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ORIGINAL RESEARCH

A clinical prognostic scoring system for resectable gastric cancer to predict survival and benefit from paclitaxel- or oxaliplatin-based adjuvant chemotherapy

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Background: Gastrectomy with D2 lymphadenectomy is a standard procedure of curative resection for gastric cancer (GC). The aim of this study was to develop a simple and reliable prognostic scoring system for GC treated with D2 gastrectomy combined with adjuvant chemotherapy.

Methods: A prognostic scoring system was established based on clinical and laboratory data from 579 patients with localized GC without distant metastasis treated with D2 gastrectomy and adjuvant chemotherapy.

Results: From the multivariate model for overall survival (OS), five factors were selected for the scoring system: ≥50% metastatic lymph node rate, positive lymphovascular invasion, pathologic TNM Stage II or III, ≥5 ng/mL preoperative carcinoembryonic antigen level, and <110 g/L preoperative hemoglobin. Two models were derived using different methods. Model A identified low- and high-risk patients for OS ($P<0.001$), while Model B differentiated low-, intermediate-, and high-risk patients for OS ($P<0.001$). Stage III patients in the low-risk group had higher survival probabilities than Stage II patients. Both Model A (area under the curve [AUC]: 0.74, 95% confidence interval [CI]: 0.69–0.78) and Model B (AUC: 0.79, 95% CI: 0.72–0.83) were better predictors compared with the pathologic TNM classification (AUC: 0.62, 95% CI: 0.59–0.71, $P<0.001$). Adjuvant paclitaxel- or oxaliplatin-based or triple chemotherapy showed significantly better outcomes in patients classified as high risk, but not in those with low and intermediate risk.

Conclusion: A clinical three-tier prognostic risk scoring system was established to predict OS of GC treated with D2 gastrectomy and adjuvant chemotherapy. The potential advantage of this scoring system is that it can identify high-risk patients in Stage II or III who may benefit from paclitaxel- or oxaliplatin-based regimens. Prospective studies are needed to confirm these results before they are applied clinically.

Keywords: gastric carcinoma, prognostic factor, TNM classification, paclitaxel, oxaliplatin

Introduction

Gastric cancer (GC) is the fourth most common cancer, ranking second in cancer-related deaths worldwide. People's Republic of China alone accounts for 42% of the total incidence of the disease.[1] Despite the improved prognosis of patients with GC due to early diagnosis, radical surgery, and development of chemotherapy, the 5-year survival rate across all stages is <40%, except in Japan and South Korea, where the rates are higher.[2,3] Surgery is the main curative treatment for localized disease. However, approximately one-third of patients undergoing radical resections relapse with a recurrence

rate as high as 70% in advanced GC.[4] To prevent recurrence, peri and postoperative therapy is widely used, but practices vary between countries due to different results in different populations.[5] In Japan and in People's Republic of China, adjuvant chemotherapy is recommended as the most frequent option for resectable GCs without distant metastases.[6,7]

Although adjuvant chemotherapy has been proved to improve survival and reduce relapse after curative resection in some large-scale Phase III trials,[7–9] its limited survival benefit and impaired quality of life require a personalized evaluation of individual patients before commencing adjuvant chemotherapy. Identification of distinct prognostic factors could, therefore, facilitate optimization of treatment and improve survival after curative resection.

The pathologic TNM (pTNM) classification for GC formulated by the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC)[10] is the current gold standard for therapeutic decision making and prognostic assessment in the adjuvant setting. However, the mortality risk varies substantially within stages, indicating a need of improved predictors for GC.[11] Tumor size is also a well-known prognostic factor in patients, which has been shown to be a substitute for tumor invasion (T) in the pTNM staging system.[12–17] In addition, the prognostic value of the number of involved lymph nodes (LNs) has been questioned, given that LN retrieval is frequently insufficient.[18,19] Therefore, the lymph node ratio (LNR) has been proposed to address the problem.[18–24] In addition to pTNM classification, serum tumor markers and hematological parameters easily accessible to clinicians preoperatively have been suggested to display prognostic potential in GC, eg, increased levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) and decreased levels of hemoglobin (Hb) or elevated white blood cell (WBC) count before treatment.[25–29]

Most of the previous prognostic studies focused only on a few variables, with limited prognostic accuracy. In the current study, we aimed to establish a more accurate and a practical, prognostic risk assessment scoring system by incorporating some of these clinical prognostic factors into the pTNM stage classification. Our findings may enable prediction of the benefit of adjuvant chemotherapy in subgroups of GC patients undergoing radical resection with a curative intent.

Materials and methods

Patient selection

The medical records of The First Affiliated Hospital of Nanjing Medical University were retrospectively searched from January 1, 2008, to August 31, 2012. Cases were included if they fulfilled the following criteria: pathologically verified locoregional GC without distant metastasis (Stage II, III, or I, except T1a) with risk factors including poor differentiation and lymphovascular or neural invasion; D2 lymphadenectomy with >15 LNs retrieved; at least two cycles of chemotherapy within at most 2 months after surgery; and available surgical pathological data, routine blood tests, and tumor markers CEA and CA19-9. Exclusion criteria were synchronous malignancies or gastrointestinal stromal tumor; neoadjuvant treatment or adjuvant radiochemotherapy; and incomplete clinicopathological data. The protocol was approved by the First Affiliated Hospital of Nanjing Medical University Ethics Committee prior to study initiation. Written informed consent was obtained from all patients.

Data collection and follow-up

Serum samples were obtained for the analysis of CEA[25,26,30–32] and CA19-9[29] levels by enzyme immunoassay, and blood routine tests (WBC, red blood cell count, platelet count, and Hb level) were conducted within 1 week prior to surgery. Postoperative histological findings, including stage, grading, Borrmann type, tumor size, invasion depth, primary tumor location, positive LN number, metastatic LNR, lymphovascular invasion (LVI), perineural involvement (PNI), and resection margin that have been proposed as prognosticators,[18,28,29,33–43] were determined retrospectively according to the 2010 UICC-pTNM stage[10] by Cong Wang and Xiao Li (Pathology Department, The First Affiliated Hospital of Nanjing Medical University). The tumor size was defined by the longest diameter. Patient records and operation notes were reviewed for demographic data, operative details, and chemotherapy for a preoperative assessment of physical status (The American Society of Anesthesiologists score),[44] type of gastrectomy, surgical complications, death within the first month after surgery due to postoperative complications, and adjuvant chemotherapy regimens. The date of surgery was regarded as the starting point of the survival follow-up until August 31, 2014. Overall survival (OS) was defined as the period from surgery to death or the last follow-up. Follow-up data were acquired from patient records, death certificates, or patients and their families by telephone calls. Patients underwent similar follow-up examinations at regular intervals. Data of patients without any event were censored as were the date of the final observation.

Cutoff determination

Cutoff values of serum levels of CEA and CA19-9 recommended by the manufacturers were 5 ng/mL and 35 units/mL,

respectively.[26,45] For blood routine analyses, 4×10^9 cells/L, 4×10^{12} cells/L, 110 g/L, and 300×10^9 cells/L were employed as cutoff points for WBC, red cell blood, Hb level, and platelet count, respectively, according to the latest standards published by the Ministry of Health of People's Republic of China. A tumor size of 6 cm and LNR of 50% were determined as cutoffs, using the median values.

