Prognostic value of immunity change after treatment for patients with locally advanced gastric cancer: a retrospective study

Ke-Shen Wang
Lanzhou University Second Hospital
Cheng-Cheng Ma
Lanzhou University Second Hospital
Yan-Xian Ren
Lanzhou University Second Hospital
Zhi-Jian Ma
Lanzhou University Second Hospital
Shu-Ze Zhang
Lanzhou University Second Hospital
Fan Li
Lanzhou University Second Hospital
Xiao-Cheng Cheng
Lanzhou University Second Hospital
Jing-Ying Xiao
Lanzhou University Second Hospital
Ze-Yuan Yu
Lanzhou University Second Hospital
Hui-Nian Zhou
Lanzhou University Second Hospital
Zuo-Yi jiao (jzyldey@163.com)
Lanzhou University Second Hospital

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Abstract

Background Although the preoperative immune status is associated with the prognosis in some tumors, less is known about the prognostic significance of immune status change during the treatment of patients with locally advanced gastric cancer (LAGC).

Methods The records of 210 patients with LAGC were retrospectively analysed. The pre-, and post-treatment (after gastrectomy and three cycles of chemotherapy) values of lymphocyte-to-monocyte ratio (LMR) and change of LMR (cLMR) were evaluated. A novel immunity change score (ICS) incorporated both preoperative LMR (pLMR) and cLMR was developed and its prognostic value was evaluated.

Results cLMR was an independent predictor and patients with cLMR >1 after treatment had a favorable survival compared with the others (51 vs 31 months, $P < 0.001$). Based on the cLMR and pLMR, the ICS was defined as follows: ICS=1 (pLMR≤4.53 and cLMR≤1); ICS=2 (pLMR≤4.53 and cLMR>1, or pLMR>4.53 and cLMR≤1); and ICS=3 (pLMR>4.53 and cLMR>1). Multivariate analysis revealed that the ICS was a significant independent biomarker ($P < 0.001$). The performances of ICS in terms of the time-dependent receiver operating characteristics (t-ROC) curve and concordance index (C-index) analysis were better than those of pLMR and cLMR. Then we established a nomogram incorporated the ICS, CEA, and TNM stage to predict the 3- and 5- year survival. Decision curve analysis and calibration curve demonstrated that the nomogram was clinically useful.

Conclusion The dynamic change of immune status is significantly associated with prognosis for LAGC patients. Combining with the cLMR and pLMR could improve the prognostication for LAGC patients.

Introduction

The prognosis of gastric cancer (GC) remains very poor, due to tumor load at the time of diagnosis and the limited efficacy of treatment [1–2]. For GC patients at an advanced stage, including stage Ⅱ-Ⅲ, the five-year survival rates are remaining at 30%–50% even if underwent radical resections [3]. Therefore, identifying patients at high risk of micrometastasis or local recurrence, and preventing deterioration are important to decrease cancer-related death [4].

Recently, with the increasing understanding of the connection between the immune system and tumor, immunotherapy is receiving increasing attention and the prognosis value of systemic immune-related markers has been investigated in various tumors [5–7]. Because of the more convenient and affordable for detecting, absolute lymphocyte count (ALC) and monocyte count (AMC) in blood routine examination have been widely used for immune surveillance in several hematologic malignancies and solid tumors [8–10]. In GC, the value of ALC, AMC, and lymphocyte to monocyte ratio (LMR) had been reported to be associated with the prognosis both before and after gastrectomy, and a higher lymphocyte or lower monocyte were found to be associated with a longer survival time [9,11–13]. However, previous studies isolated the prognostic values of ALC, AMC, and LMR at a single point in time, and ignored the alterations

in immune statue during the treatment process, especially when the tumor load changes and chemotherapy applied [9,12–13].Thus, we hypothesis that adding the stratification according to the change of LMR (cLMR) during treatment to the basis of preoperative LMR (pLMR) may help to discriminate patients accurately.

The aim of this study was to investigate the change of immune statue in response to surgery and adjuvant chemotherapy, and also assess its prognosis value. Besides, we try to establish an immunity changes score (ICS) based on both pLMR and cLMR to predict the prognosis of patients with stage Ⅱ-Ⅲ LAGC.

Methods

Study subjects.

