Prognosis values of modified Lauren classification in gastric cancer: a validation from SEER database

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Research

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Abstract

Background: It remains controversial as to which pathological classification is most valuable in predicting overall survival (OS) in patients with gastric cancer (GC). We assessed the prognostic performances of three pathological classifications in GC and developed a novel prognostic nomogram individually predicting OS.

Methods: Patients were identified from the Surveillance, Epidemiology and End Results program. Univariate and multivariate analyses were performed to identify the independent prognostic factors. Model discrimination and model-fitting were evaluated by receiver operating characteristic curves and Akaike information criteria. Decision curve analysis was performed to assess clinical usefulness. The independent prognostic factors identified by multivariate analysis were further applied to develop a novel prognostic nomogram.

Results: A total of 2,718 eligible GC patients were identified. The modified Lauren classification was identified as one of the independent prognostic factors of OS. It showed superior model discriminative ability and model-fitting performance over the other pathological classifications, and similar results were obtained in various patient settings. In addition, it showed superior net benefits over the Lauren classification and tumor differentiation grade in predicting 3- and 5-year OS. A novel prognostic nomogram incorporating the modified Lauren classification showed superior model discriminative ability, model-fitting performance, and net benefits over the American Joint Committee on Cancer (AJCC) 8th Edition TNM classification.

Conclusion: The modified Lauren classification showed superior net benefits over the Lauren classification and tumor differentiation grade in predicting OS. A novel prognostic nomogram incorporating the modified Lauren classification showed good model discriminative ability, model-fitting performance, and net benefits.

Introduction

Gastric cancer (GC) is the fifth most prevalent and the third leading cause of cancer death worldwide [1]. It is a complex, heterogeneous entity that encompasses tumors with varying histopathologies, molecular profiles, and behaviors; however, GC is considered as a single entity for the purpose of clinical management and treatment, without regard to its subtype [2, 3]. To date, the gold standard for GC prognostication and treatment guidance is the anatomical American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification [4, 5]. It has been widely applied in many clinical practices without reference to its histopathology because the value of the morphological features of GC in determining clinical outcomes is still limited [6]. In addition, many investigators are still trying to identify a more valuable classification with better prognostic value [3, 7, 8].

Due to the wide variations in the morphological features of GC, many histological classifications have been proposed, and they are currently in wide use [3, 9–13]. One of these classifications is the tumor differentiation grade. GC can be classified as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated, according to the degree of differentiation exhibited by the tumor [10]. The tumor differentiation grade has been identified as a prognostic risk factor for GC in some studies [14, 15]. However, several recent studies have reported that the tumor differentiation grade is not significantly associated with the prognosis of GC patients [16–19]. Another classification is the Lauren classification [13]. Although it dates back to 1965, it remains one of the most commonly used pathological classifications in GC. This classification categorizes GC into intestinal, diffuse, or mixed types, according to its histology, and each type has a distinct pathology and prognosis [13, 20–22]. However, several studies have reported that the Lauren classification is not significantly correlated with patient survival because anatomic and corresponding epidemiologic distinctions were not taken into account [23, 24].

Recently, it has been proposed that the Lauren classification be modified to include both the Lauren classification and the anatomical location of GC, thus yielding at least three entirely distinct types, including the proximal non-diffuse type, distal non-diffuse type, and diffuse type [3]. Molecular biology analyses further showed that there were marked differences in the mRNA expression profiles of the three types. Recent studies performed in Asia also suggested that the modified Lauren classification could be a reliable prognostic factor for patients with GC [25, 26].

However, it remains controversial as to which pathological classification is most valuable in predicting the overall survival (OS) in GC patients. Therefore, we aimed to assess the prognostic values of the tumor differentiation grade, Lauren classification, and modified Lauren classification in GC patients. We compared model discriminative ability, model-fitting performance, and net benefits to identify the optimal prognostic pathological classification for GC based on the updated Surveillance, Epidemiology, and End Results (SEER) program. We also developed a novel prognostic nomogram for individually predicting the 3- and 5-year OS by applying the optimal pathological classification.

Patients And Methods

Data source

We included data of eligible primary operable gastric cancer patients from the SEER program (https://seer.cancer.gov/). Data were extracted by SEER*Stat 8.3.6 software (www.seer.cancer.gov/seerstat). The data-use agreement for the SEER program data file was approved. Ethical review was not required because the SEER program is a publicly available database with anonymized data.

Inclusion and exclusion criteria

Patients were included if they met the inclusion criteria as follows: (1) primary carcinoma in the stomach; (2) TNM classification available; (3) no distant metastases (M0 disease); (4) solitary cancer; (5) history of curable surgery; (6) no neoadjuvant radiochemotherapy; (7) postoperative survival longer than one month; (8) aged between 18 and 75 years; (9) histological information available; and (10) defined tumor sites. (Supplementary Fig. 1) Patients were excluded if they met any of the exclusion criteria as follows: (1) metastatic carcinoma in the stomach; (2) TNM classification unavailable; (3) distant metastases (M1); (4) multiple cancers; (5) no history of surgery; (6) preoperative radiotherapy or chemotherapy; (7) postoperative survival shorter than one month; (8) aged < 18 or > 75 years; (9) histological information unavailable; and (10) undefined tumor sites (Supplementary Fig. 1).

Clinicopathologic features

The analyzed clinicopathologic features included gender, age, tumor size, depth of tumor invasion (pT stage), number of retrieved lymph nodes, number of positive lymph nodes (pN stage), tumor differentiation grade, and Lauren classification. Patients were uniformly reviewed and re-staged (pT or pN stage) according to the AJCC 8th Edition TNM classification [4]. The last follow-up was in November 2016. The OS was defined as the time of diagnosis to the time of death from any reason.

Statistical analysis

The OS was calculated from the time of diagnosis to the time of death from any reason. Kaplan–Meier survival curves with log-rank tests were applied to analyze the difference in the OS among the groups. Factors with *P*-values

less than 0.1 in univariate analysis were considered potential prognostic factors and included in the Cox proportional hazards regression model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were applied.

