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ORIGINAL RESEARCH

Prognostic Score System Using Preoperative Inflammatory, Nutritional and Tumor Markers to Predict Prognosis for Gastric Cancer: A Two-Center Cohort Study

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ABSTRACT

Introduction: Gastric cancer (GC) is the fourth leading cause of cancer-related death worldwide. Our study aimed to investigate the prognostic value of preoperative inflammatory, nutritional and tumor markers and develop an effective prognostic score system to predict the prognosis of GC patients.
Methods: We retrospectively analyzed 1587 consecutive GC patients who received curative gastrectomy from two medical centers. A novel prognostic score system was proposed based on independently preoperative markers associated with overall survival (OS) of GC patients. A nomogram based on prognostic score system was further established and validated internally and externally.
Results: Based on multivariate analysis in the training set, a novel BLC (body mass index-lymphocyte-carbohydrate antigen 19-9) score system was proposed, which showed an effective predictability of OS in GC patients (log-rank $P < 0.001$). Moreover, receiver-operating characteristic (ROC) analysis showed that BLC had better performance in predicting OS than the traditional prognostic markers. The C-index of the BLC based-nomogram was 0.710 (95% CI 0.686–0.734), and the areas under ROC curves for predicting 3- and 5-year OS were 0.781 (95% CI 0.750–0.813) and 0.755 (95% CI 0.723–0.786), respectively, which were higher than those of tumor node metastasis (TNM) staging system alone. The calibration curve for probability of 3- and 5-year OS rate showed a good fitting effect between prediction by nomogram and actual observation. Verification in the internal and external validation sets showed results consistent with those in the training set.
Conclusions: The BLC combining inflammatory, nutritional and tumor markers was an independent prognostic predictor for GC patients, and the nomogram based on BLC could accurately predict the personalized survival of patients with GC.

Keywords: Gastric cancer; Nomogram; Overall survival; Prognostic score system

Huayang Pang, Weihan Zhang, Xianwen Liang are Co-first authors.

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Key Summary Points

Why carry out this study?

Gastric cancer (GC) is a common malignancy in the world, with a low 5-year overall survival (OS) rate.

We developed and validated a novel prognostic score system using preoperative inflammatory, nutritional and tumor markers to provide additional prognostic information that would complement the current tumor node metastasis (TNM) staging system.

What was learned from this study?

Through rigorous variable selection from 15 available preoperative inflammatory, nutritional and tumor markers, three significantly independent prognostic factors including body mass index, lymphocyte and carbohydrate antigen 19-9 were included in the prognostic score system, named body mass index-lym- 28 phocyte-carbohydrate antigen 19-9 (BLC).

In the training set, the BLC score system showed an effective prognostic predictability ($P < 0.001$), whose predictive value was further verified in the internal and external validation sets (both P values < 0.001). Moreover, compared with other inflammation/nutrition-based markers, receiver-operating characteristic (ROC) analysis showed that BLC had better performance in predicting OS in the training and internal validation sets.

A nomogram based on BLC was further constructed. In the training set, the nomogram had a C-index of 0.710 and the areas under ROC curves for predicting 3- and 5-year OS of 0.781 and 0.755, respectively, which were higher than these of TNM staging system alone. The calibration curve showed a good fitting effect between prediction by nomogram and actual observation. Verification in the internal and external validation sets showed results consistent with those in the training set.

INTRODUCTION

Gastric cancer (GC) remains one of the most common causes of cancer-related death worldwide, especially in East Asia [1]. Advances in perioperative chemotherapy and the surgery-based comprehensive treatment modalities have led to favorable outcomes for GC patients [2]. However, owing to recurrence and metastasis, the 5-year survival rate of GC patients remains unsatisfactory [2]. At present, the TNM staging system has been widely used to predict the prognosis of GC patients, but this system has some limitations, such as the fact that some patients with the equivalent stage may have completely different survival [3]. Therefore, identifying new additional prognostic and predictive markers may facilitate identifying high-risk patients, increase the prognostic predictability and offer a therapeutic strategy.

It is now recognized that cancer-associated inflammation and malnutrition status are very common in most patients with malignancy, which play an important role in tumor progression and prognosis [4–6]. Also, it is interesting that several scoring systems deriving from hematologic or biochemical tests have been reported to be independently associated with prognosis of cancer patients, such as the neutrophil-to-lymphocyte ratio (NLR) [7, 8], platelet-to-lymphocyte ratio (PLR) [9], fibrinogen-to-albumin ratio (FAR) [10] and systemic immune-inflammation index (SII) [11]. Furthermore, several classic tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and CA 125 are routinely used in the diagnosis, and postoperative surveillance of GC [12, 13]. Our previous study also illustrated that these tumor markers were useful for predicting prognosis of GC patients, consistent with studies reported by others [14].

These markers are promising as useful prognostic predictors in clinical practice because they are inexpensive and easy to access. However, most previous studies have only assessed the effects of one or two of these dimensions on the long-term outcomes of patients [15–17]. Thus, we considered that the combined effect of

inflammation, nutrition and tumor markers could better reflect the global patient-related status and provide a more comprehensive prognostic information than individual parameters.

The present study was designed to establish a novel prognostic score system by systematically integrating preoperative inflammatory, nutritional and tumor markers, which give rise to a comprehensive and applicable prognostic indication for GC patients. The related test markers were carefully selected from the previous reported studies.

METHODS

Ethics Statement

This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of West China Hospital. The ethical approval number was WCH SGCPR-2021-04. Medical records were anonymized and deidentified before analysis, and informed consent of individual patients was obtained before operation.

Study Population

A total of 2425 consecutive GC patients who received gastrectomy in West China Hospital between January 2009 and December 2014 and Hai Kou Hospital between January 2012 and December 2016 were analyzed in this study. The inclusion criteria were as follows: (1) histologically proven gastric adenocarcinoma; (2) with radical resection; (3) no distal metastasis; (4) complete preoperative laboratory test information and height and weight information. The exclusion criteria of our study were patients with: (1) other malignancy history; (2) remnant gastric cancer; (3) neoadjuvant therapy; (4) any inflammatory or hematology disease affecting related laboratory parameters; (5) missing follow-up information. Finally, 1587 cases were included in this study (Fig. 1). Specially, 1419 of them, who were operated on at West China Hospital, were randomly assigned to a training set and an internal validation set, at a ratio of 2:1, while 168 cases in Hai Kou Hospital were defined as an independent external validation set.