Statistics

Differences among groups were compared by chi-square and regarded as significant when $P<0.05$. Survival curves were visualized by the Kaplan–Meier method and examined by a log-rank test. Prognostic value of clinicopathological parameters was determined by multivariate analysis using Cox proportional hazards regression models with stepwise forward likelihood ratio selection (enter 0.05/0.1). In the final prognostic model, interactions were tested and the proportional hazard hypothesis was verified. A cross-validation technique was used to avoid overfitting of the final Cox regression model, which creates a resampling simulation set of at least 100 to obtain the Harrell's concordance index (c-index).[46]

Each risk factor was assigned to a value derived from corresponding coefficients of significant variables from the multivariate Cox's model by division by the smallest coefficient *B* and rounding to the nearest integer.[47] Two risk score models were developed using different methods. The total risk score was determined by the sum of values of single factors. For Model A, the optimal cutoff point was determined by the maximally selected log-rank statistics, according to a previous study.[48] For Model B, the prognostic score was grouped into three classes with an equal distance range of values. The area under the curve (AUC) was applied to both models by receiver–operating characteristic curve to further compare their prognostic value.[49] All analyses were conducted using SPSS Version 18.0 statistical software (IBM Corporation, Armonk, NY, USA) and R Statistical Language Version 2.9 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and participants

A total of 579 patients were included in the study according to the prespecific eligibility criteria (Figure S1). The clinicopathological characteristics of patients are presented in Table 1. The primary tumor location sites included corpus (39%) and antrum (31.6%). Majority of the patients had adenocarcinoma (96.9%), poor differentiation (84.8%),

Table 1 Baseline clinicopathological features of 579 patients

Parameter	Number of patients (%)
Age, years	
Median	58
Range	18–85
<58	264 (45.6)
≥58	315 (54.4)
Sex	
Male	405 (69.9)
Female	174 (30.1)
Location	
Cardia/fundus	153 (26.4)
Corpus	226 (39.0)
Antrum	183 (31.6)
Whole	17 (2.9)
Size, cm	
<3	141 (24.4)
3–6	305 (52.7)
7–9	95 (16.4)
>9	38 (6.6)
Borrmann type	
I–III	435 (75.1)
IV	144 (24.9)
Grading	
Well/moderately (G1/2)	88 (15.2)
Poorly (G3)	491 (84.8)
Depth of tumor invasion	
T1	49 (8.5)
T2	80 (13.8)
T3	118 (20.4)
T4	332 (57.3)
Metastatic node number	
N0 (0)	147 (25.4)
N1 (1–2)	118 (20.4)
N2 (3–6)	145 (25.0)
N3 (>6)	169 (29.2)
Metastatic lymph node ratio, %	
0	147 (25.2)
1–25	170 (29.5)
26–50	118 (20.4)
51–100	144 (24.9)
Lymphovascular invasion	
Negative	414 (71.5)
Positive	165 (28.5)
Perineural invasion	
Negative	406 (70.1)
Positive	173 (29.9)
Seventh AJCC TNM Stage	
I	76 (13.1)
II	149 (25.7)
III	354 (61.1)
Type of operation	
Total gastrectomy	224 (38.7)
Subtotal gastrectomy	355 (61.3)
Resection margin	
R0	414 (71.5)
R1	165 (28.5)
Pre-CEA level, ng/mL	
<5	243 (42.0)
≥5	336 (58.0)

(*Continued*)

Table 1 (*Continued*)

Parameter	Number of patients (%)
Pre-CA19-9 level, U/mL	
<35	487 (84.1)
≥35	92 (15.9)
Pre-red blood cell, $\times10^{12}$/L	
<4	227 (39.2)
≥4	352 (60.8)
Pre-hemoglobin, g/L	
<110	252 (43.5)
≥110	327 (56.5)
Pre-white blood cell, $\times10^{9}$/L	
<4	51 (8.8)
≥4	528 (91.2)
Pre-platelet, $\times10^{9}$/L	
≥300	60 (10.4)
<300	519 (89.6)
ASA score	
0–1	568 (98.1)
≥2	11 (1.9)
Chemotherapy regimens	
Triplet	81 (14.0)
Doublet	264 (45.6)
Single	234 (40.4)

Abbreviations: AJCC, American Joint Committee on Cancer; pre-, preoperative; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ASA, The American Society of Anesthesiologists.

T4 (57.3%), LN metastasis (74.6%) with The American Society of Anesthesiologists score <2 (98.9%), and had received adjuvant chemotherapy (regimen in Table S1) following subtotal gastrectomy (61.3%) plus D2 lymphadenectomy (92.1%). The incidence of postoperative complications was 37.0%. The rate of surgical mortality was 15.1%. The adjuvant chemotherapy regimens are displayed in Table S1, and 331 (57.2%) patients completed the prespecified regimens (Table S1). At an interval of 4–8 weeks after surgery, patients received adjuvant chemotherapy (median duration: 4 months, range: 2–8.5 months). The detailed dosing and regimens are shown in Table S2.

Survival analysis

During a median follow-up of 44 months (range: 12–81 months), a total of 236 patients (41.8%) died and 16 (2.8%) were lost to follow-up. The median OS (mOS) was 52.4 months (95% confidence interval [CI]: 49.8–54.9 months), and 3- and 5-year survival rates were 62.9% and 50.1%, respectively. Eleven patients (1.9%) died of noncancer-related causes within the observation period.

Univariate analysis of baseline characteristics and laboratory factors revealed that tumor grade, depth of tumor invasion, tumor size, metastatic LN number, LNR, LVI, PNI, pTNM stage, surgical margin, type of gastrectomy, preoperative CEA, CA19-9, and Hb levels significantly affected OS (Figure 1 and Table 2). Variables were then selected by a forward stepwise selection method (P=0.05) with five factors showing independent correlation with poor prognosis in multivariate Cox regression model: LNR ≥50%, LVI positive, TNM Stage II or III, preoperative-CEA level ≥5 ng/mL, and preoperative Hb <110 g/L (Table 2). Cross-validation was further performed on the determined Cox model and a c-index value of 0.78 was acquired.

Prognostic scoring system

According to the results from the multivariate analysis, five factors were selected for the final prognostic scoring system. Each factor was assigned a score (points) ranging from 0 to 3, according to their hazard ratios (HRs; Table 3). Based on these points, we developed two risk stratification models for Stage I–III tumors. For Model A, the optimal cutoff point of dichotomization score was derived from the maximally selected log-rank statistics (Figure S2): 1) low risk of death: 0–6 (n=379) and 2) high risk of death: >6 (n=200). While three groups in Model B were cutoff by tertiles of the maximal total score: 1) low-risk group: <4 (n=152); 2) intermediate-risk group: 4–7 (n=289); and 3) high-risk group: >7 (n=138).

The survival analysis for risk score groups using the Kaplan–Meier method is presented in Table 4 and Figure 2. In Model A, the low-risk group (score 0–6) had a consistent and significantly better outcome than the high-risk group (score >6) (5-year survival: 64.6% and 20.8%, respectively, log-rank P<0.001). The mOS rates were 61.0 months (95% CI: 58.2–63.8 months) and 29.9 months (95% CI: 20.3–31.4 months), respectively. A prognostic difference was seen among three groups in Model B. The 5-year survival probability in Model B for patients in the low-risk group was 78.6%, significantly higher than that in intermediate-risk (50.5%, P<0.001) and high-risk groups (16.2%, P<0.001). The mOS rates were 66.4 months (95% CI: 63.0–69.8 months), 51.6 months (95% CI: 47.7–55.4 months), and 29.3 months (95% CI: 22.5–36.2 months), respectively.

Receiver–operating characteristic curve analysis was adopted to further assess the prognostic performances. Both Model A (AUC: 0.74, 95% CI: 0.69–0.78) and Model B (AUC: 0.79, 95% CI: 0.72–0.83) showed a significantly higher prognostic performance compared with the TNM classification alone (AUC: 0.62, 95% CI: 0.59–0.71, P<0.001) (Figure S3).