The model discriminative ability of different pathological classifications was assessed by receiver operating characteristic (ROC) curves (AUCs) [27]. The model-fitting performance was evaluated by Akaike information criteria (AIC). A higher AUC value indicated a better model discriminative ability, and a lower AIC value indicated a superior model-fitting performance. The differences in AUC values were assessed by Hanley and McNeil tests [28]. Decision curve analysis (DCA) was performed to assess clinical usefulness, and the net benefits of making a decision based on the models were calculated [29, 30].

The modified Lauren classification is an adjusted categorization of the Lauren classification, and both classifications are considered highly relevant. The Cox proportional hazards regression model was employed by incorporating either the Lauren or modified Lauren classification. Finally, the independent prognostic factors identified by multivariate analysis were applied to the nomogram.

Statistical analyses were performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA), MedCalc 15.2 (Ostend, Belgium), GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA) and R 3.5.6 (http://www.R-project.org/) software packages. All tests were two-sided, and *P*-values less than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 2,718 eligible patients with gastric cancer from the SEER program were included. The clinicopathological characteristics are summarized (Table 1). There were 1,588 males (58.4%) and 1,130 were females (41.6%). The median age of all patients was 61 years (range, 18–75 years), and the median follow-up period was 31 months (range, 2–155 months).

Table 1
Basic characteristics according to the anatomical location using the modified Lauren classification.

Variable	Distal non-diffuse type	Proximal non-diffuse type	Diffuse type
Gender (%)			
Male	416 (63.6)	324 (70.0)	848 (53.0)
Female	238 (36.4)	139 (30.0)	753 (47.0)
Age (%)			
< 60 years	200 (30.6)	167 (36.1)	850 (53.1)
≥ 60 years	454 (69.4)	296 (63.9)	751 (46.9)
Tumor size (%)			
< 4.0 cm	318 (48.6)	218 (47.1)	664 (41.5)
≥ 4.0 cm	310 (47.4)	221 (47.7)	771 (48.2)
Unknown	26 (4.0)	24 (5.2)	166 (10.4)
Retrieved lymph nodes (%)			
Adequate (n ≥ 16)	326 (49.8)	261 (56.4)	831 (51.9)
Inadequate (n < 16)	328 (50.2)	202 (43.6)	770 (48.1)
AJCC 8th pT stage (%)			
pT1	211 (32.3)	123 (26.6)	356 (22.2)
pT2	87 (13.3)	69 (14.9)	173 (10.8)
pT3	207 (31.7)	149 (32.2)	464 (29.0)
pT4a	101 (15.4)	89 (19.2)	480 (30.0)
pT4b	48 (7.3)	33 (7.1)	128 (8.0)
AJCC 8th pN stage (%)			
pN0	302 (46.2)	197 (42.5)	532 (33.2)
pN1	117 (17.9)	79 (17.1)	260 (16.2)
pN2	115 (17.6)	90 (19.4)	302 (18.9)
pN3a	95 (14.5)	70 (15.1)	347 (21.7)
pN3b	25 (3.8)	27 (5.8)	160 (10.0)
Differentiation grade (%)			
Well differentiation	66 (10.1)	26 (5.6)	3 (0.2)
Moderate differentiation	269 (41.1)	170 (36.7)	44 (2.7)
Poorly differentiation	311 (47.6)	259 (55.9)	1484 (92.7)
Undifferentiation	8 (1.2)	8 (1.7)	70 (4.4)

Variable	Distal non-diffuse type	Proximal non-diffuse type	Diffuse type

AJCC, American Joint Committee on Cancer; pN stage, pathological N stage; pT stage, pathological T stage.

Prognostic Factors Of Overall Survival

Univariate analysis identified potential prognostic factors, namely age, tumor size, number of retrieved lymph nodes, pT stage, pN stage, tumor differentiation grade, and the modified Lauren classification (log-rank tests, all $P < 0.10$). These factors were further applied in multivariate analysis with the Cox proportional hazards regression model. The results indicated that the independent prognostic factors predicting OS were age, tumor size, number of retrieved lymph nodes, pT stage, pN stage, and the modified Lauren classification (Table 2). However, neither the tumor differentiation grade ($P = 0.115$) nor the Lauren classification ($P = 0.163$) was found to be an independent predictive factor of OS in further multivariate analysis (Supplementary Table 1).

Table 2
Univariate and multivariable analyses of the prognostic factors of overall survival.

Variable	No. of patients (%)	Univariate analysis		Multivariate analysis	
		5-year OS	*P* value	HR (95% CI)	*P* value
Gender (%)			0.111		
Male	1588 (58.4)	45.9%			
Female	1130 (41.6)	49.1%			
Age (%)			< 0.001		**< 0.001**
< 60 years	1217 (44.8)	50.7%		1 (Ref)	–
≥ 60 years	1501 (55.2)	44.4%		1.157 (1.360–1.692)	< 0.001
Tumor size (%)			< 0.001		**0.001**
≤ 4.0 cm	1200 (44.2)	63.9%		1 (Ref)	–
> 4.0 cm	1302 (47.9)	33.6%		1.179 (1.038–1.339)	0.011
Unknown	216 (7.9)	40.2%		1.457 (1.191–1.782)	< 0.001
Retrieved lymph nodes (%)			0.074		**< 0.001**
Adequate (n ≥ 16)	1418 (52.2)	48.9%		1 (Ref)	–
Inadequate (n < 16)	1300 (47.8)	45.5%		1.550 (1.380–1.740)	< 0.001
AJCC 8th pT stage (%)			< 0.001		**< 0.001**
pT1	690 (25.4)	80.9%		1 (Ref)	–
pT2	329 (12.1)	66.6%		1.535 (1.193–1.975)	0.001
pT3	820 (30.2)	38.5%		2.882 (2.334–3.558)	< 0.001
pT4a	670 (24.7)	23.4%		3.415 (2.740–4.256)	< 0.001
pT4b	209 (7.7)	18.6%		4.452 (3.458–5.732)	< 0.001
AJCC 8th pN stage (%)			< 0.001		**< 0.001**
pN0	1031 (37.9)	71.6%		1 (Ref)	–