Data Collection

The following important clinical data were collected, including: (1) preoperative systemic inflammatory markers (neutrophil, lymphocyte, monocyte, platelet, globulin, fibrinogen and international normalized ratio [INR]); (2) preoperative nutritional indicators (BMI, hemoglobin, albumin, triglyceride, cholesterol); (3) preoperative tumor markers (CA19-9, CA125 and CEA); (4) other clinicopathologic variables: age, sex, gastrectomy extent, tumor location, tumor size, macroscopic type, histologic differentiation, the number of lymph nodes examined, pathologic stage and adjuvant chemotherapy.

The surgery was performed according to the Japanese gastric cancer treatment guidelines [18], and the pathologic staging of tumor was conducted based on AJCC 8th TNM system [19].

Follow-Up

The follow-up was mainly performed through telephone interviews and outpatient visits. All patients were recommended to undergo follow-up every 3–6 months in the first 3 years and at least once yearly during the subsequent years [20]. Overall survival (OS) time was calculated from the date of surgery to the time of last follow-up, January 1, 2020, or the date of death.

Statistical Analysis

Student's *t* test was used to compare continuous variables with a normal distribution. Mann-Whitney *U* test was performed to compare skewed continuous variables and ordinal categorial variables, whereas χ^2 test was used for unordered categorial variables. OS was demonstrated by Kaplan-Meier method, and the survival curves were compared by the log-rank tests.

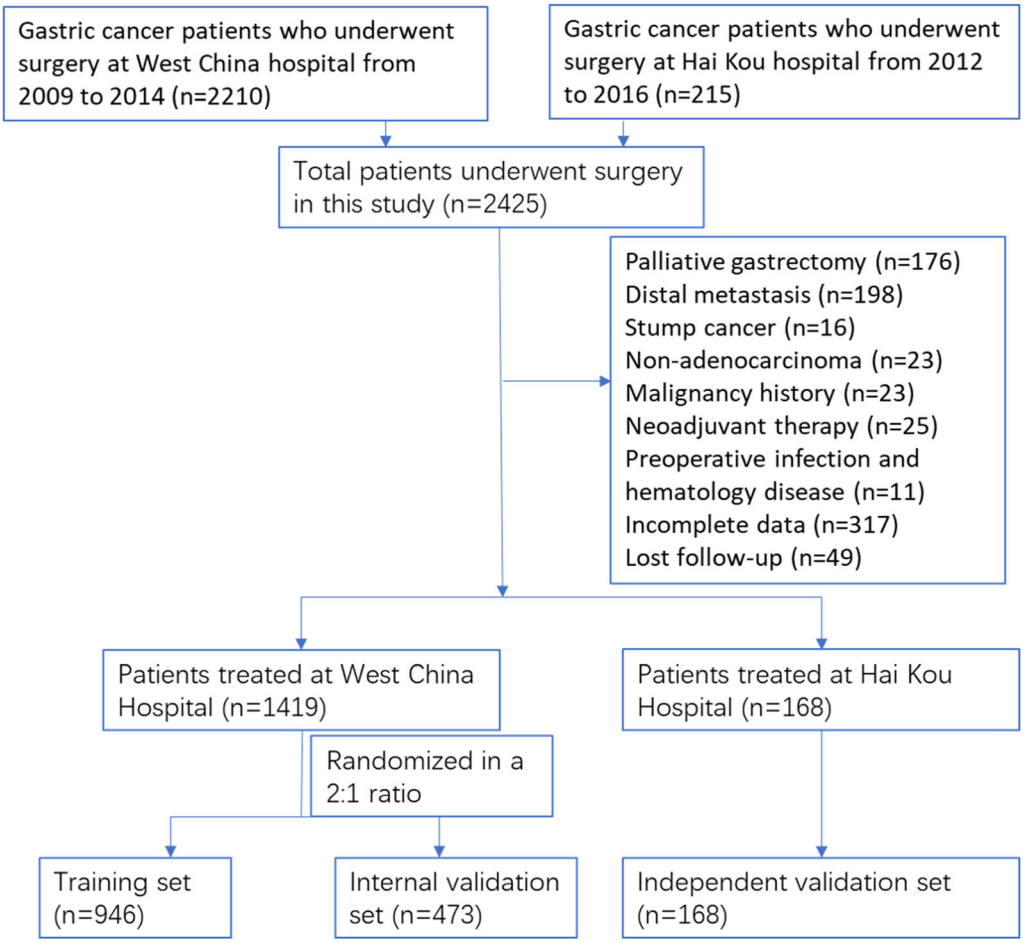


Fig. 1 The flow diagram of gastric cancer patients enrolled in this study

Continuous variables in the training set were categorized for OS before the log-rank test by using optimal cutoff values determined by using the "surv_cutpoint" function of the "survminer" package. Multivariate Cox stepwise regression analysis (both forward and backward stepwise regression) was performed to screen independent prognostic indexes, and the results were shown in the form of hazard ratios (HRs) and their 95% confidence intervals (CIs). Then, a new prognostic score system, which was derived from statistically significant preoperative indicators, was proposed. The predictive value of the prognostic score system was evaluated by the area under receiver-operating characteristic (ROC) curve (AUC) and compared with other inflammation/nutrition-based markers, such as NLR, PLR, FAR and SII. Detailed information on NLR, PLR, FAR and SII is shown in Supplementary Methods.

Furthermore, according to the results of uni- and multivariate Cox regression analysis, a comprehensive nomogram based on a prognostic score system was constructed to predict 3- and 5-year OS in GC patients. The performance of the nomogram was evaluated by measuring both discrimination and calibration in the training set, internal validation set and external validation set. Discrimination efficacy was evaluated by the concordance index (C-index) and AUC value. Calibration curves were created to compare the predicted and actual survival.

All statistical analyses were performed with R Software version 3.6.1 (https://www.r-project.org/) with the survminer, My.stepwise, rms,

survival and hmisc and timeROC statistical packages. P values < 0.05 (two-sided) were regarded as statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics of 1419 patients are shown in Table 1. The patients were then assigned to the training set ($n = 946$) and internal validation set ($n = 473$) randomly using the "set. seed ($n = 630$)" function of R package. Among all patients, 969 (68.3%) were male, and 1004 (70.8%) were $\geq$ 65 years. About 60% of patients underwent distal gastrectomy ($n = 830$; 58.5%). The distribution of TNM staging was as follows: 365 (25.7%) with stage I, 312 (22.0%) with stage II, and 742 (52.3%) with stage III, respectively. After surgery, 736 (51.9%) of them received adjuvant chemotherapy. There was no significant difference between the training and internal validation sets among these baseline variables. The basic information of the external validation set was shown in Table S1.