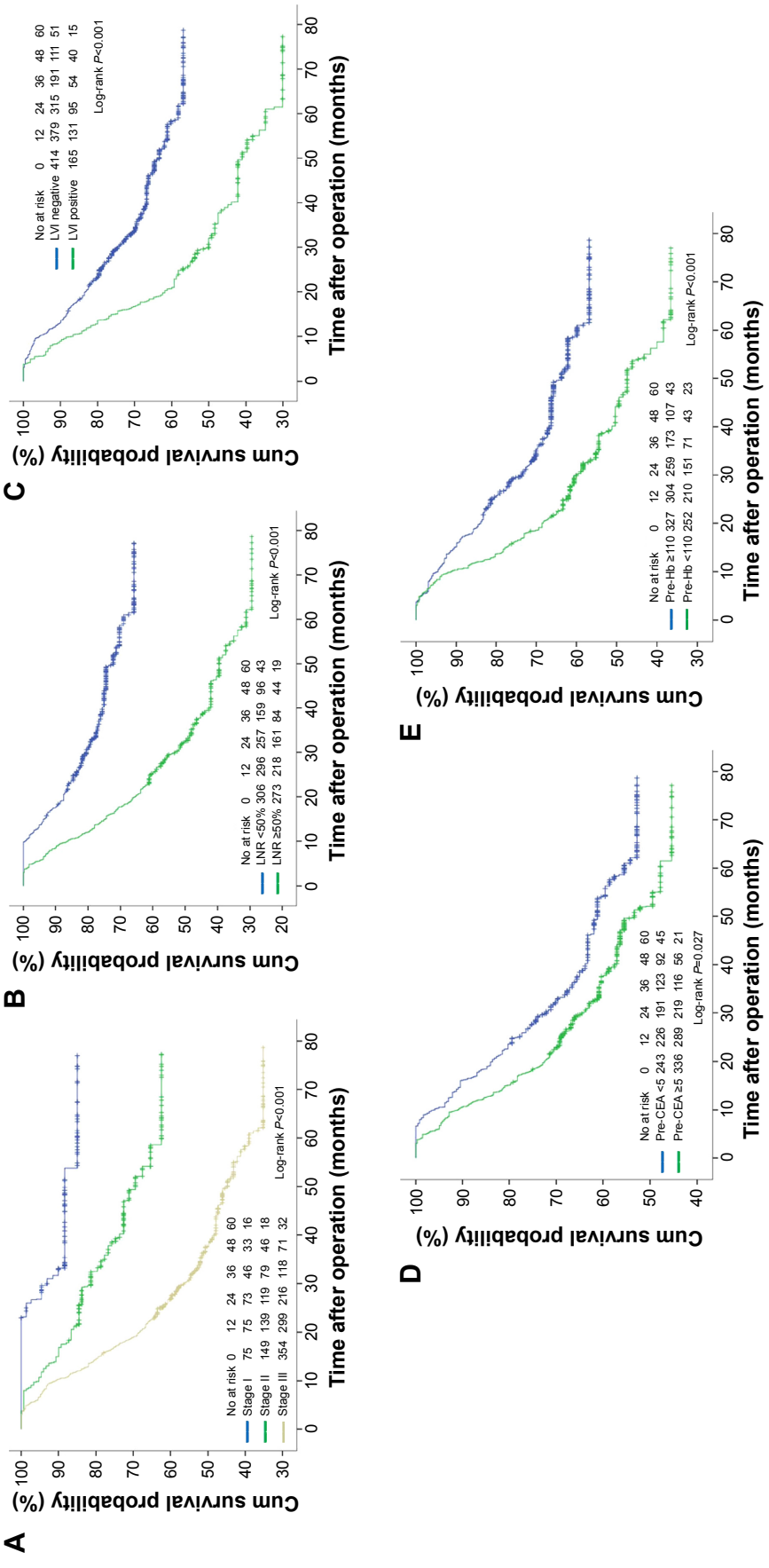


Figure 1 Unadjusted overall survival curves for independent factors by univariate analyses: TNM stage (**A**), LNR (**B**), LVI (**C**), pre-CEA (**D**), and pre-Hb (**E**).
Abbreviations: pre-, preoperative; CEA, carcinoembryonic antigen; Hb, hemoglobin; CA19-9, carbohydrate antigen 19-9; LNR, lymph node ratio; LVI, lymphovascular invasion.

Table 2 Univariate and multivariate survival analyses

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (≥58 vs <58), years	1.03	0.80–1.33	0.835	–	–	–
Sex (male vs female)	1.05	0.80–1.38	0.742	–	–	–
Location (corpus/cardia/fundus vs whole)	0.99	0.75–1.32	0.958	–	–	–
Borrmann type (IV vs I–III)	1.99	0.74–5.35	0.173	–	–	–
Grade (poorly [G3] vs well–moderately [G1/2])	1.63	1.09–2.46	0.018	–	–	–
Depth of tumor invasion (pT) (pT3/pT4 vs pT1/pT2)	3.32	2.18–5.07	<0.001	1.23	0.53–1.23	0.324
Tumor size (>6 cm vs <6 cm)	1.51	1.13–2.00	0.005	1.52	0.83–2.79	0.174
Metastatic node number (pN) (pN2/pN3 vs pN0/pN1)	2.57	1.94–3.41	<0.001	1.07	0.78–1.44	0.675
Metastatic lymph node ratio (LNR) (≥50% vs <50%)	3.02	2.30–3.96	<0.001	1.81	1.32–2.49	<0.001
Lymphovascular invasion (positive vs negative)	2.16	1.66–2.80	<0.001	1.60	1.22–2.09	0.001
Perineural invasion (positive vs negative)	1.51	1.15–1.97	0.003	0.96	0.71–1.28	0.762
TNM stage (II vs I)	2.25	1.11–4.57	0.025	2.18	1.06–4.52	0.035
TNM stage (III vs I)	5.57	2.95–10.53	<0.001	3.48	1.70–7.12	0.001
Surgical margin (R1 vs R0)	2.16	1.66–2.80	<0.001	1.57	0.99–2.06	0.121
Type of gastrectomy (total vs subtotal)	1.41	1.09–1.83	0.009	1.160	0.65–1.13	0.294
Pre-CEA level (≥5 ng/mL vs <5 ng/mL)	1.34	1.03–1.75	0.027	1.13	1.02–1.73	0.034
Pre-CA19-9 level (≥35 U/mL vs <35 U/mL)	1.84	1.35–2.49	<0.001	1.35	0.99–1.85	0.061
Pre-red blood cell (<4×10^{12}/L vs ≥4×10^{12}/L)	1.16	0.90–1.50	0.261	–	–	–
Pre-hemoglobin (<110 g/L vs ≥110 g/L)	1.81	1.40–2.34	<0.001	1.57	1.21–2.03	0.001
Pre-white blood cell (<4×10^{9}/L vs ≥4×10^{9}/L)	1.15	0.73–1.82	0.55	–	–	–
Pre-platelet (≥300×10^{9}/L vs <300×10^{9}/L)	1.10	0.85–1.42	0.464	–	–	–
ASA score (<2 vs ≥2)	1.07	0.88–1.12	0.592	–	–	–
Chemotherapy regimens (triplet vs single)	1.39	0.99–1.96	0.060	–	–	–
Chemotherapy regimens (doublet vs single)	0.82	0.61–1.09	0.173	–	–	–
Taxel-based chemotherapy (yes vs no)	0.84	0.65–1.08	0.179	–	–	–
Oxaliplatin-based chemotherapy (yes vs no)	3.15	0.44–22.48	0.252	–	–	–
FU-based chemotherapy (yes vs no)	0.84	0.64–1.09	0.189	–	–	–
Cisplatin-based chemotherapy (yes vs no)	1.58	0.89–2.83	0.121	–	–	–

Abbreviations: HR, hazard ratio; CI, confidence interval; pre-, preoperative; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ASA score, The American Society of Anesthesiologists score; FU, fluorouracil; LNR, lymph node ratio; –, not applicable.

We analyzed the 5-year survival probability predicted by the scoring system within each TNM stage (Figure 3). Both Model A and Model B had different 5-year survival probabilities in each stage (I–III). Moreover, in Model A, patients who were Stage III and in the low-risk group had higher survival probabilities than those who were Stage II. Similarly, in Model B, patients who were Stage III, but at low or intermediate risk, had better survival probability than those who were Stage II.

Table 3 Definition of score index based on the coefficient in the final Cox model

Overall survival	Score points			
	0	1	2	3
UICC-TNM stage	I	–	II	III
Metastatic lymph node ratio	0%–50%	–	>50%	–
Lymphovascular invasion	Negative	–	Positive	–
Pre-CEA level, ng/mL	<5	≥5	–	–
Pre-hemoglobin, g/L	≥110	–	<110	–

Abbreviations: UICC, International Union Against Cancer; pre-, preoperative; CEA, carcinoembryonic antigen.

