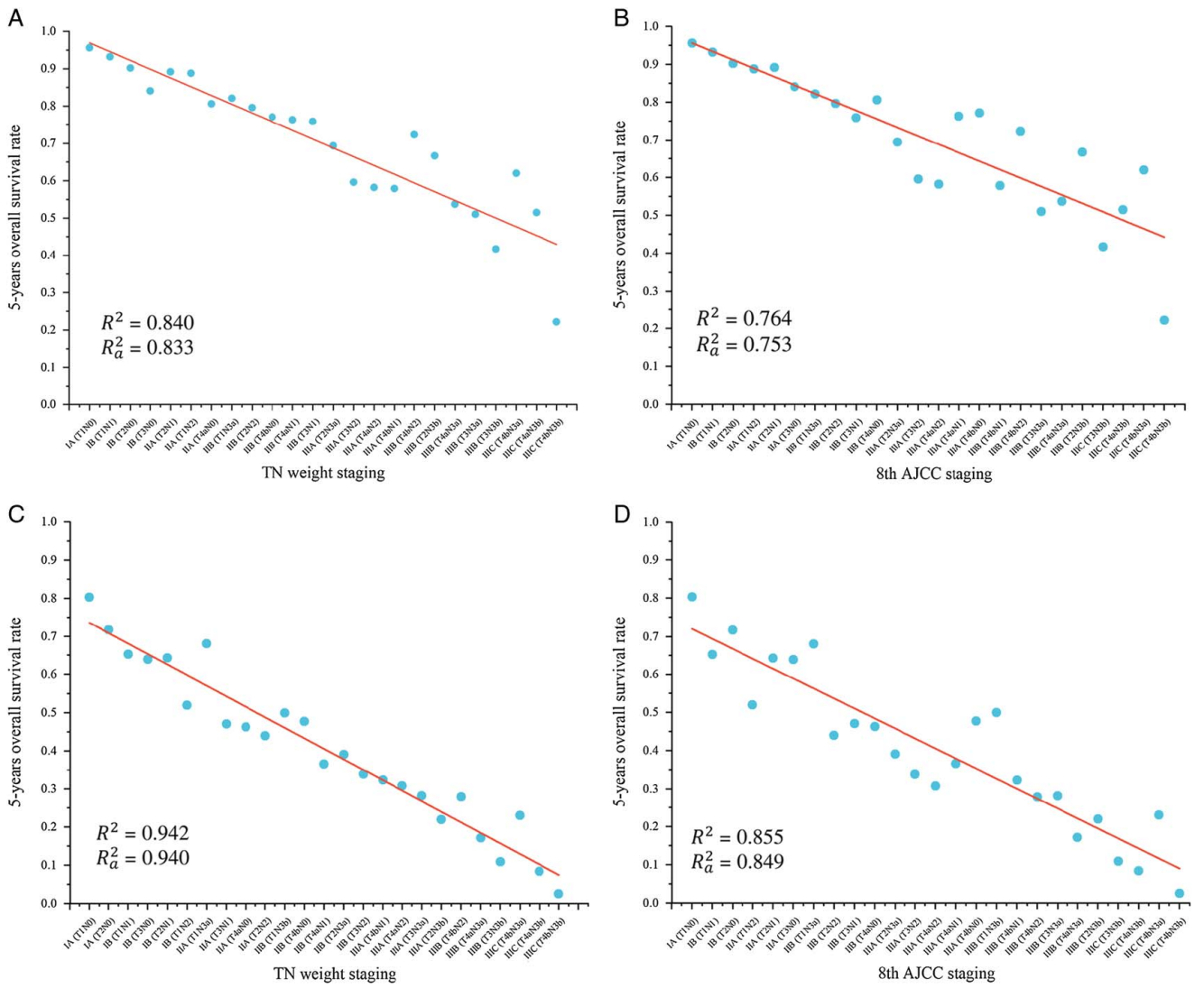

Figure 4. (A–D) Scatter plot of 5-year survival rate of wTN stage and AJCC stage in training cohort and validation cohort. (A) Scatter plot of 5-year survival rates by wTN stage in the training cohort. (B) Scatter plot of 5-year survival rate according to AJCC staging system in the training cohort. (C) Scatter plot of 5-year survival rate according to wTN-SEER staging in the validation cohort. (D) Scatter plot of 5-year survival rate according to AJCC staging system in validation cohort. R^2 is the coefficient of determination, which describes the degree of fitting of the data to the system. R_a^2 is the adjusted R^2, and R_a^2 further considers the influence of the number of samples and independent variables on the degree of fitting. R^2 and R_a^2 are approximately close to 1, indicating that the regression fitting effect is better. AJCC, American Joint Commission for Cancer; wTN, weighted TN.

homogeneity in predicting GC prognosis using the 8th AJCC. Yu *et al.*[16] discovered that the 8th AJCC did not improve predictive ability for patients with adjuvant therapy or postoperative chemotherapy. In colorectal tumors, Li *et al.*[10] proposed a novel approach using linear regression and weight combination score to improve prognostic evaluation, showing better linear relationship and stratification ability compared to the 8th TNM staging.

The insufficient ability of TNM classification in the 8th edition may be attributed to several factors. Firstly, the increasing utilization of adjuvant therapy has led to improved survival outcomes for GC patients[17], and it has been reported that patients with stage III may receive more adjuvant therapy[18,19]. This may explain why the prognosis of stage III/IV patients is sometimes better than that of stage II patients. Secondly, the data used for the 8th edition TNM staging were primarily obtained from the International Gastric Cancer Association (IGCA) between 2000 and 