Survival Data

In the training set, the median follow-up time was 84.9 months [interquartile range (IQR), 71.9–100.4 months]. The 3- and 5-year OS rates were 72.1% and 59.5%, respectively. In the internal validation set, the median follow-up time was 86.0 (IQR 72.9–99.8) months, and the corresponding 3- and 5-year OS rates were 72.1% and 59.4%. In the external validation set, the median follow-up time was 66.6 months (IQR 52.6–78.2 months), and the 3-year OS rate was 75.6%.

Independent Prognostic Factors in the Training Set

In the training set, the optimal cutoff values for inflammatory, nutritional and tumor markers were divided into dichotomous variables using the "survminer" R package (Table 2). Then, all of these variables and other clinicopathologic parameters were included in the multivariate Cox stepwise regression model. Finally, three indexes including BMI ($P < 0.001$), lymphocyte count ($P = 0.004$) and CA19-9 ($P < 0.001$), along with gastrectomy extent, TNM stage and adjuvant chemotherapy, were identified as independent prognostic factors of OS (Table 2; Fig. 2).

Development of Novel Prognostic Score System

Based on the survival analysis above, the BMI, lymphocyte and CA19-9 level were used to construct a novel BLC (BMI-lymphocyte-CA19-9) prognostic score system. The weight of each index was evaluated by the Cox regression model and visualized by a nomogram (Fig. 3). The results showed that CA19-9 (10.0 points) had the greatest impact on prognosis, followed by lymphocytes (5.0 points) and BMI (4.0 points). According to summing the weight scores of the three indexes, each patient was given a total BLC score, which ranged from 0 to 19.0 points. As shown in supplementary file (Figure S1), the log-rank test demonstrated that the BLC tool showed a significant prognostic performance in GC patients (log rank $P < 0.001$).

To simplify this tool and increase its clinical value, we used a score of 5.0 points as the criterion to divide this scoring tool into two categories according to the statistical significance and population distribution. Consequently, the patients with scores $\leq$ 5.0 point ($n = 620$) were assigned to the low-risk group; otherwise, they were assigned to the high-risk group ($n = 326$).

Prognostic Efficacy of BLC

In the training set, The Kaplan-Meier survival curve showed that the patients in the high-risk group had a worse OS ($P < 0.001$) (Fig. 4a). Similarly, in the internal and external validation sets, the survival curves of the simplified BLC showed an effective prognostic predictability (both P values < 0.001) (Fig. 4b, c). In addition, time-dependent ROC curves at 3 and 5 years of OS were constructed to compare

Table 1 Baseline characteristics of included gastric cancer patients

Variable	Total cohort (n = 1419)	Training set (n = 946)	Validation set (n = 473)	P value
Sex				0.809
Male	969(68.3)	644(68.1)	325(68.7)	
Female	450(31.7)	302(31.9)	148(31.3)	
Age, years				
≥ 65	415(29.2)	286(30.2)	129(27.3)	0.248
< 65	1004(70.8)	660(69.8)	344(72.7)	
Gastrectomy extent				
Distal gastrectomy	830(58.5)	561(59.3)	269(56.9)	0.661
Total gastrectomy	385(27.1)	253(26.7)	132(27.9)	
Proximal gastrectomy	204(14.4)	132(14.0)	72(15.2)	
Tumor location				
Upper	378(26.6)	253(26.7)	125(26.4)	0.883
Middle	110(7.8)	70(7.4)	40(8.5)	
Lower	807(56.9)	542(57.3)	265(56.0)	
Multiple	124(8.7)	81(8.6)	43(9.1)	
Tumor size, cm				
≥ 5	766(54.0)	502(53.1)	264(55.8)	0.327
< 5	653(46.0)	444(46.9)	209(44.2)	
Macroscopic type				0.830
Type 0	296(20.9)	204(21.6)	92(19.5)	
Type 1	36(2.5)	23(2.4)	13(2.7)	
Type 2	567(40.0)	365(38.6)	202(42.7)	
Type 3	438(30.9)	297(31.4)	141(29.8)	
Type 4	82(5.8)	57(6.0)	25(5.3)	
Histologic differentiation				0.400
G1/G2	462(32.6)	315(33.3)	147(31.1)	
G3/G4	957(67.4)	631(66.7)	326(68.9)	
No. of LNs examined				0.649
< 15	152(10.7)	104(11.0)	48(10.2)	
15–24	455(32.0)	304(32.1)	151(31.9)	
> 24	812(57.3)	538(56.9)	274(57.9)	
T stage				0.983
T1	322(22.7)	219(23.2)	103(21.8)	

Table 1 continued

Variable	Total cohort (n = 1419)	Training set (n = 946)	Validation set (n = 473)	P value
T2	197(13.9)	132(14.0)	65(13.7)	
T3	254(17.9)	159(16.8)	95(20.1)	
T4	646(45.5)	436(46.1)	210(44.4)	
N stage				0.443
N0	462(32.6)	310(32.8)	152(32.1)	
N1	258(18.2)	174(18.4)	84(17.8)	
N2	259(18.3)	179(18.9)	80(16.9)	
N3	440(31.0)	283(29.9)	157(33.2)	
TNM stage				0.311
I	365(25.7)	245(25.9)	120(25.4)	
II	312(22.0)	218(23.0)	94(19.9)	
III	742(52.3)	483(51.1)	259(54.8)	
Adjuvant chemotherapy				0.348
Yes	736(51.9)	499(52.7)	237(50.1)	
No	683(48.1)	447(47.3)	236(49.9)	
Body mass index, kg/m^2	22.0 ± 3.2	22.1 ± 3.3	22.0 ± 3.0	0.821
Hemoglobin, g/l	124.4 ± 25.3	124.4 ± 25.3	124.3 ± 26.0	0.899
Albumin, g/l	40.5 ± 4.3	40.5 ± 4.3	40.6 ± 4.4	0.586
Triglyceride, mmol/l	1.3 ± 0.9	1.3 ± 1.0	1.3 ± 0.9	0.861
Cholesterol, mmol/l	4.5 ± 0.9	4.5 ± 0.9	4.5 ± 0.9	0.966
Globulin, g/l	25.9 ± 4.1	26.0 ± 4.1	25.8 ± 4.2	0.096
Platelet, 10^9/l	198.7 ± 76.8	198.0 ± 76.1	200.1 ± 78.3	0.629
Neutrophil, 10^9/l	3.5 ± 1.4	3.5 ± 1.5	3.5 ± 1.4	0.478
Lymphocyte, 10^9/l	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	0.342
Monocyte, 10^9/l	0.3 ± 0.2	0.3 ± 0.1	0.3 ± 0.2	0.370
International normalized ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.123
Fibrinogen, g/l	3.1 ± 0.8	3.1 ± 0.8	3.1 ± 0.8	0.451
CA125, U/ml	15.5 ± 16.9	15.4 ± 16.6	15.8 ± 17.3	0.815
CA19-9, U/ml	29.8 ± 98.1	27.0 ± 82.5	35.4 ± 123.3	0.357
CEA, ng/ml	7.8 ± 54.5	8.5 ± 64.5	6.5 ± 24.3	0.639