To further evaluate the role of the prognostic score within diverse adjuvant chemotherapy regimens, we also analyzed the survival difference of paclitaxel- (Taxol), oxaliplatin-, and cisplatin-based chemotherapies stratified by Model A (Figure 4) and Model B (Figure S4). The data showed that patients who received paclitaxel had better outcomes, but only in the high-score group (Model A score >6, log-rank *P*=0.001). No difference was observed in the low-score group (Model A score 0–6, log-rank *P*=0.169). A similar trend was found regarding oxaliplatin (Model A score 0–6, log-rank *P*=0.697; score >6, *P*=0.002). In Model B, patients in the high-risk group also seemed to benefit from paclitaxel- or oxaliplatin-based chemotherapy, but not those in the low- and intermediate-risk groups. In addition, patients in both low- and high-risk groups did not achieve any survival benefit from cisplatin-based chemotherapy in Model A and Model B. Given that only five patients did not receive 5-fluorouracil, the survival data could not be analyzed. The prognostic value of the number of cytotoxic agents was also examined within

Table 4 Survival outcomes according to risk stratification by Model A and Model B

Model	Prognostic score	Median survival (95% CI), months	1-year survival	2-year survival	3-year survival	4-year survival	5-year survival
Model A							
Low-risk group	0–6	61.0 (58.2–63.8)	95.3%	84.6%	74.8%	70.8%	64.6%
High-risk group	>6	29.9 (20.3–31.4)	76.5%	52.5%	39.9%	32.2%	20.8%
Model B							
Low-risk group	<4	66.4 (63.0–69.8)	99.3%	96.7%	86.9%	84.5%	78.6%
Intermediate-risk group	4–7	51.6 (47.7–55.4)	90.7%	73.9%	62.4%	56.4%	50.5%
High-risk group	>7	29.3 (22.5–36.2)	73.2%	46.4%	33.8%	26.6%	16.2%

Abbreviation: CI, confidence interval.

Model A and Model B. Triple chemotherapy correlated with a better prognosis compared with dual combination or monotherapy, but again only in high-risk subgroups according to Model A and Model B (Figure 5).

Discussion

Prognostic tools for the treatment of resectable GC are very important in selecting the best strategy and improving outcome. In the current study, we analyzed a large GC cohort retrospectively and developed two clinical prognostic models that improved the pTNM identification of high-risk subgroups that benefit from adjuvant chemotherapy. Both the models significantly discriminated the outcomes of patients, but the three-class Model B (AUC: 0.79) had a higher accuracy in long-term prognosis than Model A (AUC: 0.74). Therefore, the scoring system with the three-class model is recommended for predicting prognosis.

Although the benefit of gastrectomy for patients with resectable GC is clear, and that some kind of neoadjuvant, perioperative chemotherapy, or adjuvant therapy is needed to improve the survival,[50–53] there is no international consensus on the best approach, resulting in varying guidelines in countries and regions.[5] Several recent randomized controlled studies conducted in Asia[7–9,54] showed significantly improved OS and progression-free survival after adjuvant chemotherapy, which thus became a treatment of choice in patients with resectable GC in these populations. Given the limited survival benefit and also the considerable adverse effects of adjuvant chemotherapy,[7–9,11,54] accurate assessment of individual prognosis is important in making a therapeutic choice.

Among the several proposed prognostic factors, pTNM staging is the most widely used as it displays a strong prognostic value for GC. However, due to the limitations associated with pTNM staging, several alternative prognostic models for GC have been proposed,[55–58] which showed improved prognostic ability. Some prognostic models have focused upon resectable gastric carcinoma. Becker et al[55] investigated neoadjuvant-treated GC. Kattan et al proposed a nomogram predicting disease-free survival (DFS) after an R0 resection for gastric carcinoma.[43] A multi-institutional cohort of gastric adenocarcinoma patients in USA was analyzed for nomogram to predict OS and DFS after R0 curative resection.[58] Han et al built a prognostic nomogram of long-term survival after D2 lymphadenectomy of gastric carcinoma in Asian populations.[59] However, to our knowledge, neither a prognostic model for adjuvant chemotherapy nor the

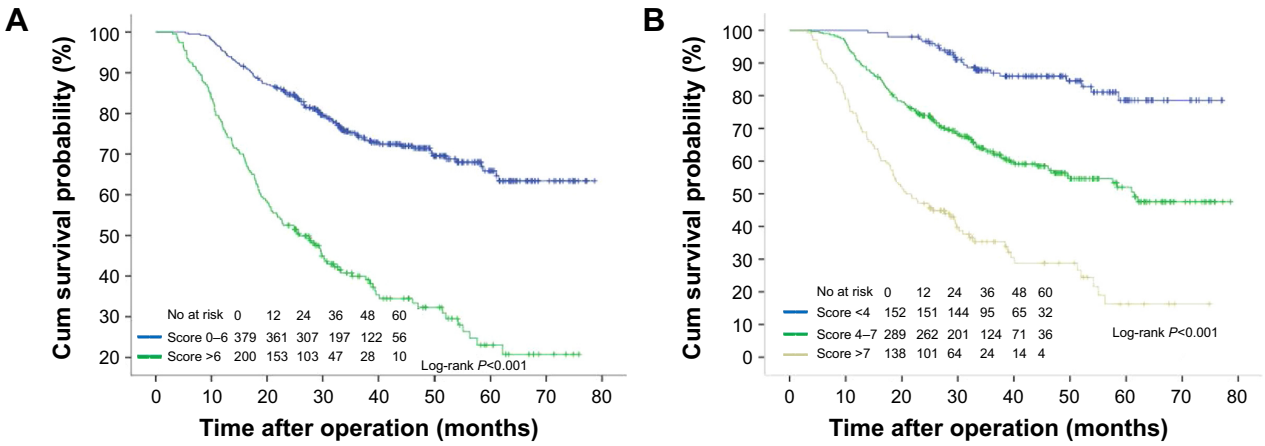
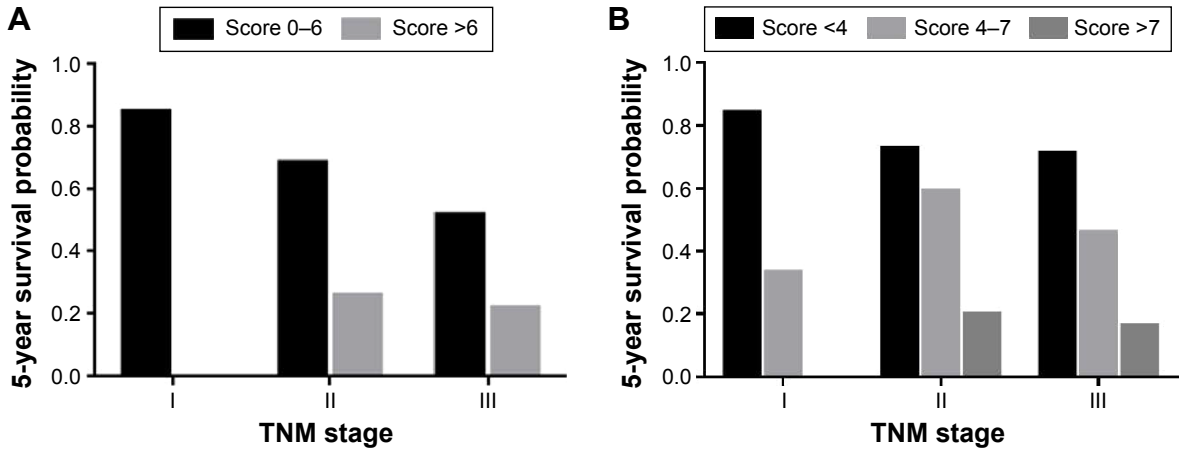


Figure 2 Kaplan–Meier analysis of overall survival, according to risk prognostic score from Model A (two classes, **A**) and Model B (three classes, **B**).