2004[20], which predates recent phase II or III clinical trials[21,22]. Consequently, the impact of new adjuvant therapies on patient survival may not have been adequately considered, resulting in an inaccurate reflection of current prognosis. Importantly, the superior prognostic performance of wTN staging underscores the significant influence of tumor biological behavior on patient outcomes. The increasing incidence of early GC in Asia and the rising prevalence of advanced GC in Western countries have contributed to variations in patient survival[1,23–25]. Furthermore, differences in molecular biology and histological manifestations, such as the higher proportion of diffuse GC and proximal GC in Western populations, have been associated with poorer prognosis[25,26]. Zhao *et al.*[27] found that the survival time of patients with diffuse GC was shorter, and the 80-month

Table 3

Prognostic performance of wTN and TNM in the training cohort and validation cohort.

Characteristics	C-index	Likelihood ratio (*P*)	Wald test (*P*)	Score (log-rank) test (*P*)
Training cohort				
wTN	0.729 (0.722–0.736)	109.78 ($P<0.001$)	82.71 ($P<0.001$)	111.93 ($P<0.001$)
AJCC	0.714 (0.707–0.721)	108.28 ($P<0.001$)	80.04 ($P<0.001$)	109.50 ($P<0.001$)
Validation cohort				
wTN	0.688 (0.682–0.695)	143.76 ($P<0.001$)	133.83 ($P<0.001$)	163.62 ($P<0.001$)
AJCC	0.685 (0.678–0.691)	142.62 ($P<0.001$)	132.22 ($P<0.001$)	160.91 ($P<0.001$)

AJCC, American Joint Commission for Cancer; TNM, tumor–node–metastasis; wTN, weighted TN.

survival rate was less than 40% ($P<0.001$), and the risk of death was higher and the prognosis was worse in patients with proximal GC than in those with distal GC ($P=0.002$). In this study, we also revealed variations in tumor location between the Chinese and SEER databases, further supporting the notion that wTN staging, which considers these biological characteristics, provides better predictive value across different countries and regions (Table 1).