Table 2 Uni- and multivariate Cox regression analysis of the training set gastric cancer population

Variable	Univariate analysis		Multivariate analysis	
	No. of patients (n = 946)	**Log-rank P value**	**HR (95% CI)**	**P value**
Age, years (≥ 65 vs. < 65)	286/660	0.525		
Sex (male vs. female)	644/302	0.399		
Gastrectomy extent (total vs. partial)	**253/693**	**< 0.001**	**1.546 (1.262–1.894)**	**< 0.001**
Tumor size, cm (≥ 5 vs. < 5)	502/444	**< 0.001**		
Macroscopic type (type 3–4 vs. type 0–2)	354/592	**< 0.001**		
No. of LNs examined (> 24 vs. 15–24 vs. < 15)	538/304/104	0.807	0.903 (0.781–1.043)	0.164
Histologic differentiation (G3/G4 vs. G1/G2)	631/315	< 0.001	1.170 (0.941–1.454)	0.159
TNM stage (III vs. II vs. I)	**483/218/245**	**< 0.001**	**2.143 (1.836–2.500)**	**< 0.001**
Adjuvant chemotherapy (yes vs. no)	**499/447**	**0.487**	**0.820 (0.674–0.998)**	**0.047**
BMI, kg/m^2 (≥ 21.08 vs. < 21.08)	**548/398**	**< 0.001**	**0.696 (0.575–0.843)**	**< 0.001**
Hemoglobin, g/l (≥ 122.00 vs. < 122.00)	550/396	0.003		
Albumin, g/l (≥ 38.90 vs. < 38.90)	642/304	0.056		
Globulin, g/l (≥ 23.10 vs. < 23.10)	727/219	0.019	1.156 (0.908–1.473)	0.239
Platelet, 10^9/l (≥ 253.00 vs. < 253.00)	185/761	< 0.001	1.242 (0.992–1.556)	0.059
Neutrophil, 10^9/l (≥ 4.60 vs. < 4.60)	154/792	0.012		
Lymphocyte, 10^9/l (≥ 1.41 vs. < 1.41)	**552/394**	**< 0.001**	**0.754 (0.620–0.918)**	**0.004**
Monocyte, 10^9/l (≥ 0.47 vs. < 0.47)	104/842	0.021	1.30 6 (0.984–1.725)	0.065
Triglyceride, mmol/l (≥ 1.16 vs. < 1.16)	383/563	0.186		
Cholesterol, mmol/l (≥ 4.47 vs. < 4.47)	452/494	0.001	0.845 (0.694–1.029)	0.094
International normalized ratio (≥ 1.07 vs. < 1.07)	164/782	0.070		
Fibrinogen, g/l (≥ 3.01 vs. < 3.01)	434/512	< 0.001		
CA125, U/ml (≥ 13.63 vs. < 13.63)	366/580	0.001		

Table 2 continued

Variable	Univariate analysis		Multivariate analysis	
	No. of patients (n = 946)	Log-rank P value	HR (95% CI)	P value
CA19-9, U/ml (≥ 24.25 vs. < 24.25)	**163/783**	**< 0.001**	**1.642 (1.318–2.045)**	**< 0.001**
CEA, ng/ml (≥ 4.52 vs. < 4.52)	161/785	0.002		

The bold values highlight that the related variables are significant in the multivariate analysis

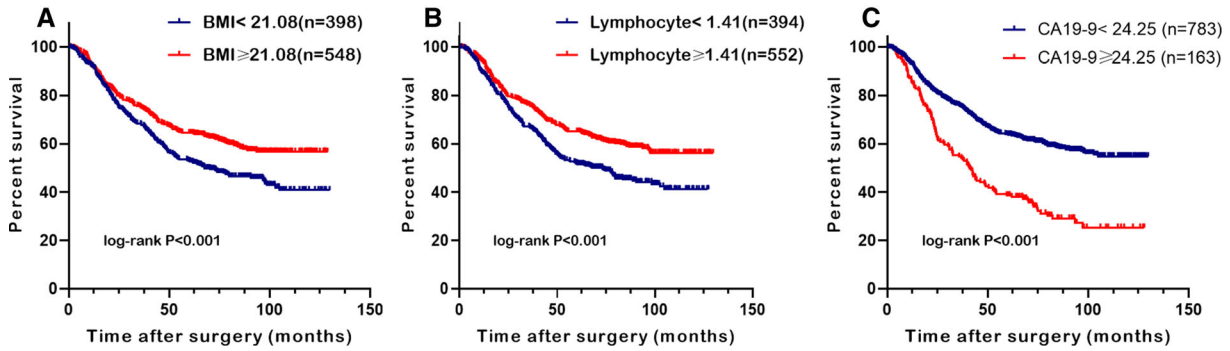


Fig. 2 Survival curves of variables selected from stepwise Cox regression model. **A** BMI, **B** lymphocyte and **C** CA19-9