Variable	No. of patients (%)	Univariate analysis		Multivariate analysis	
		5-year OS	*P* value	HR (95% CI)	*P* value
pN1	456 (16.8)	46.9%		1.467 (1.225–1.757)	< 0.001
pN2	507 (18.7)	37.5%		1.611 (1.353–1.919)	< 0.001
pN3a	512 (18.8)	24.8%		2.356 (1.976–2.809)	< 0.001
pN3b	212 (7.8)	9.2%		4.138 (3.306–5.181)	< 0.001
Differentiation grade (%)			0.011		0.135
Well differentiation	95 (3.5)	69.4%		1 (Ref)	–
Moderate differentiation	483 (17.8)	58.9%		0.974 (0.649–1.462)	0.898
Poorly differentiation	2054 (75.5)	44.0%		1.123 (0.755–1.670)	0.566
Undifferentiation	86 (3.2)	35.6%		1.415 (0.876–2.285)	0.156
Modified Lauren classification (%)			< 0.001		**0.013**
Distal non-diffuse type	654 (24.1)	58.8%		1 (Ref)	–
Proximal non-diffuse type	463 (17.0)	48.3%		1.230 (1.033–1.466)	0.020
Diffuse type	1601 (58.9)	42.4%		1.246 (1.068–1.452)	0.005

AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; No., number; OS, overall survival; Ref, reference; pN stage, pathological N stage; pT stage, pathological T stage.

Variables with *P* values less than 0.1 were included in the multivariate analysis.

Predictive Performance Evaluations Of Pathological Classifications

We compared the model discriminative ability and model-fitting performance of the tumor differentiation grade, Lauren classification, and modified Lauren classification. The modified Lauren classification showed superior model discriminative ability (3-year OS, AUC, 0.679 vs. 0.666, Hanley and McNeil test, $P = 0.002$; 5-year OS, AUC, 0.702 vs. 0.681, $P < 0.001$) and model-fitting performance (AIC, 25,877 vs. 25,923) over the Lauren classification (Table 3, Fig. 1A and 1B). The modified Lauren classification also showed superior model discriminative ability (3-year OS, AUC, 0.679 vs. 0.626, Hanley and McNeil test, $P < 0.001$; 5-year OS, AUC, 0.702 vs. 0.620, $P < 0.001$) and model-fitting performance (AIC, 25,877 vs. 25,971) over the tumor differentiation grade (Table 3, Fig. 1A and 1B). In addition, the Lauren classification showed superior model discriminative ability (3-year OS, AUC, 0.666 vs. 0.626, Hanley and

McNeil test, $P < 0.001$; 5-year OS, AUC, 0.681 vs. 0.620, $P < 0.001$) and model-fitting performance (AIC, 25,923 vs. 25,971) over the tumor differentiation grade (Table 3, Fig. 1A and 1B, Fig. 2).

Table 3
Comparison of the predictive performances between different pathological classifications and prognostic models.

Pathological classifications/prognostic models	AUC (95% CI)		AIC
	3-year overall survival	5-year overall survival	
Differentiation grade	0.626 (0.608–0.644)	0.620 (0.601–0.638)	25971
Lauren classification	0.666 (0.647–0.683)	0.681 (0.663–0.699)	25923
Modified Lauren classification	0.679 (0.661–0.696)	0.702 (0.685–0.719)	25877
Hanley and McNeil tests for AUCs			
Differentiation grade vs. Lauren	$P < 0.001$	$P < 0.001$	–
Lauren vs. modified Lauren	$P = 0.002$	$P < 0.001$	–
Modified Lauren vs. differentiation grade	$P < 0.001$	$P < 0.001$	–
Novel prognostic model	0.803 (0.786–0.819)	0.804 (0.787–0.820)	20010
Age, tumor size, retrieved lymph nodes, pT stage, pN stage, modified Lauren classification			
Control model	0.776 (0.759–0.793)	0.776 (0.759–0.793)	20144
AJCC 8th pTNM stage (pT stage, pN stage)			

AIC, Akaike's Information Criterion; AJCC, American Joint Committee on Cancer; AUC, Area Under Curve; CI, confidence interval; pN stage, pathological N stage; pT stage, pathological T stage.

A higher AUC indicated better model discrimination and a lower AIC indicates superior model-fitting;

Differentiation grade, well vs. moderate vs. poorly vs. undifferentiation;

Lauren classification, intestinal type vs. diffuse type vs. mixed type;

Modified Lauren classification, distal non-diffuse vs. proximal non-diffuse vs. diffuse type.

The modified Lauren classification also showed superior model discriminative ability (higher AUC values) and model-fitting performance (lower AIC values) in patients that were stratified by gender, age (female, male), tumor size (< 60 years, ≥ 60 years), number of retrieved lymph nodes (< 16, ≥ 16), pT stage (pT1, pT2–4), and pN stage (pN0, pN1–3) (Table 4). These results confirmed that the modified Lauren classification showed the best model discriminative ability and model-fitting performance among the three pathological classifications.

Table 4
Comparisons of the predictive performances between different pathological classifications and stratifications.

Variable	No.	Differentiation grade		Lauren		Modified Lauren		P^1	P^2	P^3
		AIC	AUC, 95% CI	AIC	AUC, 95% CI	AIC	AUC, 95% CI			
Overall	2718	25971	0.624 0.605–0.642	25923	0.677 0.659–0.695	25877	0.698 0.681–0716	< 0.001	< 0.001	< 0.001
Gender										
Female	1130	9744	0.600 0.571–0.629	9701	0.682 0.654–0.709	9684	0.695 0.667–0.722	< 0.001	0.042	< 0.001
Male	1588	13802	0.632 0.608–0.656	13804	0.678 0.655–0.701	13777	0.705 0.682–0.728	0.002	< 0.001	< 0.001
Age, years										
< 60	1217	10744	0.588 0.560–0.616	10738	0.649 0.621–0.676	10725	0.662 0.635–0.689	< 0.001	0.023	< 0.001
≥ 60	1501	12769	0.640 0.615–0.664	12728	0.698 0.674–0.721	12696	0.727 0.703–0.749	< 0.001	< 0.001	< 0.001
Tumor size										
< 4 cm	1200	8841	0.618 0.589–0.645	8823	0.671 0.643–0.697	8807	0.694 0.667–0.720	0.001	< 0.001	< 0.001
≥ 4 cm	1302	12389	0.618 0.591–0.645	12348	0.703 0.678–0.728	12327	0.728 0.703–0.752	< 0.001	0.005	< 0.001
rLNs										
< 16	1300	11158	0.616 0.589–0.642	11142	0.663 0.636–0.688	11114	0.688 0.662–0.713	0.004	< 0.001	< 0.001
≥ 16	1418	12347	0.624 0.598–0.649	12324	0.698 0.674–0.722	12307	0.716 0.692–0.739	< 0.001	0.014	< 0.001