This study provides the first evidence of the prognostic significance of the weight ratio between T stage and N stage in GC patients. In the training cohort, the weight ratio of N stage was found to be higher than that of T stage (0.625 vs. 0.375), which contrasts with the findings of a study on colorectal diseases[10]. This difference suggests that GC has its unique biological properties that influence staging and prognosis. GC is characterized by extensive and complex perigastric lymph node drainage[28], leading to a high likelihood of lymph node metastasis[29]. The rate of lymph node metastasis in GC ranges from 54% to 64% in different countries[30–33], and patients with lymph node metastasis generally have a worse prognosis[34,35]. Studies have demonstrated the benefits of more extensive lymph node dissection[36], particularly in advanced-stage patients[37,38]. The involvement of specific lymph node groups, such as the posterior

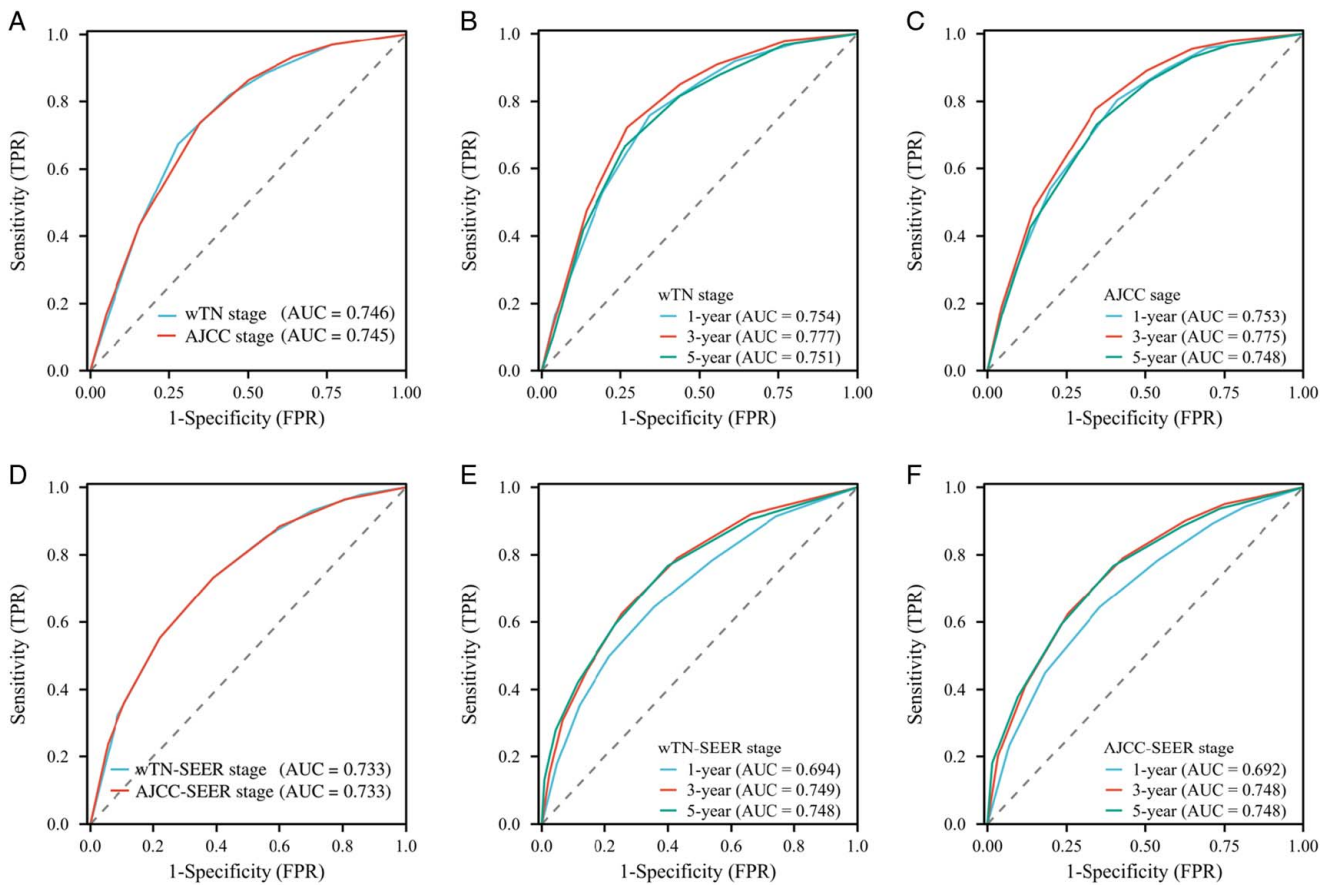

Figure 5. (A–F) Nomogram ROC and time-dependent ROC results of training cohort and validation cohort. (A) ROC model of wTN stage and AJCC stage in the training cohort. (B) AUC values of time-related ROC of wTN staging in the training cohort at 1, 3, and 5 years. (C) AUC values of time-related ROC of AJCC stage in training cohort at 1, 3, and 5 years. (D) To validate the ROC model of wTN staging and AJCC staging in the validation cohort. (E) AUC values of time-related ROC of wTN stage at 1, 3, and 5 years in the validation cohort. (F) AUC values of the time-related ROC of AJCC stage at 1, 3, and 5 years in the validation cohort. AJCC, American Joint Commission for Cancer; AUC, area under the curve; ROC, receiver operating characteristic curve; wTN, weighted TN.