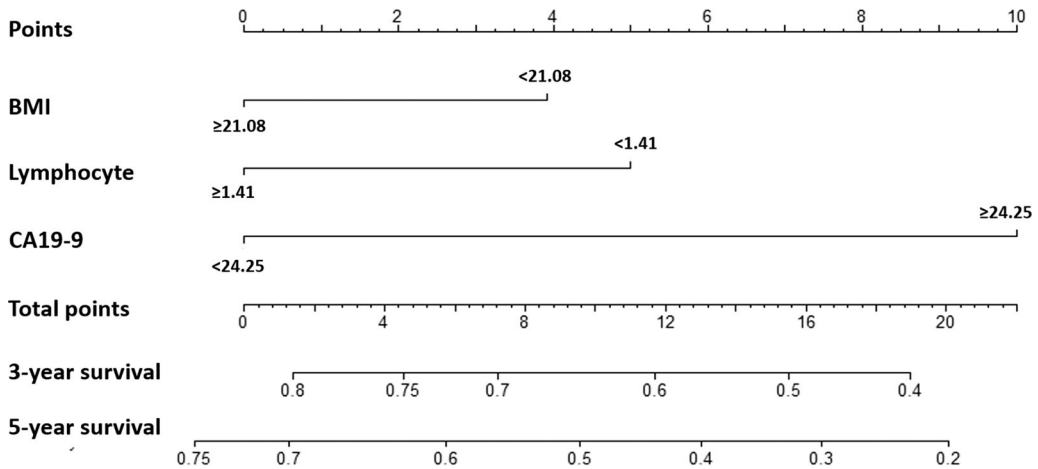


Fig. 3 Index weights of BLC scoring tool according to the visualization of nomogram model

the performance of the BLC with other inflammation/nutrition-based markers (NLR, PLR, FAR and SII). As shown in Fig. 5, the AUCs of BLC were higher than these of other markers in both the training set (3-year: 0.595 [95% CI 0.554–0.636]; 5-year: 0.597 [95% CI 0.559–0.634]) and internal validation set (3-year: 0.591 [95% CI 0.533–0.648]; 5-year: 0.589

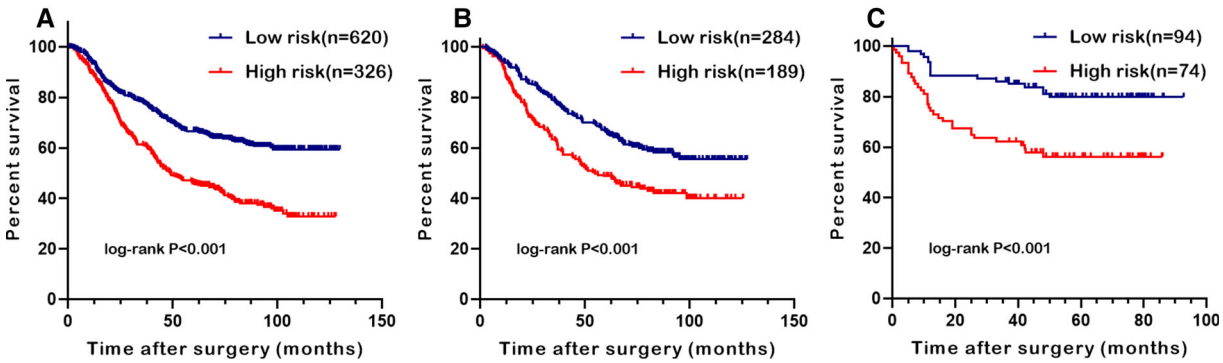


Fig. 4 Kapan-Meier curves of BLC scoring tool in the training, internal validation and external validation set

[95% CI 0.536–0.641]), which suggested that the BLC assessment tool had a better prognostic performance.

Construction and Validation of a Survival Nomogram

Based on the multivariate Cox regression analysis results for OS in the training set (Table 3), four independent prognostic variables including BLC, gastrectomy extent, pTNM stage and adjuvant chemotherapy were used to construct a prognostic nomogram to predict 3- and 5-year survival rates of GC patients who received curative gastrectomy (Fig. 6).

The nomogram exhibited quite good accuracy in estimating the survival with a higher C-index of 0.710 (95% CI 0.686–0.734) in the training set and 0.710 (95% CI 0.679–0.741) and 0.785 (95% CI 0.730–0.840) in the internal and external set, respectively. In addition, the calibration curves presented good fitting between prediction and observation for predicting 3- and 5-year OS in the training and internal validation set and for predicting 3-year OS in the external validation set. The predictive value of our nomograms for OS were significantly higher than those based on the TNM staging system alone (training set: 0.671 [95% CI0.649–0.693]; internal validation set: 0.680 [95% CI, 0.653–0.707]; external validation set: 0.664 [0.615–0.713]) (Fig. 7).

Moreover, the ROC curves (AUC) of the nomogram for the prediction of 3- and 5-year OS in the training set were 0.781 (95% CI 0.750–0.813) and 0.755 (95% CI 0.723–0.786), respectively. The AUCs of the nomogram in predicting 3- and 5-year OS were 0.750 (95% CI 0.705–0.795) and 0.778 (95% CI 0.736–0.820) in the internal validation set and in predicting 3-year OS was 0.821 (95% CI 0.744–0.897) in the external validation set. Compared to the TNM staging system (in the training set: 3-year, 0.727; 5-year, 0.708; in the internal validation set: 3-year, 0.720; 5-year, 0.731; in the external validation set: 3-year, 0.700), our nomogram for OS showed superior predictability (Fig. 8).

DISCUSSION

Currently, surgery is considered the only means of curative treatment for non-metastatic GC [21]. Due to the limitation of diagnostic techniques, it is often difficult to detect GC early, which resulted in poor prognosis of many patients [22]. Therefore, it is essential to understand the biologic mechanism underlying tumor progression and identify factors for stratifying individual risk.

In this study, we assessed the prognostic value of preoperative nutritional, inflammatory and tumor markers along with other clinicopathologic parameters. According to rigorous index selection, we found that only BMI, lymphocyte and CA19-9 were independently associated with OS as well as gastrectomy extent, TNM stage and adjuvant chemotherapy. Therefore, we established a novel prognostic score system, named BLC. Results of multivariate analysis showed that BLC was an

