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Contents

ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

ORIGINAL ARTICLE

Retrospective Study

Prognostic value of modified Lauren classification in gastric cancer

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Abstract

BACKGROUND

It remains controversial as to which pathological classification is most valuable in predicting the overall survival (OS) of patients with gastric cancer (GC).

AIM

To assess the prognostic performances of three pathological classifications in GC

and develop a novel prognostic nomogram for 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 2718 eligible GC patients were identified. The modified Lauren classification was identified as one of the independent prognostic factors for 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 8th edition tumor-node-metastasis classification.

CONCLUSION

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

Key Words: Gastric cancer; Pathological classification; Prognostic model; Tumor-node-metastasis classification; Survival outcome

Core Tip: In this study, we compared the prognostic performances among the modified Lauren classification, the Lauren classification, and tumor differentiation grade. The modified Lauren classification was identified as one of the independent prognostic factors for overall survival. It showed superior model discriminative ability, model-fitting performance, and net benefits over the other classifications. We further developed a novel prognostic nomogram of individually predicting overall survival by incorporating the modified Lauren classification.

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]. Despite dating back to 1965, it remains one of the most commonly used pathological classifications in GC. This classification categorizes GC into intestinal, diffuse, and 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, namely, 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 value 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.

MATERIALS AND METHODS

Data source
We included data of eligible primary operable GC patients from the SEER program (https://seer.cancer.gov/). Data were extracted with SEER*Stat 8.3.6 software (www.seer.cancer.gov/seerstat). The data-use agreement for the SEER program data file was approved. This study was approved by the Institutional Review Boards of The Fourth Affiliated Hospital of China Medical University (EC-2021-KS-047).

Inclusion and exclusion criteria
Patients were included if they met the inclusion criteria as follows: (1) Primary carcinoma of 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. Patients were excluded if they met any of the exclusion criteria as follows: (1) Metastatic carcinoma of 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 1 mo; (8) aged < 18 or > 75 years; (9) histological information unavailable; and (10) undefined tumor sites.

Clinicopathologic features
The analyzed clinicopathologic features were 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.

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 with 95%CIs were applied.

The model discriminative ability of different pathological classifications was assessed by areas under the receiver operating characteristic curves (AUC)[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 DeLong test[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, United States), MedCalc 15.2 (Ostend, Belgium), GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, United States), 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 2718 eligible patients with GC from the SEER program were included. The clinicopathological characteristics are summarized in Table 1. There were 1588 males (58.4%) and 1130 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 mo (range, 2–155 mo).

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, $P < 0.10$). 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 for OS in further multivariate analysis (Supplementary Table 1).

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, Delong test, $P < 0.001$; 5-year OS, AUC, 0.702 *vs* 0.681, $P < 0.001$) and model-fitting performance (AIC, 25877 *vs* 25923) over the Lauren classification (Table 3, Supplementary Figure 1A and B). The modified Lauren classification also showed superior model discriminative ability (3-year OS, AUC, 0.679 *vs* 0.626, DeLong test, $P < 0.001$; 5-year OS, AUC, 0.702 *vs* 0.621, $P < 0.001$) and model-fitting performance (AIC, 25877 *vs* 25971) over the tumor differentiation grade (Table 3, Supplementary Figure 1A and B). In addition, the Lauren classification showed superior model discriminative ability (3-year OS, AUC, 0.666 *vs* 0.626, DeLong test, $P < 0.001$; 5-year OS, AUC, 0.681 *vs* 0.621, $P < 0.001$) and model-fitting performance (AIC, 25923 *vs* 25971) over the tumor differentiation grade (Table 3, Supplementary Figure 1A and B, Supplementary Figure 2).

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 (female, male), age (< 60 years, ≥ 60 years),

Table 1 Basic characteristics according to 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 yr	200 (30.6)	167 (36.1)	850 (53.1)
≥ 60 yr	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)
Poor 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.

tumor size (< 4.0 cm, ≥ 4.0 cm, unknown), number of retrieved lymph nodes (< 16, ≥ 16), pT stage (pT1, pT2–4), and pN stage (pN0, pN1–3). These results confirmed that the modified Lauren classification showed the best model discriminative ability and model-fitting performance among the three pathological classifications.

Clinical utility of pathological classifications

We conducted 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 (Supplementary Figure 1C and D). 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 (Supplementary Figure 1C and D). In addition, the modified Lauren

Table 2 Univariate and multivariable analyses of prognostic factors for overall survival

Variable	No. of patients (%)	Univariate analysis		Multivariate analysis	
		5-yr 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 yr	1217 (44.8)	50.7%		1 (Ref)	–
≥ 60 yr	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
Poor 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; HR: Hazard ratio; OS: Overall survival; pN stage: Pathological N stage; pT stage: Pathological T stage. Variables with *P* values less than 0.1 were included in the multivariate analysis.

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 (Supplementary Figure 1C and D).

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

Pathological classification/prognostic model	AUC (95%CI)		AIC
	3-yr overall survival	5-yr overall survival	
Differentiation grade	0.626 (0.608–0.644)	0.621 (0.602–0.639)	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
DeLong tests for AUCs			
Differentiation grade *vs* Lauren	*P* < 0.001	*P* < 0.001	–
Lauren *vs* modified Lauren	*P* < 0.001	*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; pN stage: Pathological N stage; pT stage: Pathological T stage. A higher area under the curve indicated better model discrimination and a lower Akaike's Information Criterion indicates superior model-fitting; Differentiation grade, well *vs* moderate *vs* poor *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.

Novel prognostic nomogram model vs 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 for 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 (Supplementary Figure 3A).

This novel prognostic model showed superior model discriminative ability (3-year OS, AUC, 0.803 *vs* 0.776, DeLong test; 5-year OS, AUC, 0.804 *vs* 0.776) and model-fitting performance (AIC, 20010 *vs* 20144) over the AJCC 8th edition TNM classification (pT stage, pN stage) (Table 3, Supplementary Figure 2C and D, Supplementary Figure 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 (Supplementary Figure 1E and F).

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 for 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 *Helicobacter 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 GC compared with diffuse GC[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 (HER2 positivity rate, approximately 30%) and least prevalent in diffuse GC (HER2 positivity rate, approximately 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]. 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 shows good model discriminative ability, model-fitting performance, and net benefits. However, the findings of the current study require further validation.

ARTICLE HIGHLIGHTS

Research background

It remains controversial as to which pathological classification is most valuable in predicting overall survival (OS) in patients with gastric cancer (GC).

Research motivation

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, namely, the proximal non-diffuse type, distal non-diffuse type, and diffuse type.

Research objectives

To assess the prognostic performances of three pathological classifications in GC and develop a novel prognostic nomogram for individually predicting OS.

Research methods

We retrospectively reviewed and analyzed the data identified from the Surveillance, Epidemiology, and End Results program.

Research results

A total of 2718 eligible GC patients were identified. The modified Lauren classification was identified as one of the independent prognostic factors for 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 8th edition tumor-node-metastasis classification.

Research conclusions

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

Research perspectives

A large prospective study is needed to validate our findings.

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