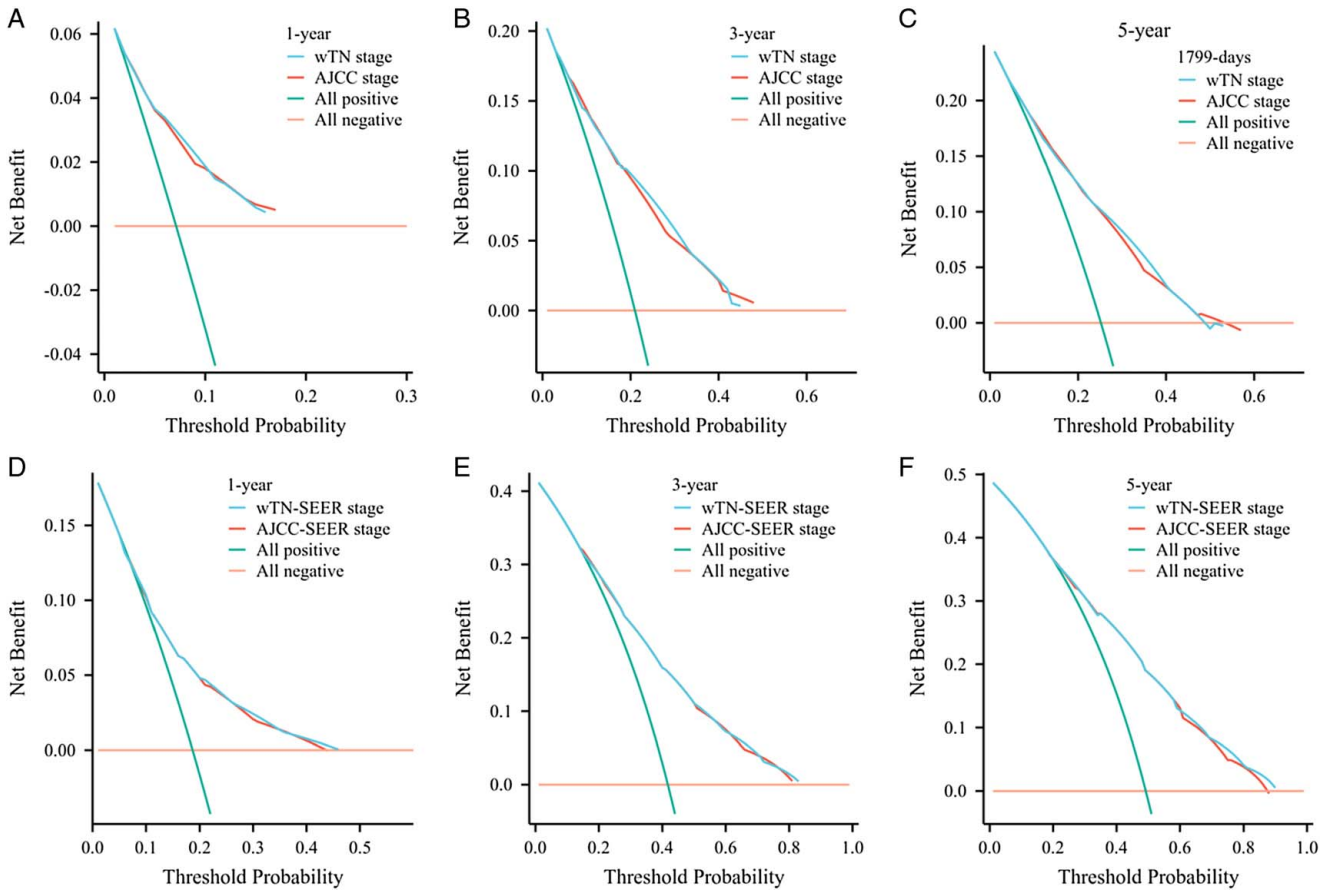

Figure 6. (A–F) Nomogram DCA analysis of training cohort and validation cohort. (A–C) Prediction of 1-year, 3-year, and 5-year decision curves by wTN stage and AJCC stage in the training cohort. (D–F) Prediction of 1-year, 3-year, and 5-year decision curves by wTN-SEER stage and AJCC-SEER stage in the validation cohort. AJCC, American Joint Commission for Cancer; DCA, decision curve analysis; wTN, weighted TN.

lymph nodes (8p, 12b/p, 13, etc.), has been associated with a worse prognosis[39]. Tumor location has also been shown to influence lymph node metastasis patterns, with greater curvature tumors more likely to metastasize to specific lymph node groups[40]. Studies have shown that tumors in the greater curvature are more likely to metastasize to group 6 lymph nodes[41], and then to group 14v and group 16 lymph nodes[42,43]. Jung *et al.*[44] found that the prognosis of patients with tumors located on the greater curvature was worse, and the reason may be related to the stronger migration ability of lymph nodes adjacent to the greater curvature. These studies highlight the correlation between lymph node metastasis, tumor location, lymph node drainage, and patient survival. In this study, multiple linear regression analysis was conducted using patient survival as the endpoint, and it was determined that N stage carries a higher prognostic weight. The wTN staging, rearranged based on the normalized weight score and cluster analysis of T and N weights, exhibited a better linear relationship (Fig. 4). Importantly, this calculation method was also applicable to the SEER stage. In the validation cohort, the higher weight ratio of N stage (compared to T stage) further emphasized the importance of