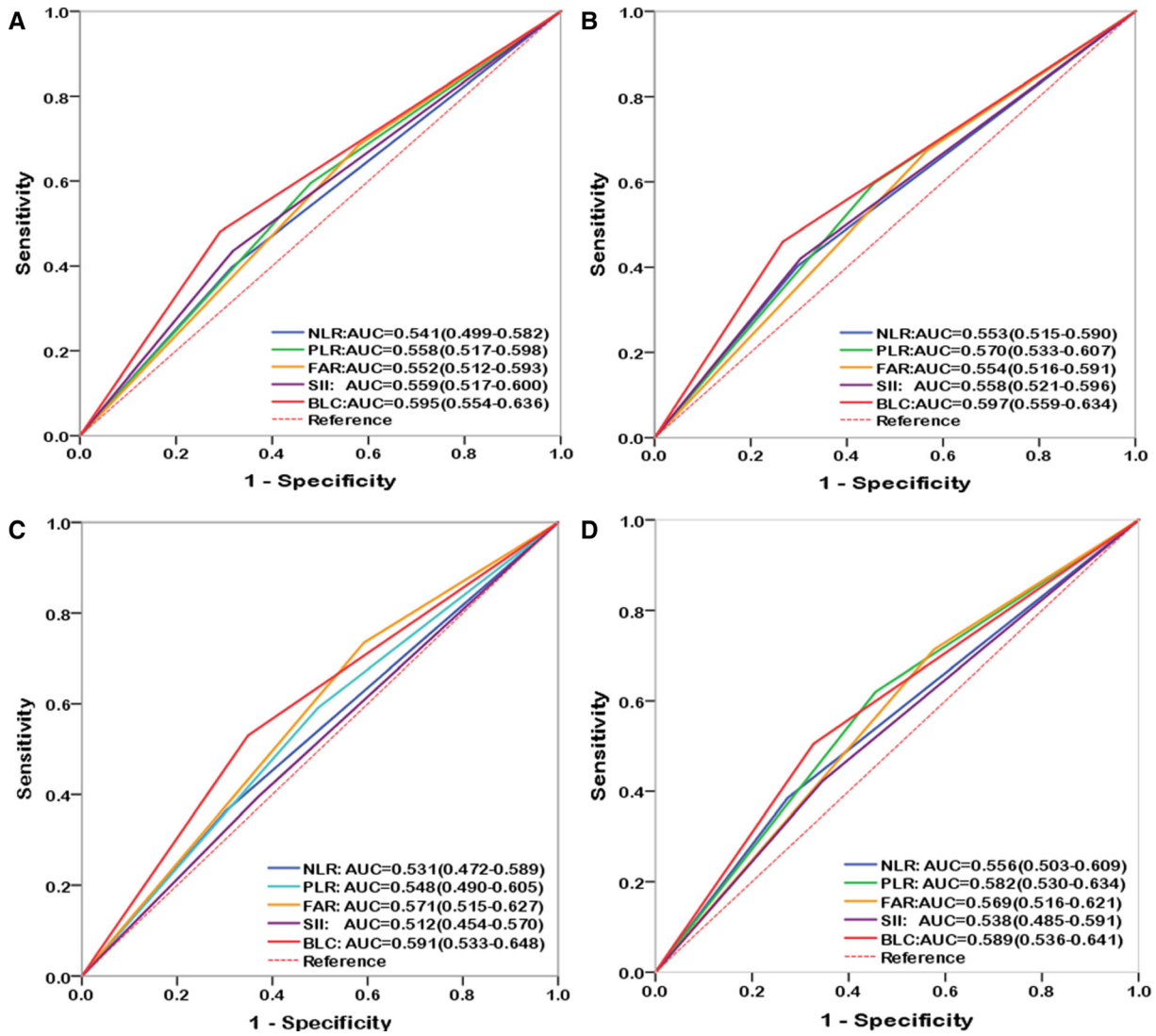


Fig. 5 ROCs for the BLC scoring tool and other inflammation-based markers in the training (**A** 3-year OS, **B** 5-year OS) and internal validation sets (**C** 3-year OS, **D** 5-year OS)

independent prognostic factor of OS for GC patients with curative resection. Kaplan-Meier analysis indicated that BLC could significantly classify patients into two groups. Moreover, compared with other inflammation/nutrition-based markers, including NLR, PLR, FAR and SII, the BLC scoring tool allowed superior discrimination in prognosis due to its higher AUC value. These data suggested that BLC might provide additional prognostic information that would complement the current TNM staging system.

In fact, our present findings are in line with previous reports. Accumulating evidence has demonstrated systemic inflammatory factors are closely associated with the occurrence and progression of malignancies [23–25]. In GC, several studies have reported a series of inflammatory factors are involved in tumor progression, such as neutrophils [26], lymphocytes [27], monocytes [28], platelets [29] and fibrinogen [30]. In this study, these factors were significantly associated with OS in the univariate analysis, while only lymphocyte count was the independent prognostic factor in the subsequent multivariate analysis. As we know, lymphocytes play an essential role in blocking

tumor proliferation and migration by secreting cytokines, such as interferon gamma and tumor necrosis factor [31–33]. However, systemic inflammation can significantly decrease the capacity of CD4 + T lymphocytes and CD8 + T lymphocytes of the host [34]. Thus, in GC

Fig. 7 Calibration curves of the training set (**A** 3-year OS, **B** 5-year OS), internal validation set (**C** 3-year OS, **D** 5-year OS) and external validation set (**E** 3-year OS) ▶

Table 3 Multivariate Cox regression analysis of BLC assessment tool in the training set

Variable	Multivariate analysis	
	HR (95% CI)	***P* value**
Age, years (≥ 65 vs. < 65)	0.998 (0.805–1.237)	0.984
Sex (male vs. female)	1.068 (0.871–1.309)	0.527
Gastrectomy extent (total vs. partial)	**1.516 (1.228–1.871)**	**< 0.001**
Tumor size, cm (≥ 5 vs. < 5)	1.126 (0.889–1.426)	0.326
Macroscopic type (type 3–4 vs. type 0–2)	1.050 (0.853–1.293)	0.646
Histologic differentiation (G3/G4 vs. G1/G2)	1.192 (0.954–1.490)	0.123
No. of LNs examined		
15–24 vs. < 15	0.943 (0.673–1.320)	0.732
> 24 vs. < 15	0.850 (0.616–1.174)	0.324
TNM stage		
Stage II versus stage I	**2.438 (1.650–3.601)**	**< 0.001**
Stage III versus stage I	**4.880 (3.362–7.085)**	**< 0.001**
Adjuvant chemotherapy (yes vs. no)	**0.818 (0.670–0.997)**	**0.046**
BLC (high risk vs. low risk)	**1.661 (1.370–2.013)**	**< 0.001**