Variable	No.	Differentiation grade		Lauren		Modified Lauren		P^1	P^2	P^3
		AIC	AUC, 95% CI	AIC	AUC, 95% CI	AIC	AUC, 95% CI			
pT stage										
pT1	690	3593	0.616 0.578–0.652	3580	0.661 0.624–0.696	3560	0.691 0.655–0.725	0.022	< 0.001	< 0.001
pT2-4	2028	20623	0.605 0.583–0.626	20574	0.689 0.668–0.709	20551	0.709 0.689–0.729	< 0.001	0.002	< 0.001
pN stage										
pN0	1031	6393	0.616 0.585–0.646	6366	0.665 0.635–0.694	6325	0.700 0.671–0.728	0.002	< 0.001	< 0.001
pN1-3	1687	17323	0.587 0.563–0.610	17281	0.685 0.662–0.707	17269	0.702 0.680–0.724	< 0.001	0.019	< 0.001

AIC, Akaike's Information Criterion; AUC, Area Under Curve; CI, confidence interval; No., number of patients;

pN stage, pathological N stage; pT stage, pathological T stage; rLNs, number of retrieved lymph nodes; y, years;

A higher AUC indicated better model discrimination and a lower AIC indicates superior model-fitting.

[1]Hanley and McNeil test comparing AUCs of differentiation grade versus Lauren classification;

[2]Hanley and McNeil test comparing AUCs of Lauren classification vs. modified Lauren classification;

[3]Hanley and McNeil test comparing AUCs of modified Lauren classification vs. differentiation grade.

Clinical Utility Of Pathological Classifications

We conducted decision curve analysis (DCA) to assess the clinical utility of the different pathological classifications. The results revealed that the modified Lauren classification had superior net benefits over the Lauren classification and tumor differentiation grade in predicting both 3- and 5-year OS (Fig. 1C and 1D). Specifically, the modified Lauren classification showed superior net benefits over the tumor differentiation grade between threshold probabilities of 50–65% and 40–80% in predicting 3- and 5-year OS, respectively (Fig. 1C and 1D). In addition, the modified Lauren classification also showed superior net benefits over the Lauren classification between threshold probabilities of 30–45% and 40–60% in predicting 3- and 5-year OS, respectively (Fig. 1C and 1D).

Novel prognostic nomogram model versus AJCC 8th Edition TNM classification

We further developed a novel prognostic model of age, tumor size, number of retrieved lymph nodes, pT stage, pN stage, and the modified Lauren classification by multivariate analysis using the Cox proportional hazards regression model. A novel nomogram individually predicting 3- and 5-year OS was established by applying significant prognostic factors, including age, tumor size, number of retrieved lymph nodes, pT stage, pN stage, and the modified Lauren classification (Fig. 3A).

This novel prognostic model showed superior model discriminative ability (3-year OS, AUC, 0.803 vs. 0.776, Hanley and McNeil test; 5-year OS, AUC, 0.804 vs. 0.776) and model-fitting performance (AIC, 20,010 vs. 20,144) over the AJCC 8th Edition TNM classification (pT stage, pN stage) (Table 3, Fig. 2C-2D, Fig. 3B).

We further conducted DCA to assess the clinical utility of the novel prognostic model and the AJCC 8th Edition TNM classification. The novel prognostic model showed superior net benefits over the AJCC 8th Edition TNM classification between threshold probabilities of 40–90% and 50–95% in predicting 3- and 5-year OS, respectively (Fig. 1E and 1F).

Discussion

Several pathological classifications of GC are currently in use due to the various morphological characteristics of GC [3, 9–13]. However, it remains controversial as to which classification is best. Therefore, we performed a systematic analysis of the three most well-known pathological classifications and compared prognostic predictive performance with clinical use. In addition to the commonly used Lauren classification and tumor differentiation grade, we also compared a new classification, the modified Lauren classification. In our study, pN and pT stages were the most important prognostic factors for survival, thus validating the quality of the participants.

Tumor differentiation grades are commonly used for GC, and the four types of GC are defined as well differentiated, moderately differentiated, poorly differentiated, and undifferentiated [31]. It has been widely accepted that poorly differentiated tumors usually spread more extensively than well differentiated tumors by the time of surgery, and patients with more differentiated tumors have obvious survival advantages after curative resection [14, 15]. However, recent studies have reported that the tumor differentiation grade is not significantly associated with the prognosis of patients with GC [16–19]. In the current study, the tumor differentiation grade was significantly associated with the prognosis in log-rank tests; however, it was not an independent prognostic factor of OS. This discrepancy may be due to the mixture of differentiated and undifferentiated GC histologies [18, 32]. In addition, it suggests that some well-differentiated types of GC can change to poorly differentiated types with tumor progression [33, 34]. Therefore, further studies are needed to understand the significance of the tumor differentiation grade of GC.

The Lauren classification of GC is one of the most widely applied histological grading systems in predicting survival [21]. It has been reported that Lauren-classified tumor subtypes can respond differently to chemotherapy, thus yielding different survival outcomes [20]. However, the Lauren classification has also been demonstrated to have inadequate prognostic discriminative performance, and therefore, its prognostic accuracy remains controversial [23, 24]. Specific pathogenetic and morphologic features of intestinal and diffuse types may underlie their different behaviors [22]. Population-based studies have reported the different epidemiological features of Lauren-classified subtypes and cancer of the cardia [35, 36]. Epidemiologically, the intestinal type of GC, particularly that of the antrum, is often strongly associated with chronic inflammation as a consequence of chronic infection with *H. pylori* [37, 38]. Anatomically, proximal GC can be classified as a third type of GC for which inflammation of a different type may be the driving force for carcinogenesis [39]. Furthermore, the anatomical location of GC is clinically relevant, and proximal third GC is associated with a worse prognosis than middle or distal third GC [40, 41].