C

		I		II		III	
		No (percent)	5-year survival	No (percent)	5-year survival	No (percent)	5-year survival
Model A							
Low-risk group	Score 0–6	76 (100%)	0.85	135 (90.6%)	0.69	168 (47.5%)	0.52
High-risk group	Score >6	0 (0%)	0	14 (9.4%)	0.26	186 (52.5%)	0.22
Model B							
Low-risk group	Score <4	73 (96.1%)	0.84	60 (40.3%)	0.73	19 (5.4%)	0.71
Intermediate-risk group	Score 4–7	3 (3.9%)	0.33	84 (56.4%)	0.59	202 (57.1%)	0.46
High-risk group	Score >7	0 (0.0%)	0	5 (3.4%)	0.20	133 (37.6%)	0.16

Figure 3 The relationship between 5-year survival and UICC stage classification of patients in Models A and B.
Notes: (**A** and **B**) Diagrams of 5-year survival for prognostic score Models A and B within UICC stage classification. (**C**) Percentage and 5-year survival rate of Models A and B according to UICC stage.
Abbreviation: UICC, International Union Against Cancer.

role of preoperative serum markers has been published in this setting. Given the essential role of D2 gastrectomy[60–62] and the survival benefit from adjuvant chemotherapy for resectable gastric carcinoma,[7–9,54] we developed prognostic models for Chinese patients treated with standard D2 gastrectomy and adjuvant chemotherapy.

One major finding of this study is that the current scoring system identified patients with different long-term prognoses within each pTNM stage (I–III), suggesting that a number of high-risk patients are understaged using only the pTNM classification. These high-risk subgroups eventually benefit from a more intensive postoperative treatment.

Moreover, although the survival benefits from adjuvant treatment with various combinations of fluorouracil, oxaliplatin, and paclitaxel have been demonstrated for patients after gastrectomy in several recent randomized controlled trials,[7–9,54] no consensus has been reached on the optimal treatment schedule. In general, for advanced disease, dual combinations are preferred. However, in selected patients, for example, those with a high tumor burden, triple regimens resulted in higher response rates and enhanced efficacy.[63–65] In this study, we analyzed the prognostic value of a number of adjuvant cytotoxic agents and regimens, which were found to be independent prognostic factors. This result is similar to those of a previous study.[59] However, when stratified by the current scoring system, high-risk patients (Model A: score >6 and Model B: score >7) obtained survival benefits from postoperative treatment with paclitaxel or oxaliplatin, while low-risk patients did not. Additionally, triple combination prolonged the outcome of high-risk patients compared with dual or single chemotherapy, but not for the low-risk subpopulation. Importantly, the variables included in the current scoring system were all confirmed prognostic factors that are usually available and easily accessible in the daily practice. Therefore, compared with high-throughput biomarker analysis, the current system is more simple, practical, and cost-effective.

LN metastasis confers poor prognosis in malignancies. In the TNM staging system, the N category was on the basis of the absolute number of involved nodes and can be influenced by the number of LNs retrieved.[18,19] According to some studies, 15 LNs is the minimum number of harvested LNs for

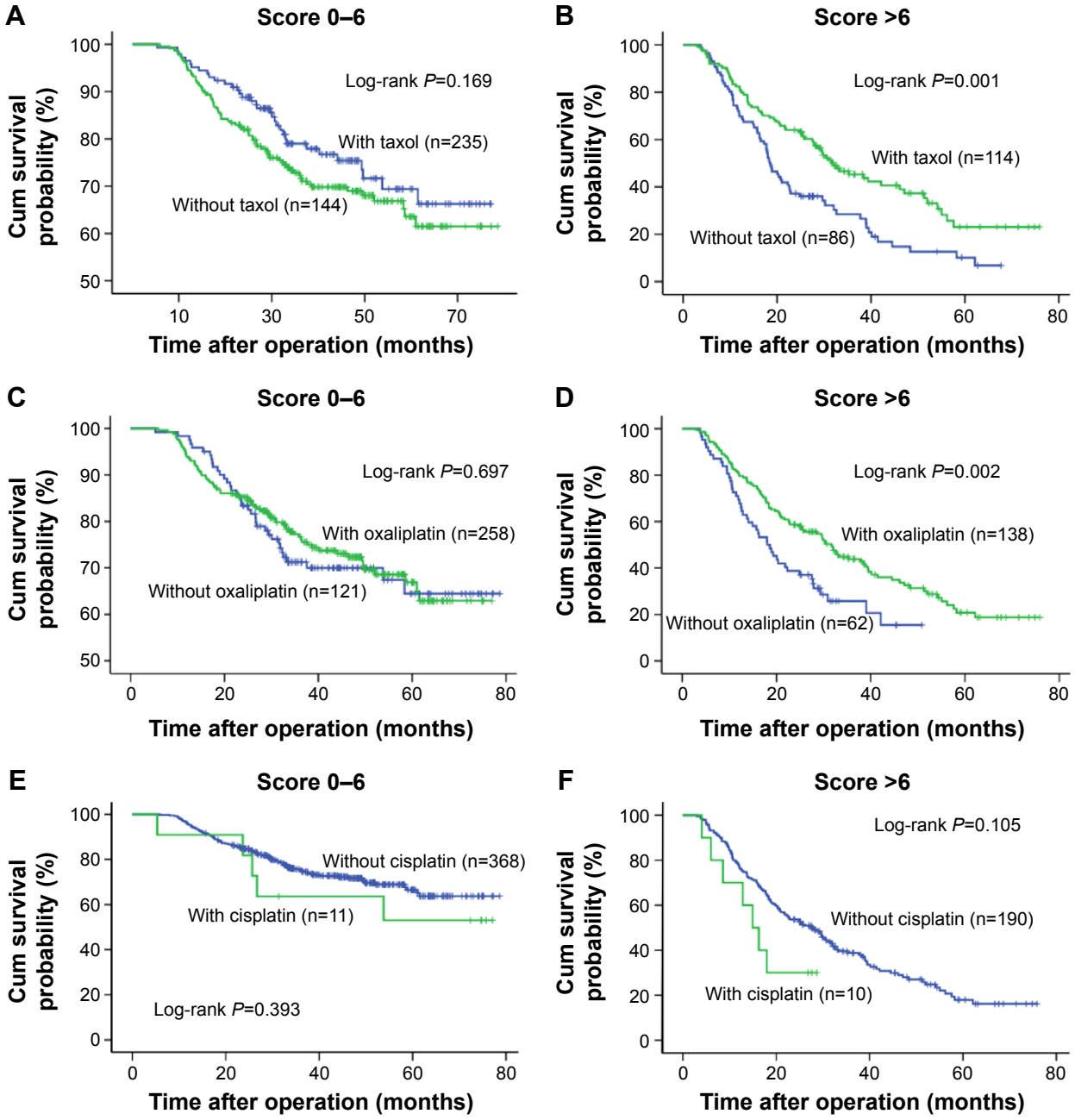


Figure 4 Kaplan–Meier curves of overall survival (OS) in gastric cancer patients according to adjuvant chemotherapy with or without paclitaxel (**A** and **B**), oxaliplatin (**C** and **D**), and cisplatin (**E** and **F**) stratified by Model A.

optimal LN assessment.[18,19,66] Insufficient LN retrieval could result in stage migration, which might deprive postoperative patients of adjuvant therapy with poor prognosis as a consequence.[20] In contrast, LNR showed little dependence on the number of LN resected and was superior to LN evaluation in GC.[18,19,21,67] Our data also revealed that LNR has a stronger predictive potential than N category in local GC after D2 lymphadenectomy and adjuvant chemotherapy. The group of LNR <50% presented a significantly longer mOS (61.9 months vs 30.7 months) and 5-year survival (51.39% vs 18.1%) compared with the group of LNR >50% ($P<0.0001$). LNR is also a predictive factor for adjuvant chemotherapy in our system, which was supported by several previous studies. Significant benefits from postoperative chemoradiotherapy were achieved in the resected NSCLC patients with LNR >0.31 compared with adjuvant chemotherapy alone or no adjuvant therapy.[68] A recent multicenter prospective study in the UK showed that colon cancer treated with curative resection, with a LNR within 0.05–0.19, was an indication for adjuvant chemotherapy.[69] Advanced GC patients with LNR >0.65 showed a 3-year DFS following the adjuvant chemoradiation than the chemotherapy alone.[70] Nevertheless,