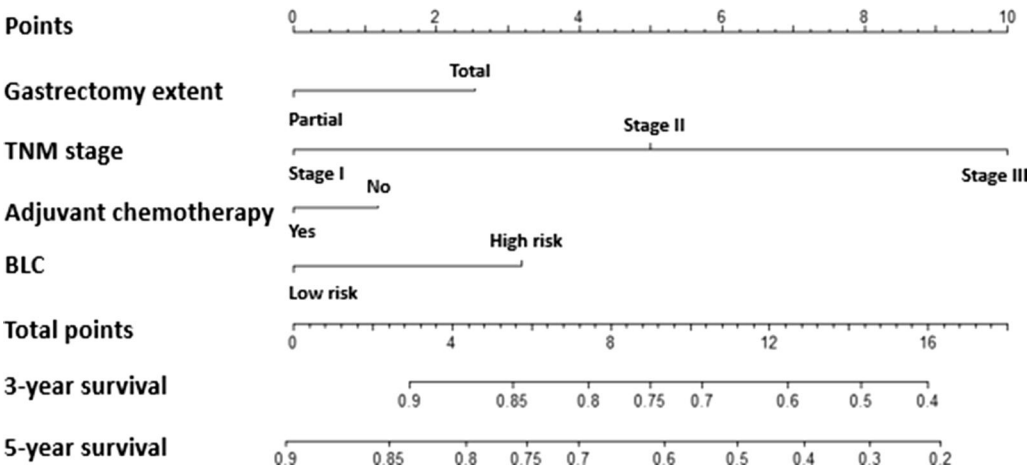
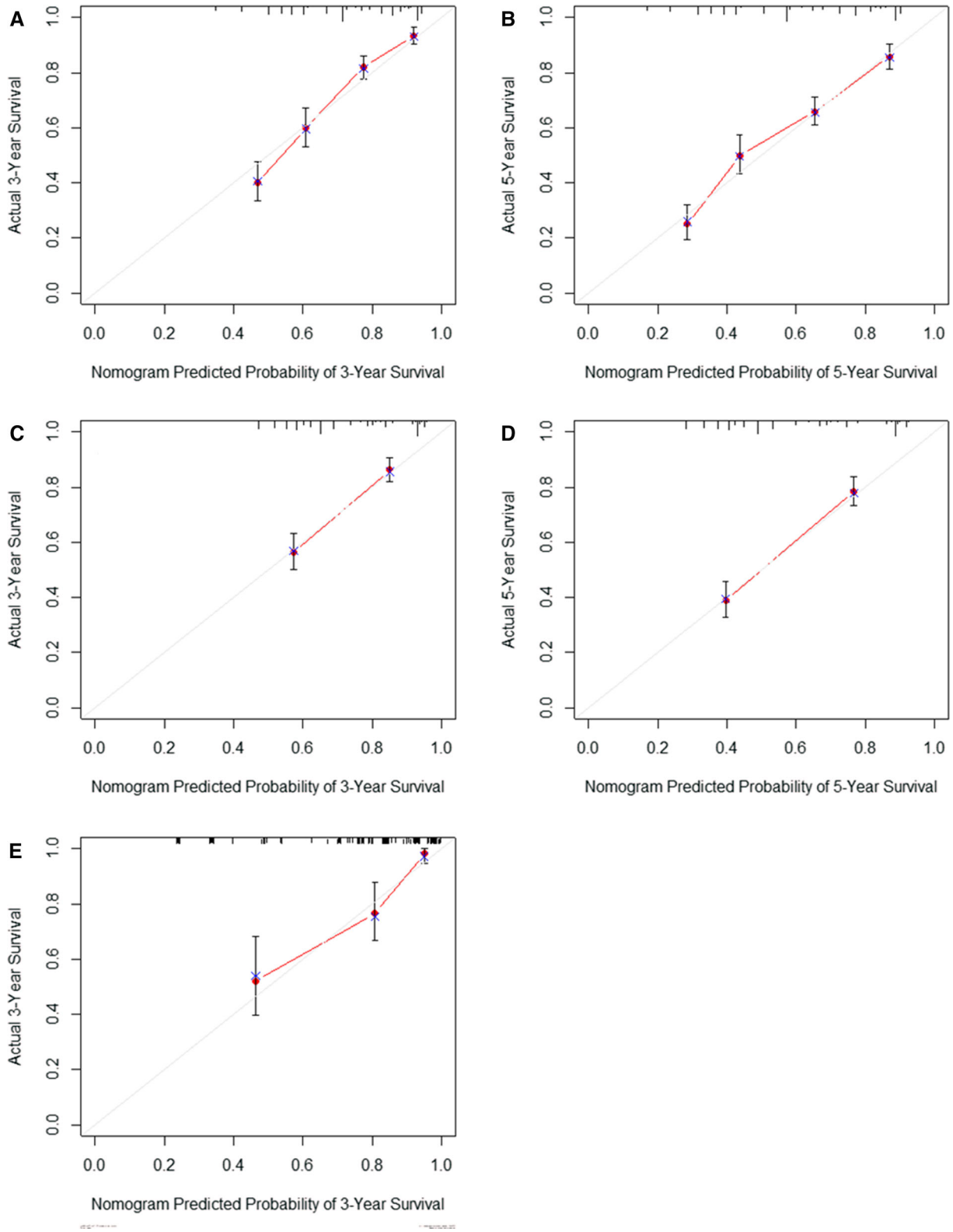


Fig. 6 Nomograms based on the BLC scoring tool in the training set


A
Actual 3-Year Survival
Nomogram Predicted Probability of 3-Year Survival
B
Actual 5-Year Survival
Nomogram Predicted Probability of 5-Year Survival
C
Actual 3-Year Survival
Nomogram Predicted Probability of 3-Year Survival
D
Actual 5-Year Survival
Nomogram Predicted Probability of 5-Year Survival
E
Actual 3-Year Survival
Nomogram Predicted Probability of 3-Year Survival
0.0
0.2
0.4
0.6
0.8
1.0