Therefore, a location-modified Lauren classification has been proposed. It defines the subtypes of GC by incorporating epidemiological and histopathological data together with the anatomical location.[3] Several studies have revealed that the modified Lauren classification has better discriminative ability and monotonicity than the Lauren classification [25, 26]. The results of the current study demonstrated that the modified Lauren classification showed superior model discriminative ability, model-fitting performance, and net benefits compared with other classifications. Similar findings were also obtained in populations stratified by gender, age, tumor size, number of retrieved lymph nodes, pT stage, and pN stage. Decision curve analysis confirmed its clinical usefulness over other classifications.

It remains unclear why the modified Lauren classification showed a significantly better prognostic performance. A previous study has reported that the Kirsten Rat Sarcoma Viral Oncogene Homolog pathway was downregulated in proximal non-diffuse gastric cancer compared with diffuse gastric cancer [42]. In addition, genomic analysis has confirmed that the modified Lauren classification can achieve a clear molecular distinction [3]. Moreover, HER2 amplification or overexpression is not uniform across different GC subtypes; it is most prevalent in proximal GC (a HER2 positivity rate of ~ 30%) and least prevalent in diffuse GC (a HER2 positivity rate of ~ 5%) [43]. Furthermore, whole-genome sequencing of diffuse GC uncovered mutations in *RHOA*, a gene encoding a well-studied small GTPase, in 15–25% of diffuse tumors but not in non-diffuse tumors [44].

Nomograms are visualization tools for individually predicting survival [45, 46] with improved predictive accuracy and comprehensive outcomes for many types of cancers [47–52]. Therefore, we developed a novel prognostic nomogram of age, tumor size, number of retrieved lymph nodes, pT stage, pN stage, and the modified Lauren classification. This novel prognostic model achieved superior model discriminative ability, model-fitting performance, and net benefits over the AJCC 8th Edition TNM classification. These findings support the consideration of more factors spanning different aspects of the disease as the most promising approach to improve the clinical management of GC. However, the findings of the current study still need to be interpreted with caution because specific intervention factors of the surgical procedures, chemo-radiotherapeutic regimens, and drug doses were not applied in the current study.

Conclusion

In summary, the modified Lauren classification provides superior model discriminative ability, model-fitting performance, and net benefits over the tumor differentiation grade and Lauren classification. It also shows good applicability in various clinical settings. The novel prognostic nomogram incorporating the modified Lauren classification showed good model discriminative ability, model-fitting performance, and net benefits. However, the findings of the current study require further validation.

Abbreviations

AIC, Akaike's information criterion; AJCC, American Joint Committee on Cancer; AUC, area under curve; CI, confidence interval; DCA, Decision curve analysis; GC, gastric cancer; HR, hazard ratio; OS, overall survival; OR, Odds ratio; pN stage, pathological N stage; pT stage, pathological T stage; ROC, receiver operating characteristic; SEER, Surveillance, Epidemiology, and End Results; TNM, tumor/node/metastasis

Declarations

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Ethics approval and consent to participate

SEER is a publicly available database with anonymized data, no ethical review was required.

Consent for publication

Not applicable. SEER is a publicly available database with anonymized data.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the SEER database.

Competing interests

All authors declare no potential conflicts of interest.

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Tables

Table 1 Basic characteristics according to the anatomical location using the modified Lauren classification.

Variable	Distal non-diffuse type	Proximal non-diffuse type	Diffuse type
Gender (%)			
Male	416 (63.6)	324 (70.0)	848 (53.0)
Female	238 (36.4)	139 (30.0)	753 (47.0)
Age (%)			
< 60 years	200 (30.6)	167 (36.1)	850 (53.1)
≥ 60 years	454 (69.4)	296 (63.9)	751 (46.9)
Tumor size (%)			
< 4.0 cm	318 (48.6)	218 (47.1)	664 (41.5)
≥ 4.0 cm	310 (47.4)	221 (47.7)	771 (48.2)
Unknown	26 (4.0)	24 (5.2)	166 (10.4)
Retrieved lymph nodes (%)			
Adequate (n ≥16)	326 (49.8)	261 (56.4)	831 (51.9)
Inadequate (n <16)	328 (50.2)	202 (43.6)	770 (48.1)
AJCC 8^{th} pT stage (%)			
pT1	211 (32.3)	123 (26.6)	356 (22.2)
pT2	87 (13.3)	69 (14.9)	173 (10.8)
pT3	207 (31.7)	149 (32.2)	464 (29.0)
pT4a	101 (15.4)	89 (19.2)	480 (30.0)
pT4b	48 (7.3)	33 (7.1)	128 (8.0)
AJCC 8^{th} pN stage (%)			
pN0	302 (46.2)	197 (42.5)	532 (33.2)
pN1	117 (17.9)	79 (17.1)	260 (16.2)
pN2	115 (17.6)	90 (19.4)	302 (18.9)
pN3a	95 (14.5)	70 (15.1)	347 (21.7)
pN3b	25 (3.8)	27 (5.8)	160 (10.0)
Differentiation grade (%)			
Well differentiation	66 (10.1)	26 (5.6)	3 (0.2)
Moderate differentiation	269 (41.1)	170 (36.7)	44 (2.7)
Poorly differentiation	311 (47.6)	259 (55.9)	1484 (92.7)
Undifferentiation	8 (1.2)	8 (1.7)	70 (4.4)

AJCC, American Joint Committee on Cancer; pN stage, pathological N stage; pT stage, pathological T stage.

Table 2 Univariate and multivariable analyses of the prognostic factors of overall survival.