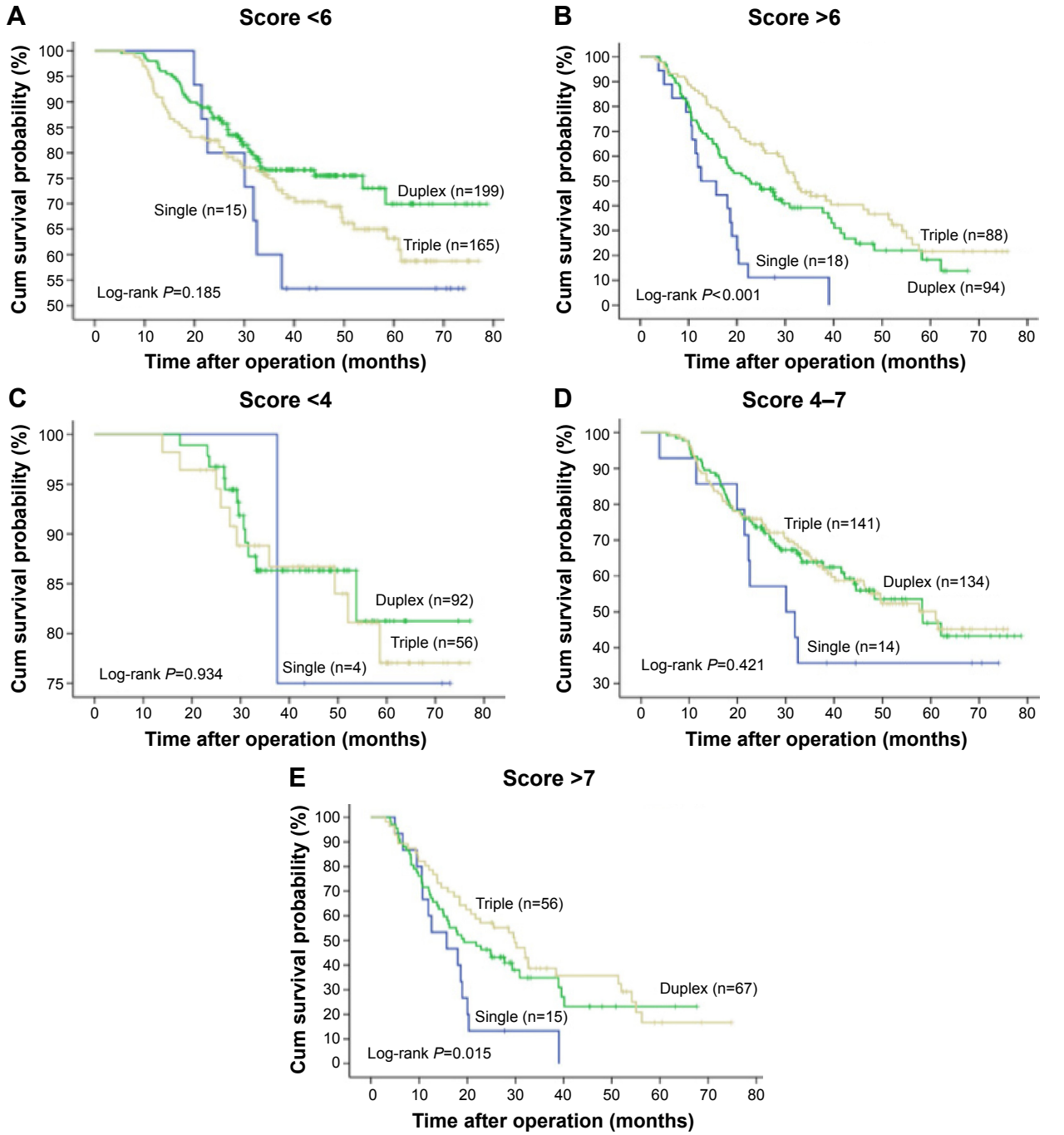


Figure 5 Kaplan–Meier curves depicting OS of gastric cancer patients according to the number of cytotoxic agents stratified by Model A (**A** and **B**) and Model B (**C**–**E**).
Abbreviation: OS, overall survival.

the optimal cutoff of LNR remains to be further validated in various scenarios.

LVI, indicating aggressive behavior of carcinomas, is an established strong negative prognostic factor,[71,72] which was confirmed by our data. LVI also indicates the need for adjuvant therapy in gastric malignancies.[73] In a study of 1,880 patients with Stage I GC, T2N0 with positive LVI may be candidates for adjuvant chemotherapy.[73] In another larger data set of Stage I GC after curative resection, six risk factors, including age, sex, Stage IB, LVI, PNI, and elevated CEA level, were selected to identify the subgroup with high risk of recurrence or death, who may gain benefits of adjuvant chemotherapy.[72]

Elevated levels of serum CEA and CA19-9 have been used as markers to detect cancer progression after surgery.[27] However, the prognostic value of preoperative CEA in GC is still debated.[25–27,29,31,32,45,72] In the present study, despite a low HR for CEA compared with CA19-9 according to univariate

analysis, elevated preoperative levels of CEA had a higher prognostic value than CA19-9 in the multivariate analysis. This phenomenon was probably due to other confounding factors affecting the unadjusted HR. Significant differences in the 3- and 5-year survival rates and median survival rates were also observed when comparing positive and negative levels of serum CEA (Figure 1D). High preoperative CEA levels can also be used to monitor the efficacy of paclitaxel in patients with advanced breast cancer and non-small cell lung cancer,[30,74,75] assess response to irinotecan-based chemotherapy in metastatic colorectal cancer patients,[76,77] and predict disease progression after irinotecan-containing neoadjuvant chemotherapy in GC.[78] These are consistent with the current results that a score containing CEA can help predict the survival benefit of adjuvant chemotherapy. Preoperative CEA levels should thus be considered when selecting further chemotherapy after curative gastrectomy for gastric carcinoma.

Although posttherapy anemia mainly results from chemotherapy-induced myelosuppression, renal-related erythropoietin deficiency, or marrow involvement,[79] anemia at diagnosis may be predominately due to chronic bleeding or nutritional dysfunction, consequently leading to poor tolerability of adjuvant chemotherapy and shorter survival.[80] Preoperative low Hb level has been proposed as an independent prognostic factor for several cancers in recent studies.[37,81–83] In gastric malignancy, iron-deficiency anemia was most frequent after gastrectomy[84] and predicted an increased risk of developing surgical complications[37] and unfavorable outcomes.[81–83] In addition, preoperative anemia has been linked to poor control during paclitaxel-based chemotherapy, which was possibly due to paclitaxel-induced HO-1 gene expression,[85] a microsomal enzyme catalyzing the breakdown of heme.[86,87] Supporting this, preoperative Hb $<$110 g/L was closely associated with a poor outcome in our cohort with a mOS of 62.1 months compared with 52.0 months in patients with Hb $>$110 g/L. Preoperative Hb level could be informative in selecting optimal subpopulation who could most benefits from the specific chemotherapy regimen.

Our prognostic model with both preoperative and postoperative data could not account for other scenarios, eg, neoadjuvant, perioperative chemotherapy, or adjuvant radiochemotherapy. The prognostic value of preoperative data is appealing, as it can be used to predict the response of treatment prior to pre and perioperative approaches. However, considering the essential role of adjuvant chemotherapy in Asian patients with radically resected GC compared with those in USA and Europe,[6,88–93] we felt the need to analyze the case of postoperative chemotherapy. Our postoperative data combined with preoperative data could be utilized for response prediction and patient selection before commencing adjuvant chemotherapy. Pre and perioperative treatments require additional investigation. Prognostic scoring systems are not "one-size fits all" and need to be tailored to various settings.