lymph node metastasis in different regions. Consequently, the wTN staging was deemed consistent with the biological behavior of the tumor and capable of addressing the differences in GC nature across various regions. It is proposed that wTN staging could serve as a new staging system, replacing the existing TNM staging.

We evaluated the prognostic value of wTN stage and TNM stage using various indicators and a validation cohort. The wTN stage demonstrated superior prognostic performance and judgment ability compared to the TNM stage, even when applied to cohorts with different characteristics. This suggests that the wTN staging method is versatile and can be extended to other regions. We used the LASSO method to select relevant clinical features by narrowing down regression coefficients. This reduced the initial 32 candidate clinical features to eight potential predictors; Cox analysis was then further used to identify independent risk factors. The LASSO method not only selects predictors based on their association with prognostic outcomes but also allows these selected features to be combined with wTN staging to construct nomograms. The effectiveness of LASSO has been validated in genetic analysis, as demonstrated by de Gonzalo-Calvo *et al.*[45], who used LASSO to screen miRNA in COVID-19 patients and reduce patient severity and mortality. The study identified age, tumor size, MLNs, and tumor location as independent risk factors for prognosis. Nomograms were developed using these factors and wTN stage, providing a statistical tool for evaluating individual patients' long-term prognosis[46]. In clinical practice, wTN staging can help stratify patients and guide treatment decisions based on accurate prognostic scores from the nomograms.