Variable	No. of patients (%)	Univariate analysis		Multivariate analysis	
		5-year OS	*P* value	HR (95% CI)	*P* value
Gender (%)			0.111		
Male	1588 (58.4)	45.9%			
Female	1130 (41.6)	49.1%			
Age (%)			<0.001		**<0.001**
< 60 years	1217 (44.8)	50.7%		1 (Ref)	–
≥ 60 years	1501 (55.2)	44.4%		1.157 (1.360–1.692)	<0.001
Tumor size (%)			<0.001		**0.001**
≤ 4.0 cm	1200 (44.2)	63.9%		1 (Ref)	–
> 4.0 cm	1302 (47.9)	33.6%		1.179 (1.038–1.339)	0.011
Unknown	216 (7.9)	40.2%		1.457 (1.191–1.782)	<0.001
Retrieved lymph nodes (%)			0.074		**<0.001**
Adequate (n ≥16)	1418 (52.2)	48.9%		1 (Ref)	–
Inadequate (n <16)	1300 (47.8)	45.5%		1.550 (1.380–1.740)	<0.001
AJCC 8th pT stage (%)			<0.001		**<0.001**
pT1	690 (25.4)	80.9%		1 (Ref)	–
pT2	329 (12.1)	66.6%		1.535 (1.193–1.975)	0.001
pT3	820 (30.2)	38.5%		2.882 (2.334–3.558)	<0.001
pT4a	670 (24.7)	23.4%		3.415 (2.740–4.256)	<0.001
pT4b	209 (7.7)	18.6%		4.452 (3.458–5.732)	<0.001
AJCC 8th pN stage (%)			<0.001		**<0.001**
pN0	1031 (37.9)	71.6%		1 (Ref)	–
pN1	456 (16.8)	46.9%		1.467 (1.225–1.757)	<0.001
pN2	507 (18.7)	37.5%		1.611 (1.353–1.919)	<0.001
pN3a	512 (18.8)	24.8%		2.356 (1.976–2.809)	<0.001
pN3b	212 (7.8)	9.2%		4.138 (3.306–5.181)	<0.001
Differentiation grade (%)			0.011		0.135
Well differentiation	95 (3.5)	69.4%		1 (Ref)	–
Moderate differentiation	483 (17.8)	58.9%		0.974 (0.649–1.462)	0.898
Poorly differentiation	2054 (75.5)	44.0%		1.123 (0.755–1.670)	0.566
Undifferentiation	86 (3.2)	35.6%		1.415 (0.876–2.285)	0.156
Modified Lauren classification (%)			<0.001		**0.013**
Distal non-diffuse type	654 (24.1)	58.8%		1 (Ref)	–
Proximal non-diffuse type	463 (17.0)	48.3%		1.230 (1.033–1.466)	0.020
Diffuse type	1601 (58.9)	42.4%		1.246 (1.068–1.452)	0.005

AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; No., number; OS, overall survival; Ref, reference; pN stage, pathological N stage; pT stage, pathological T stage.
Variables with *P* values less than 0.1 were included in the multivariate analysis.

Table 3 Comparison of the predictive performances between different pathological classifications and prognostic models.

Pathological classifications/prognostic models	AUC (95% CI)		AIC
	3-year overall survival	5-year overall survival	
Differentiation grade	0.626 (0.608–0.644)	0.620 (0.601–0.638)	25971
Lauren classification	0.666 (0.647–0.683)	0.681 (0.663–0.699)	25923
Modified Lauren classification	0.679 (0.661–0.696)	0.702 (0.685–0.719)	25877
Hanley and McNeil tests for AUCs			
Differentiation grade vs. Lauren	$P<0.001$	$P<0.001$	–
Lauren vs. modified Lauren	$P=0.002$	$P<0.001$	–
Modified Lauren vs. differentiation grade	$P<0.001$	$P<0.001$	–
Novel prognostic model	0.803 (0.786–0.819)	0.804 (0.787–0.820)	20010
Age, tumor size, retrieved lymph nodes, pT stage, pN stage, modified Lauren classification			
Control model	0.776 (0.759–0.793)	0.776 (0.759–0.793)	20144
AJCC 8th pTNM stage (pT stage, pN stage)			

AIC, Akaike's Information Criterion; AJCC, American Joint Committee on Cancer; AUC, Area Under Curve; CI, confidence interval; pN stage, pathological N stage; pT stage, pathological T stage.
A higher AUC indicated better model discrimination and a lower AIC indicates superior model-fitting;
Differentiation grade, well vs. moderate vs. poorly vs. undifferentiation;
Lauren classification, intestinal type vs. diffuse type vs. mixed type;
Modified Lauren classification, distal non-diffuse vs. proximal non-diffuse vs. diffuse type.

Table 4 Comparisons of the predictive performances between different pathological classifications and stratifications.

Variable	No.	Differentiation grade		Lauren		Modified Lauren		P^1	P^2	P^3
		AIC	AUC, 95% CI	AIC	AUC, 95% CI	AIC	AUC, 95% CI			
Overall	2718	25971	0.624 0.605–0.642	25923	0.677 0.659–0.695	25877	0.698 0.681–0716	<0.001	<0.001	<0.001
Gender										
Female	1130	9744	0.600 0.571–0.629	9701	0.682 0.654–0.709	9684	0.695 0.667–0.722	<0.001	0.042	<0.001
Male	1588	13802	0.632 0.608–0.656	13804	0.678 0.655–0.701	13777	0.705 0.682–0.728	0.002	<0.001	<0.001
Age, years										
<60	1217	10744	0.588 0.560–0.616	10738	0.649 0.621–0.676	10725	0.662 0.635–0.689	<0.001	0.023	<0.001
≥60	1501	12769	0.640 0.615–0.664	12728	0.698 0.674–0.721	12696	0.727 0.703–0.749	<0.001	<0.001	<0.001
Tumor size										
<4 cm	1200	8841	0.618 0.589–0.645	8823	0.671 0.643–0.697	8807	0.694 0.667–0.720	0.001	<0.001	<0.001
≥4 cm	1302	12389	0.618 0.591–0.645	12348	0.703 0.678–0.728	12327	0.728 0.703–0.752	<0.001	0.005	<0.001
rLNs										
<16	1300	11158	0.616 0.589–0.642	11142	0.663 0.636–0.688	11114	0.688 0.662–0.713	0.004	<0.001	<0.001
≥16	1418	12347	0.624 0.598–0.649	12324	0.698 0.674–0.722	12307	0.716 0.692–0.739	<0.001	0.014	<0.001
pT stage										
pT1	690	3593	0.616 0.578–0.652	3580	0.661 0.624–0.696	3560	0.691 0.655–0.725	0.022	<0.001	<0.001
pT2-4	2028	20623	0.605 0.583–0.626	20574	0.689 0.668–0.709	20551	0.709 0.689–0.729	<0.001	0.002	<0.001
pN stage										
pN0	1031	6393	0.616 0.585–0.646	6366	0.665 0.635–0.694	6325	0.700 0.671–0.728	0.002	<0.001	<0.001
pN1-3	1687	17323	0.587 0.563–0.610	17281	0.685 0.662–0.707	17269	0.702 0.680–0.724	<0.001	0.019	<0.001

AIC, Akaike's Information Criterion; AUC, Area Under Curve; CI, confidence interval; No., number of patients; pN stage, pathological N stage; pT stage, pathological T stage; rLNs, number of retrieved lymph nodes; y, years; A higher AUC indicated better model discrimination and a lower AIC indicates superior model-fitting.