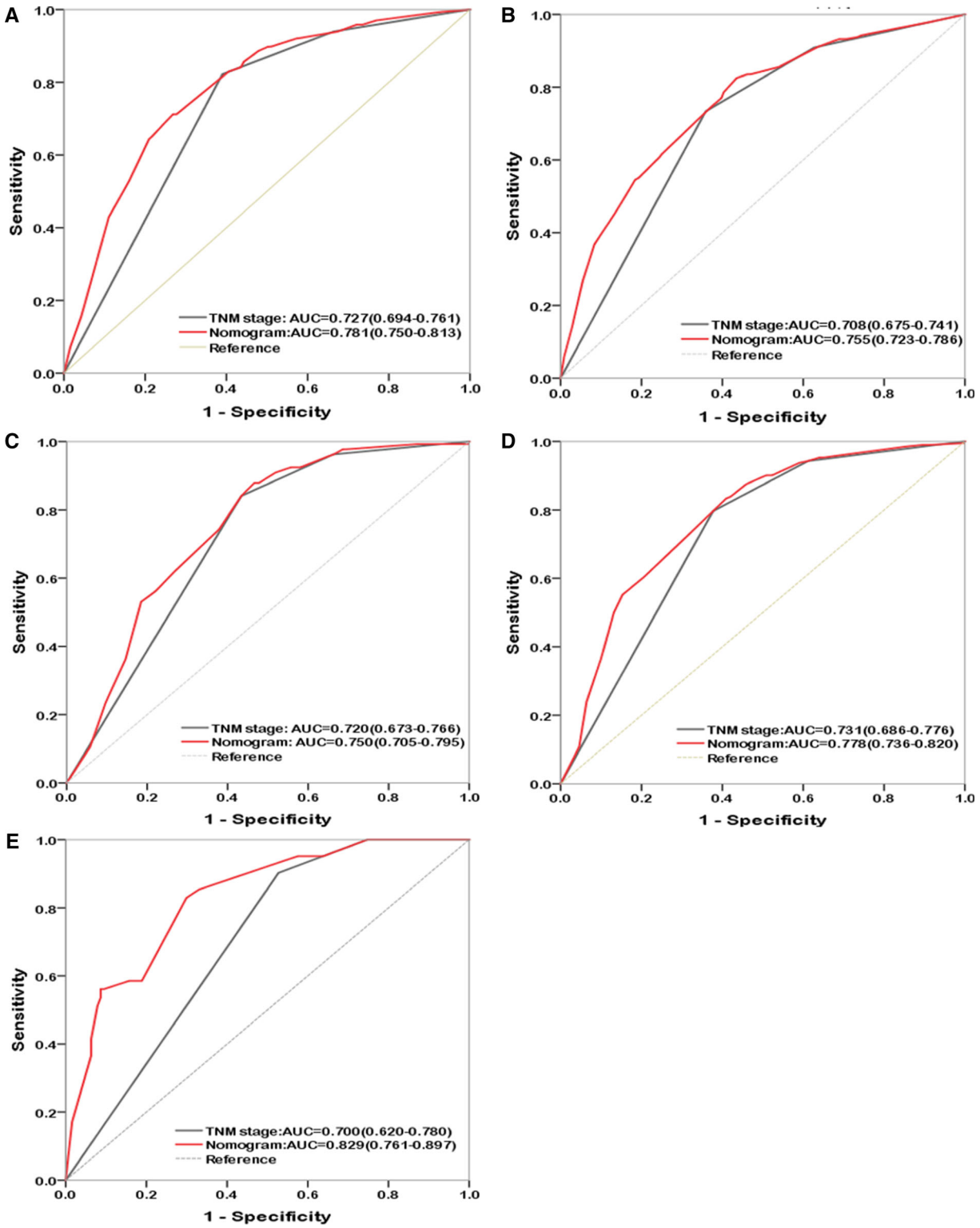


Fig. 8 ROCs for the BLC based nomogram and TNM staging system in the training (**A** 3-year OS, **B** 5-year OS) and internal validation sets (**C** 3-year OS, **D** 5-year OS) and external validation set (**E** 3-year OS)

patients, numerous studies have illustrated that high numbers of TILs correlate with improved survival while lymphopenia has been shown to be associated with poor prognosis [35–37]. On the other hand, nutritional status is also an important factor affecting survival outcomes in several types of malignancies, including GC [38–40]. Owing to chronic consumption and disorders of nutrition absorption, GC is always accompanied with malnutrition and cachexia [41]. Meanwhile, studies have confirmed that malnutrition leads to poor quality of life, reduces treatment efficacy and increases severe postoperative complications [42]. As an objective and common measurement reflecting patients' nutritional status, baseline BMI has been reported repeatedly to be positively correlated with survival outcomes of GC patients and has been used to triage patients in clinic care [41, 43, 44]. Similarly, tumor markers, such as CA19-9, CA125 and CEA are also widely applied in the patient management and prognosis prediction [13, 14]. Recently, a meta-analysis reported by Song et al. [45] demonstrated that the elevated CA19-9 predicts poor prognosis in GC, consistent with our previous research [14]. According to the aforementioned results, the BLC assessment tool based on preoperative BMI, lymphocytes and CA19-9 may enable better understanding of the functional state of patients and predict the prognosis of GC patients.

The nomogram is a visualized and practical method to predict the prognosis of individual patients with possible risk factors and has been shown to be more accurate than traditional staging systems in several cancers [46]. In this study, we established a nomogram by incorporating BLC, gastrectomy extent, TNM stage and adjuvant chemotherapy. The calibration curve showed that the nomogram could predict the prognosis of GC patients accurately. The TNM staging system is regarded as the benchmark for classifying cancer patients and predicting prognosis [19]. Compared with the TNM staging system, the BLC-based nomogram had higher C-index and AUC value, which indicated better clinical applicability of our nomogram.

There are several limitations in our study. First, the BLC scoring tool was developed and validated in two independent cohorts in China; it would be better if multi-center validation could be conducted to verify its universality in other countries. Second, due to the complicated and specific biologic features of malignancies, some factors affecting the prognosis of GC, such as genomics biomarkers, were not included in our parameters. Third, the precise recurrence time for these patients is not available in this study because of the ambiguous or unknown recurrence information from their relatives. Thus, we could not evaluate the association between our prognostic score model and cancer-specific survival, even though the OS outcomes can be effectively predicted.

CONCLUSIONS

The BLC scoring tool can effectively predict the prognosis of GC patients with curative resection. As a simple and easily available marker, it may have important clinical utility in improving prognostic estimates and guiding treatment strategies.

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Authorship. Huayang Pang, Weihan Zhang, Xianwen Liang, Ziqi Zhang, Xiaolong Chen, Linyong Zhao, Kai Liu, Danil Galiullin, Kun Yang, Xinzu Chen and Jiankun Hu meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship contribution. Conceptualization: Huayang Pang, Weihan Zhang; Methodology: Huayang Pang, Weihan Zhang, Xianwen Liang, Xiaolong Chen, Linyong Zhao, Kai Liu, Kun Yang, Xinzu Chen; Formal analysis and investigation: Huayang Pang, Weihan Zhang, Ziqi Zhang; Writing - original draft preparation: Huayang Pang, Weihan Zhang; Writing - Review & Editing: Xianwen Liang, Danil Galiullin; Funding acquisition: Weihan Zhang, Jiankun Hu; Supervision: Jiankun Hu.

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Compliance with Ethics Guidelines. Patient records from two medical centers were anonymized and de-identified prior to analysis, and signed patient informed consent was obtained before operation. This retrospective study was approved by the Research Ethics Committee of West China Hospital, which is the principal affiliation of this study. The ethical approval number was no. WCH SGCPR-2021–04. The study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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