From January 2013 to December 2017, patients with LAGC diagnosed and treated in Lanzhou University Second Hospital were retrospectively studied. All patients underwent D2 lymphadenectomy or extend D2 lymphadenectomy based on the guidelines of the Japanese Research Society for the Study of GC [14], and suffered from stage pT2–4NxM0 according to the criteria of the 7th edition of the TNM classification [15]. To ensure the homogeneity of treatment, patients who received any previous chemotherapy or radiotherapy, and received less than three cycles of adjuvant chemotherapy were excluded from this study. Finally, 210 consecutive patients were included.

All patients were followed up by giving a telephone call or posting letters. The last time of follow-up was 1 June 2019. All follow-up findings were collected and recorded in the database. The current study was performed following the Declaration of Helsinki and approved by the institutional review board.

Data collection and definition

Blood routine examinations were tested conventionally during the perioperative period and the following course of adjuvant chemotherapy. The values of ALC and AMC within 3 days before the operation and the fourth course of adjuvant chemotherapy were collected. The normal value of peripheral blood ALC and AMC were $0.8–4x10^9$/L and $0.12–0.8x10^9$/L, respectively. Immune statue was quantized by LMR, which was equivalent to the ratio of ALC to AMC.

Additional variables on clinicopathologic characteristics including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, tumor location, tumor size, Lauren classification, degree of differentiation, nerve invasion, vessel invasion, pathological TNM stage (pTNM) and the preoperative values of Carbohydrate antigen 199 (CA–199) as well as Carcinoembryonic Antigen (CEA) were obtained. All the patients in this study underwent total, subtotal, or distal gastrectomy based on the primary tumor size and location, and also accepted at least three cycles of adjuvant chemotherapy, which including FLOT, SOX, and FOLFOX6 regimen [15].

Definition of immune-related indicators and ICS

The changes in overall immune status throughout the treatment process including surgery and adjuvant was evaluated by the cLMR, which was determined by dividing the LMR before the fourth chemotherapy (fLMR) by the preoperative one (pLMR), and immunity increased was defined as cLMR > 1. The optimal cut-off value for continuous variables including pLMR in terms of survival was calculated by the software X-tile (Tale University, New Haven, CT, the United States of American) [16]. According to the cut-off value of pLMR, all patients were divided into four groups: HG, patients with high pLMR and cLMR greater than one; HL: patients with high preoperative LMR and cLMR equal to or lesser than one; LG: patients with low preoperative LMR and cLMR greater than one; and LL: patients with low preoperative LMR and cLMR equal to or lesser than one. Different degree of ICS will be given to the above four groups based on survival.

Statistical analysis

Paired samples Wilcoxon test were used to compare the value of pLMR and fLMR. For categorical variables, the Chi-square test or Fisher's exact test were used. Overall survival (OS) was defined as the time between diagnosis and last contact or death, and which between different subgroups were plotted using the Kaplan-Meier curves and compared with the log-rank tests. The prognosis abilities of pLMR and ICS were compared by generating time-dependent receiver operating characteristic (t-ROC), which evaluated the discriminatory of continuous variables for time-dependent disease outcomes[17].The area under the curve (AUC) represents the discriminative power of these two variables and can be calculated to comparing the ROC curves visually [18]. Besides, to quantify the discrimination performance of pLMR and ICS, Harrell's concordance-index (C-index) was measured. Univariate analysis was performed firstly to screen out the potential prognostic factors, and then the COX proportional hazards regression analysis was used to identify the independent factors. Finally, a nomogram based on the basic of multivariable COX analysis and ICS was built to assist the clinician in predicting prognosis individually. Calibration curves and C-index were used to assess the calibration and quantify the predictive accuracy of the predictive nomogram. To investigate the clinical usefulness of the nomogram for predicting 3-year survival, the decision curve analysis (DCA) was performed, which could quantify the net the benefits at different threshold probabilities in the validation dataset [19]. All hypothesis tests were two-sides and $P < 0.05$ was recognized as statistical significance. All statistical analysis was conducted with Statistical Product for Social Sciences (SPSS) software (version 24.0; Inc, Chicago, IL, United States) and R ver. 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). The R packages used in this study were including "rms", "timeROC", "stdca", and "survival".