[1]Hanley and McNeil test comparing AUCs of differentiation grade versus Lauren classification;

[2]Hanley and McNeil test comparing AUCs of Lauren classification vs. modified Lauren classification;

[3]Hanley and McNeil test comparing AUCs of modified Lauren classification vs. differentiation grade.

Figures

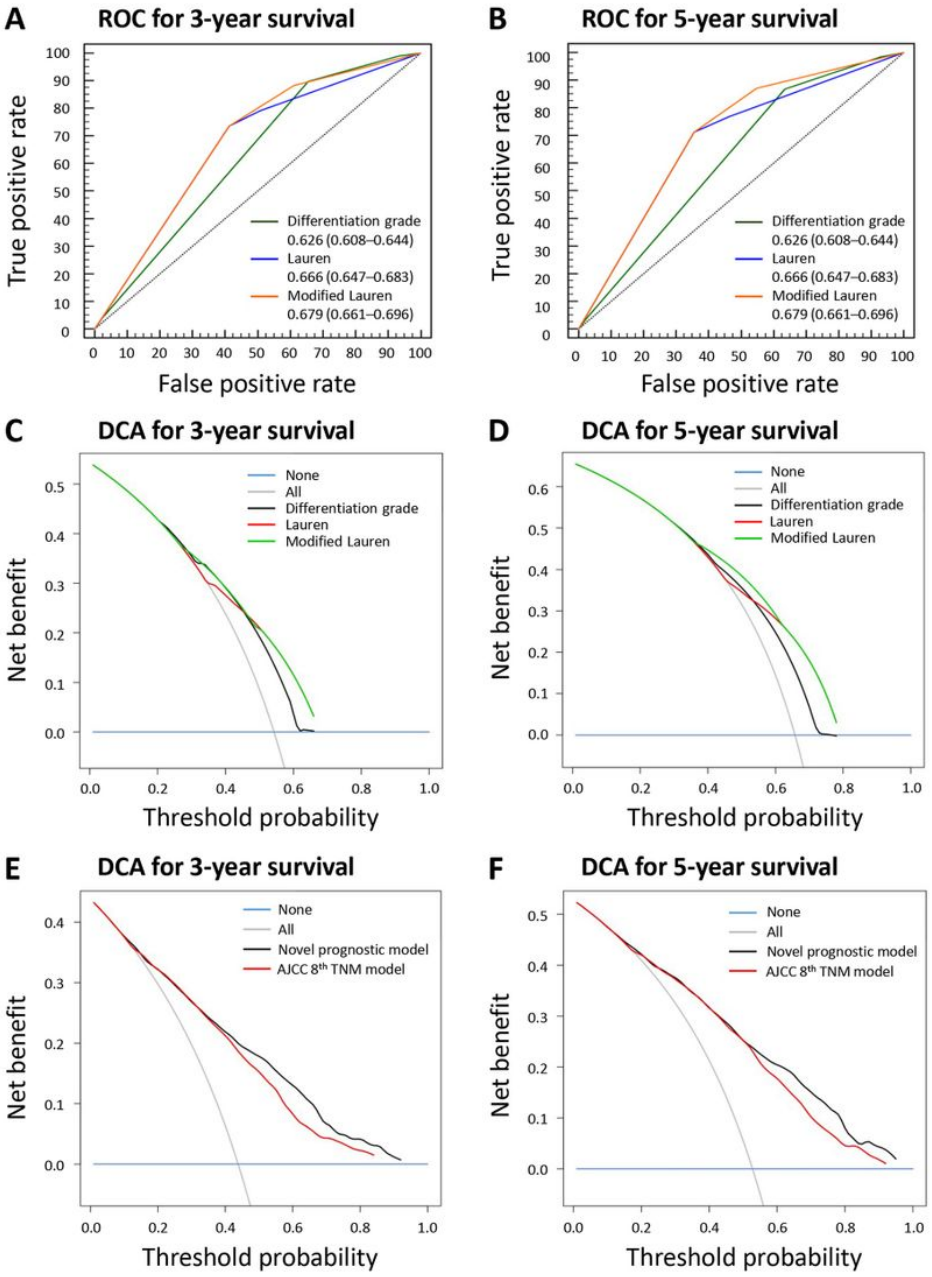

Figure 1

Receiver operating characteristics (ROCs) to compare the discriminative ability, and decision curve analysis (DCA) to assess clinical usefulness. (A) ROCs of different pathological classifications for 3-year overall survival (OS); (B) ROCs of different pathological classifications for 5-year OS; (C) DCA of different pathological classifications for 3-year OS; (D) DCA of different pathological classifications for 5-year OS; (E) DCA of different models for 3-year OS; and (F) DCA of different models for 5-year OS.