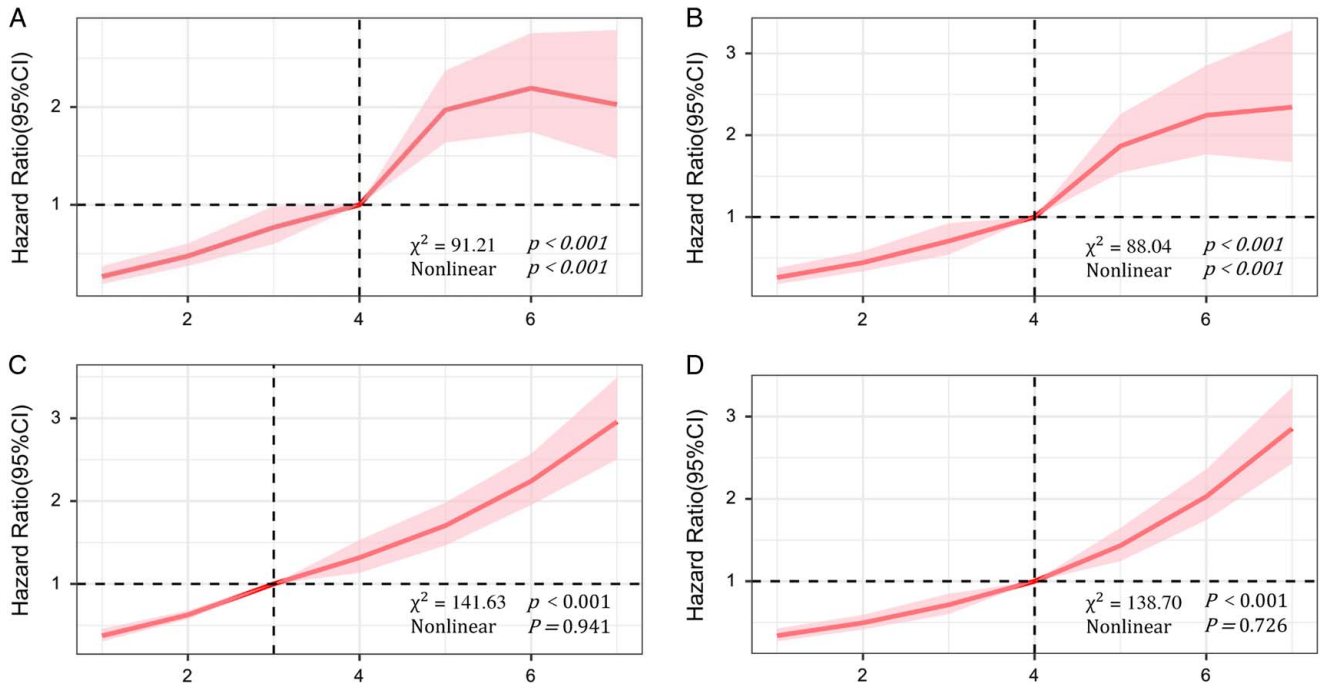

Figure 7. (A–D) Results of restricted cubic spline of nomogram model in training cohort and validation cohort. (A) The relationship between HR and wTN stage in the training cohort. (B) Relationship between HR and AJCC stage in the training cohort. (C) The relationship between HR and wTN stage in the validation cohort. (D) The relationship between HR and AJCC stage in the validation cohort. The red curve represents the estimated HR, the shaded area is the 95% confidence interval, and the dashed line intersection of the axes is the tumor stage status at HR = 1. The numbers on the horizontal axis represent 1 = IA, 2 = IB, 3 = IIA, 4 = IIB, 5 = IIIA, 6 = IIIB, and 7 = IIIC, respectively. AJCC, American Joint Commission for Cancer; HR, hazard ratio; wTN, weighted TN.