Given the discrepancy of surgical techniques and pathological examinations, and the differences in serum detection criteria and methods, our system cannot be generalized to other settings. In addition, there are other study limitations. First, comorbidity was not considered in the current model, although OS was defined as the final point. OS can be affected by comorbidity. Although carcinoma was the most frequent cause of death, to minimize the effect of comorbidity on the outcome, patients with synchronous malignancies were excluded from the study, and only eleven subjects died of noncancer causes before the end point. Therefore, comorbidity likely exerted little influence on the model. Second, some biological markers have recently been identified as prognostic factors, including Her2 (human epidermal growth factor receptor-2),[94,95] Fhit (fragile histidine triad),[47,96] TP53 mutations,[97,98] and CDH1 (E-cadherin).[99,100] In the future, biological markers will be inevitably incorporated in the decision-making process along with traditional clinicopathological parameters. Recently, Bria et al proposed a clinical–biological risk stratification model for resected GC in which the levels of HER2, Fhit, and APC combined with five clinical factors were used for evaluating survival.[47] However, considering that the expression of certain genes may vary according to the genetic background, country of origin, and size of the mass, clinical–biological risk models should be validated using unified criteria in diverse populations. Third, the Lauren classification was absent in the current scoring system. In light of the influence of missing data on statistical power, during data collection, we excluded the Lauren classification, which is not routinely reported in our cancer center. Furthermore, a few GC prognostic studies failed to demonstrate a significant role of this classification in outcome prediction.[59] Finally, due to inherent bias associated with a retrospective analysis, we cannot simply conclude that the prognostic risk scoring system is more accurate than TNM classification. Although we have conducted cross-validation and demonstrated good discriminative potential of the scoring models, a prospective multicenter external validation study of the scoring system with a larger sample size is needed.

Conclusion

In conclusion, a three-class prognostic risk assessment scoring system was established by integrating preoperative serum

Hb, CEA levels, postoperative status of LVI, involved LNR into the seventh UICC-pTNM stage system with an elevated predictive ability for long-term survival of patients with local GC who have undergone D2 gastrectomy. This system can identify the high-risk subsets of Stage II or III patients who may be candidates for more intensive follow-up and predict potential benefits of paclitaxel- or oxaliplatin-based chemotherapy before administration of adjuvant chemotherapy. This system may be of value to oncologists for clinical decision making before adjuvant chemotherapy, although a prospective validation is needed.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Method S1

Indications for adjuvant chemotherapy

Histologically confirmed gastric cancer of seventh UICC-TNM Stage II, III, or I (T1b/T2N0) with risk factors including poor differentiation; lymphovascular or neural invasion; adequate organ function (a leukocyte count of $>4\times10^9$/L or the lower limit of the normal range; a platelet count of $>100\times10^9$/L; a total bilirubin level of <1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase levels not more than two times the upper limit of the normal range; and a serum creatinine level no greater than the upper limit of the normal range); and an age of 20–85 years.

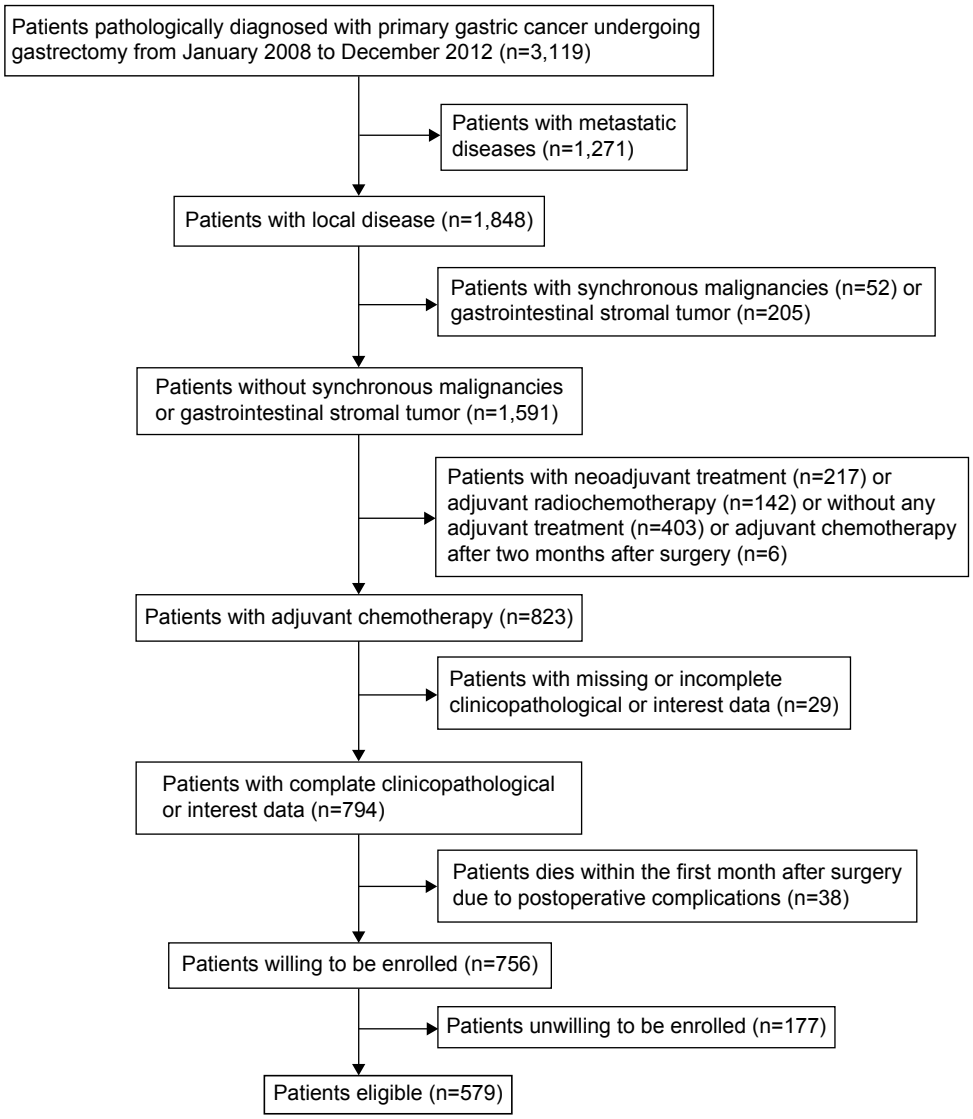

Figure S1 Flow chart outlining patient selection.

Table S1 Adjuvant chemotherapy regimens

Adjuvant regimen	N	%	Adherence N	Adherence rate (%)
Total	579	100.0	331	57.2
Oxaliplatin/paclitaxel/5-FU	214	37.0	125	58.4
Oxaliplatin/capecitabine	95	16.4	69	72.6
Paclitaxel/capecitabine	60	10.4	35	58.3
Oxaliplatin/S-1	43	7.4	27	62.8
Paclitaxel/5-FU	40	6.9	12	30.0
Oxaliplatin/5-FU/leukovorin	37	6.4	19	51.3
Paclitaxel/S-1	30	5.2	16	53.3
5-FU/cisplatin	22	3.8	10	45.5
Capecitabine	21	3.6	13	61.9
Oxaliplatin/paclitaxel	5	0.9	1	20.0
S-1	12	2.1	4	33.3

Note: Paclitaxel in the study is Taxol only.
Abbreviation: FU, fluorouracil.