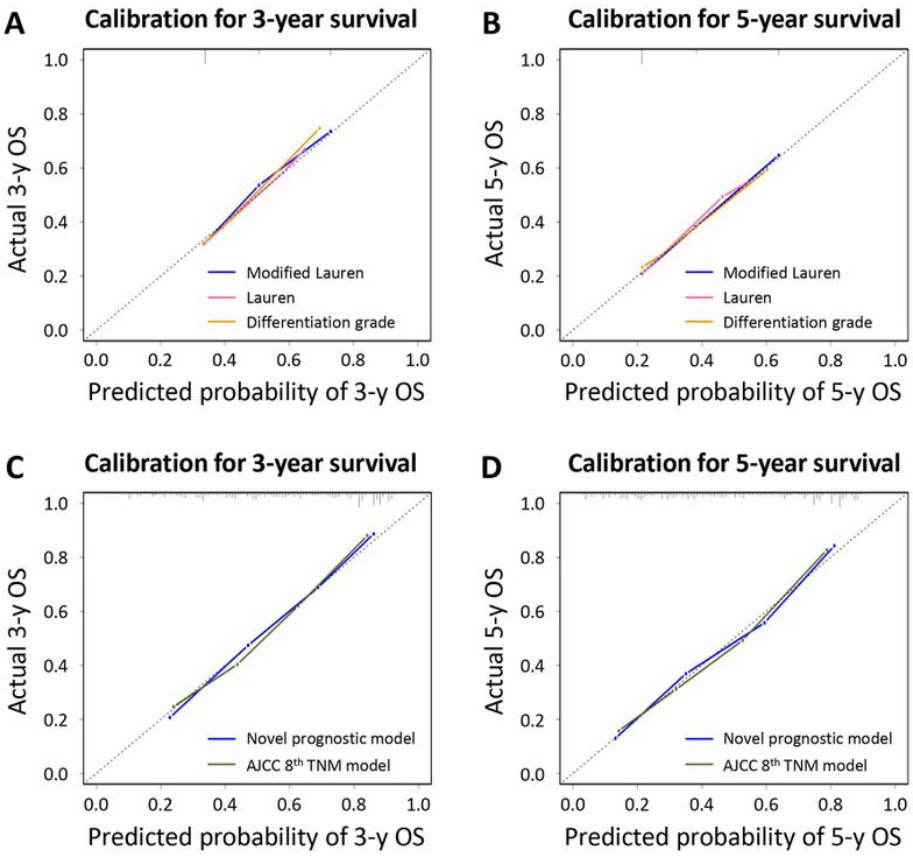

Figure 2

The calibration curve for predicting overall survival (OS). (A) Three-year OS for different pathological classifications; (B) Five-year OS for different pathological classifications; (C) Three-year OS in different prognostic models; and (D) Five-year OS in different prognostic models.

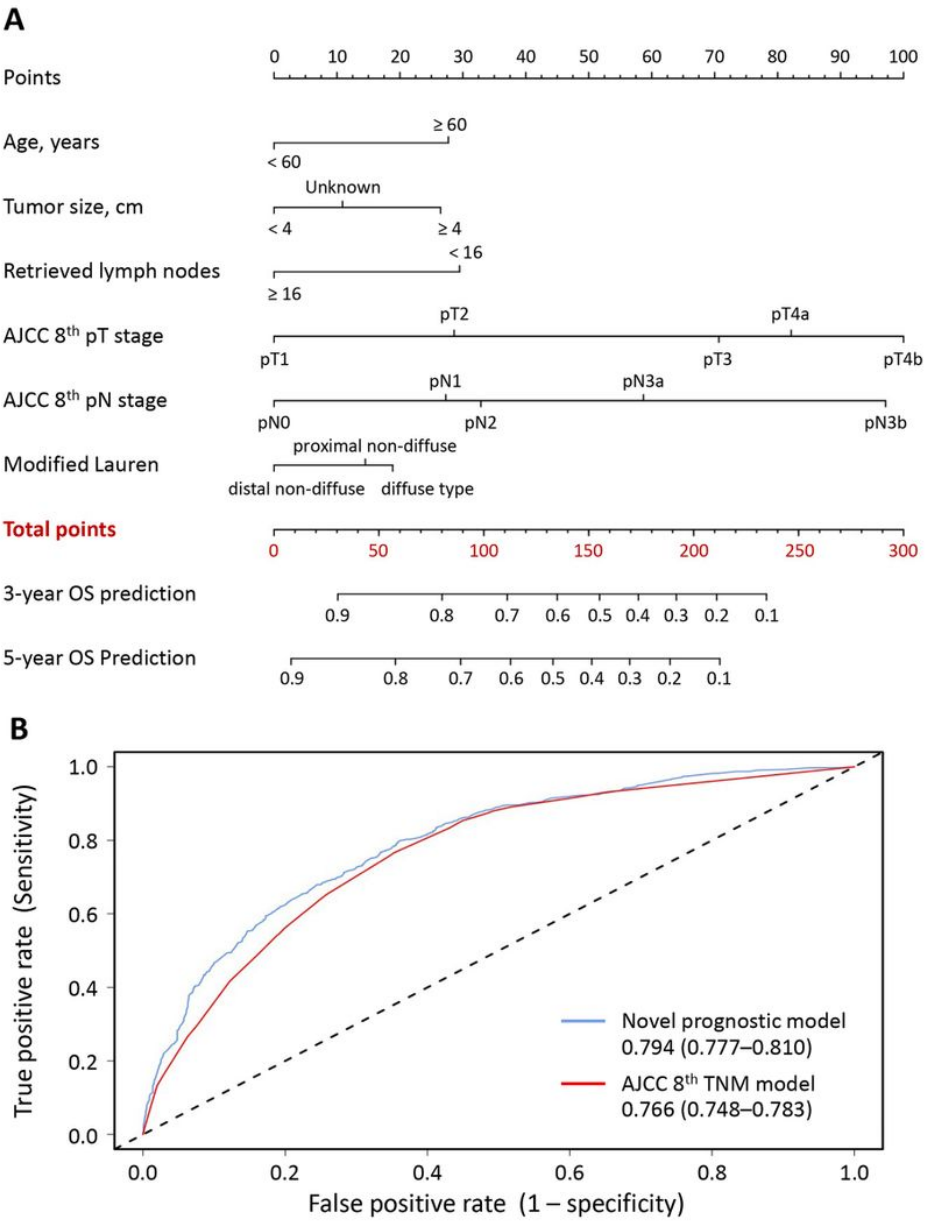

Figure 3

(A) A novel prognostic nomogram in predicting 3- and 5-year overall survivals; (B) Receiver operating characteristics (ROCs) to compare the discriminative ability of the novel prognostic nomogram with the American Joint Committee on Cancer (AJCC) 8th Edition TNM classification.

Supplementary Files

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