Furthermore, recognizing the profound impact of diverse pathological types on GC prognosis, we delved into the suitability of the wTN staging system across these variations. Signet-ring cell carcinoma, a notably aggressive pathological subtype, significantly influences patient prognosis[47]. This specific pathology has led to conflicting findings in related studies[48–50]. Piessen *et al.*[51], after accounting for variables like gender, age, and tumor stage, highlighted signet-ring cell carcinoma as an independent prognostic factor for poor patient outcomes. This association may arise from deeper tumor invasion and higher affinity for lymphoid tissue, leading to more severe lymph node infiltration in these patients. In alignment with these observations, our study assessed the predictive potency of wTN staging for signet-ring cell carcinoma patients. The results consistently demonstrated superior prognostic accuracy for wTN stage across diverse conditions. This reaffirms that wTN staging directly reflects patients' clinical characteristics, thus aligning well with the biological attributes of distinct tumor subtypes. This finding further underscores the advantages of the wTN staging system.

This study has limitations. Firstly, patients who received adjuvant therapy after surgery were not excluded, which is consistent with the inclusion criteria of the 8th AJCC[3]. The main reason is that this study is a retrospective study, which inevitably leads to missing information and inconsistent adjuvant treatment plans. Making separate analysis of patients after adjuvant therapy impossible. Excluding these patients would lead to selection bias and loss of data for stage II/III patients, affecting the overall assessment. Secondly, the study is a retrospective single-center study, although validation was conducted using the SEER database. Further expansion of data sources and multicenter prospective studies are needed to enhance the reliability of the improved wTN staging for GC prognosis. In addition, since this study was a retrospective study, only relevant data of clinical features of GC patients were included to construct wTN staging, and no features related to gene expression, such as those based on co-stimulatory molecules, angiogenic genes, etc., were cited. We hope to conduct future prospective studies to make the wTN model more perfect.

Conclusion

In conclusion, this study demonstrates that the N stage has a greater influence on the prognosis of GC patients compared to the T stage. The newly developed wTN staging system, which incorporates the weights of N and T stages, exhibits improved prognostic value over the 8th AJCC TNM staging. The nomogram model further confirms the superior predictive performance and accuracy of wTN staging across various evaluation indicators. These findings are validated in the independent validation cohort. For different pathological stratification, wTN staging system still showed better prediction performance.

Ethical approval

The study was approved by the Ethics Committee of the Harbin Medical University Cancer Hospital. The ethic code for our study is 2018-02-R.

Consent

Written informed consent was obtained from the patients for the publication of this case report and accompanying images. A copy

of the written consent is available for review by the Editor-in-Chief of this journal on request. Written informed consent was obtained from all enrolled patients, and all personal patient data and information were anonymized before analysis.

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Author contribution

J.W. and H.W.: worked together to design and conceive the project and to write the paper; J.W., X.Y., Y.W., and Z.L.: interpreted and analyzed the data; Y.X.: revised the manuscript for important key contents; J.W., H.W., X.Y., Y.W., Z.L., J.Z., and Y.Z.: participated in patient information collection. All the authors have read and approved the manuscript for publication.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. This study is registered at ClinicalTrials.gov, ClinicalTrials.gov ID is NCT02130752.
2. The registration center is: Harbin Medical University Cancer Hospital.
3. The hyperlink to the registration is: https://beta.clinicaltrials.gov/study/NCT02130752.

Guarantor

Junpeng Wu and Professor Yingwei Xue can act as guarantors.

Data availability statement

This study is a retrospective study. A total of 4060 patients who underwent radical gastrectomy with standard D2/D2 + lymph node dissection in the Department of Gastrointestinal Surgery, Harbin Medical University Cancer Hospital, from 20 October 2014 to 15 March 2017 were used in the training cohort. The validation cohort included 4514 patients from 1 January 2014 to 31 December 2016 in the SEER database.

Due to patient privacy, no data availability statement was provided for this article.

Provenance and peer review

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