Table S2 Adjuvant chemotherapy regimens and dosing schedules

Regimen	Schedules
FOLFOX6	85 mg/m^2 oxaliplatin, 400 mg/m^2 leucovorin, and 400 mg/m^2, 5-FU iv D1 followed by 2,400 mg/m^2 civ 46–48 h, q2w 8 cycles
SOX	S-1 40–60 mg bid, D1–14, oxaliplatin 130 mg/m^2, iv drip for 2 h, D1, q3W 8 cycles
XELOX	130 mg/m^2 oxaliplatin D1 and 1,000 mg/m^2 capecitabine bid, po, D1–14, q3W 8 cycles
Oxaliplatin/paclitaxel/5-FU	Paclitaxel 80 mg/m^2 iv D1,8, oxaliplatin 30 mg/m^2, iv drip for 2 h, D1, q3W 8 cycles
POX	Paclitaxel 80 mg/m^2 iv D1,8, oxaliplatin 130 mg/m^2 iv, D1, q3W 8 cycles
Paclitaxel/capecitabine	Paclitaxel 80 mg/m^2 iv D1,8, 1,000 mg/m^2 bid, po, D1–14, q3W 8 cycles
Paclitaxel/5-FU	Paclitaxel 80 mg/m^2 iv D1,8, 5-Fu 300 mg/m^2 civ D1–5, q2W 8–10 cycles
Paclitaxel/S-1	Paclitaxel 80 mg/m^2 iv D1,8, q3W 8 cycles
CF	5-FU iv D1 followed by 2,400 mg/m^2 civ 46–48 h, cisplatin 70–100 mg/m^2 iv D1, q3W 8 cycles
Capecitabine	1,000 mg/m^2 bid, po, D1–14, q3W 8 cycles
S-1	80 mg/m^2, po, D1–28, continuous 4 weeks stop 2 weeks

Abbreviations: FU, fluorouracil; iv, intravenous; po, orally; h, hours; civ, continuous intravenous infusion.

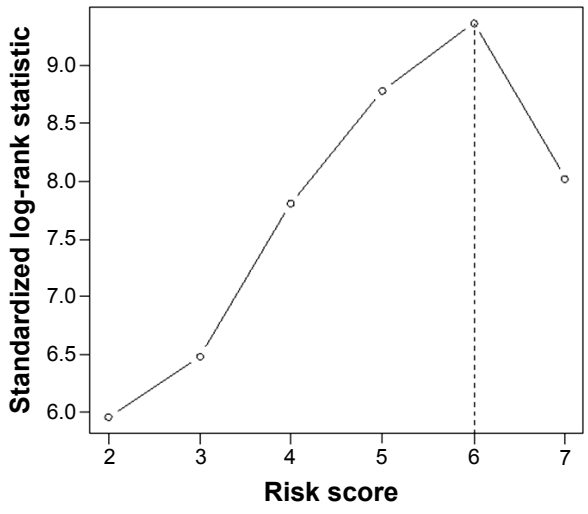

Figure S2 Maximally selected log-rank statistics plot for optimal cutoff point identification in Model A.

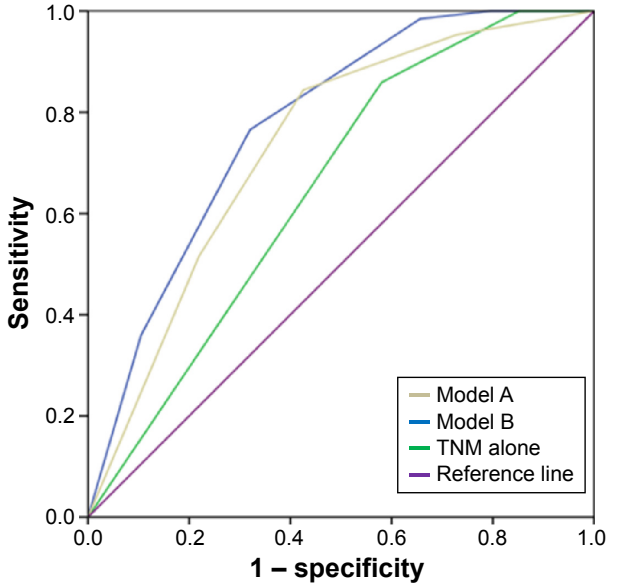

Figure S3 ROC analysis of two prognostic models compared with TNM alone to predict patient probability for 5-year survival.
Abbreviation: ROC, Receiver Operating Characteristic curve.

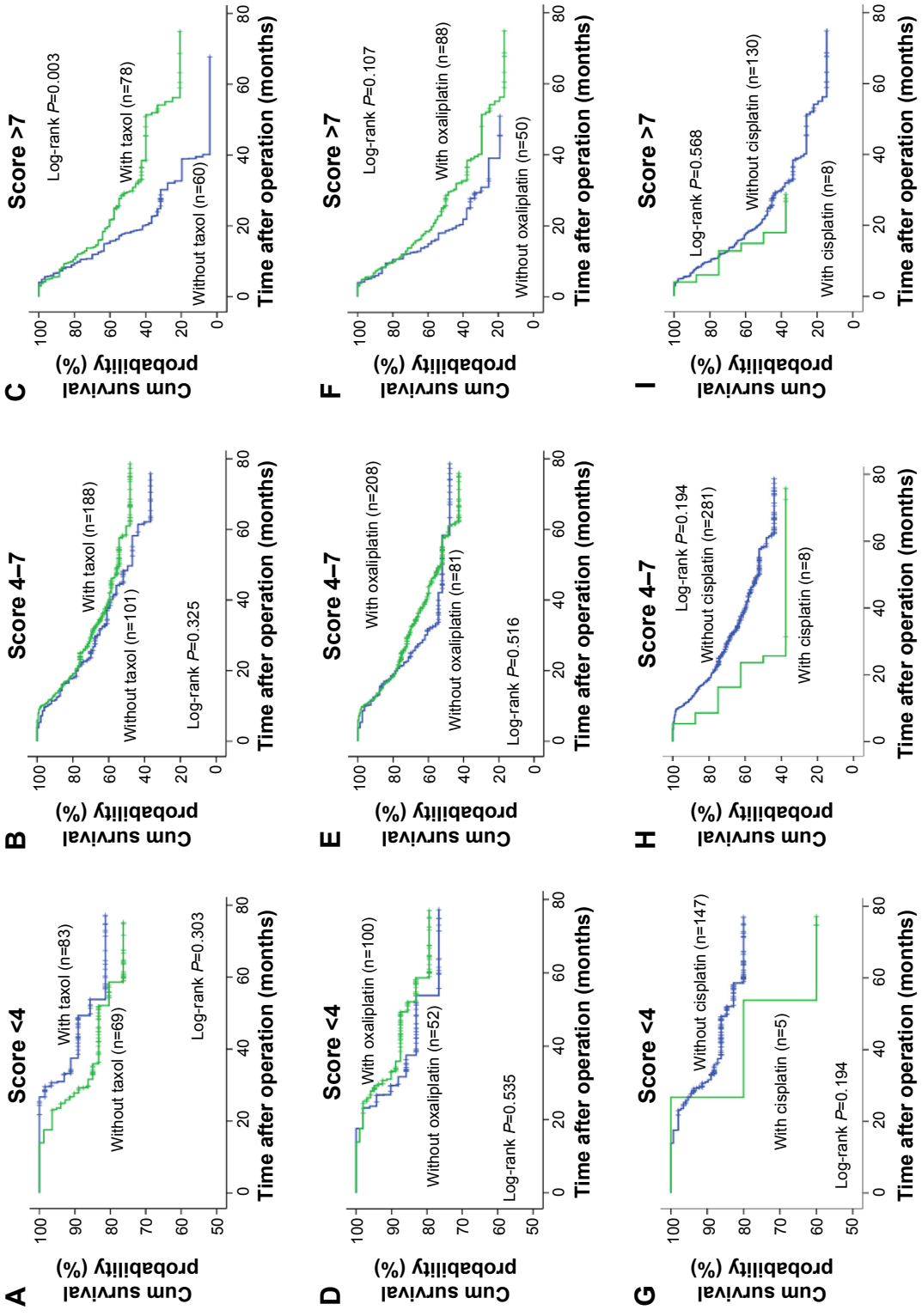

Figure S4 Kaplan–Meier curves of OS in gastric cancer patients according to adjuvant chemotherapy with or without taxol (**A–C**), oxaliplatin (**D–F**), and cisplatin (**G–I**) stratified by Model B.
Abbreviation: OS, overall survival.