Results

Patients characteristics

Two hundred and ten consecutive stage II-III LAGC patients who received surgery and followed by adjuvant chemotherapy were meeting our inclusion criteria. The median age was 57.6 years (range, 31–80 years), and 61(29.05%) patients were female. Patients demographics are described in SupplementaryTable S1. According to the pathological confirmation, 92(43.81%) patients were at stage II and 118(56.19%) patients were at stage III. The surgical procedures included total gastrectomy in 68(32.38%), subtotal gastrectomy in 44(20.95%), and distal gastrectomy in 98(46.67%). Besides, 138(65.71%) patients received adjuvant chemotherapy with docetaxel.

Changes in immune status during treatment

The median LMR increased from 4.816 (range 0.636–22.75, IQR3.68–6.408) at baseline to 5.358 (range 0.547–24.9, IQR3.943–7.114) (P = 0.039) after radical resection and three cycles of chemotherapy, and 111 (52.86%) patients showed an increase in LMR. The relationship between cLMR and clinicopathological variables were shown in Table 1. Patients with a well histologic type or intestinal type of Lauren classification were more likely to have an elevated immunity after treatment.

Survival analysis

The median follow-up time for the entire cohort was 46 months (range, 5–75 months), and the median survival time was 42 months. In the last time of data analysis, 115 (54.76%) patients had died. In this study, the threshold value for pLMR was 4.53, with the 2 value of 18.766, P < 0.001, and a relative risk ratio of 1:2.263 (Supporting Information figure 1). Additionally, other optimal cut-off values also calculated by X-tile for CA–199, CEA, and tumor size were 27U/ml, 5.15ng/ml, and 4cm (Supporting Information figure 2, 3, and 4). As shown in Figure 1A, patients with cLMR > 1 had a longer median survival time than patients with cLMR≤1, (51 months vs 31 months, P < 0.001). Besides, univariate analysis showed that Lauren classification, tumor size, adjuvant chemotherapy, and pTNM stage were all significantly associated with OS (all P < 0.05, Table 2). The multivariable Cox model was performed using these factors, and the results demonstrated that the pTNM stage (HR: 2.963, 95%CI: 1.817–4.883, P < 0.001), CEA > 5.15ng/ml (HR:1.71, 95%CI: 1.705–2.721, P = 0.024), pLMR > 4.53 (HR:0.352, 95%CI: 0.235–0.528, P < 0.001), and cLMR>1 (HR:0.402, 95%CI: 0.269–0.601, P < 0.001) were independent prognosis factors (Table 2).

Establishment of ICS

Among the 210 patients,122 (58.1%) with a high pLMR and 88 (41.9%) with a low pLMR as well as 111(52.86%) patients with cLMR >1 and 99(47.14) patients with cLMR ≤ 1. Then patients were primarily divided into four groups: 65(31%) in HL (pLMR > 4.53 and cLMR ≤ 1), 57 (27.1%) in HG (pLMR > 4.53 and cLMR > 1), 34(16.2%) in LL (pLMR ≤ 4.53 and cLMR ≤ 1), and 54(25.7%) in LG (pLMR ≤ 4.53 and cLMR > 1). Overall, patients in four groups had a significantly different OS (P<0.001) with assessed by Kaplan-Meier methods (Figure 1B). However, there were no significant differences in OS between HL and LG (P = 0.987). Therefore, the ICS was defined as follows: patients in LL were assigned a score of 1; patients in whether HL or LG were assigned a score of 2; and patients in HG were assigned a score of 3.

Additionally, the relationship between clinicopathologic characteristics and ICS was investigated (Table 3). There were 34 (16.19%) patients in the ICS = 1 group, 119(56.67%) patients in the ICS = 2 group, and 57(27.14%) patients in the ICS = 3 group. An elevated ICS was found to be significantly associated with intestinal Lauren classification and low tumor size (all $P < 0.05$).

Prognosis value of ICS

The 5-year OS rates calculated by the Kaplan-Merier curves for patients with different ICS were 6.4% (ICS = 1), 25.3% (ICS = 2), and 69.5% (ICS = 3) ($P<0.001$, Figure 1C). The result of multivariate analyses demonstrated that ICS was still an independent factor for OS (ICS = 2, HR:0.442, 95%CI:0.288–0.677; ICS = 3, HR:0.098, 95%CI: 0.05–0.192, $P < 0.001$, SupplementaryTable S2). To further compare the prognostic value of ICS, cLMR and pLMR, the t-ROC curves were employed. The results of t-ROC curves demonstrated that ICS was the best prognostic indicator because its AUC was persistently superior to these of cLMR and pLMR throughout the observation period (Figure 2). Moreover, according to the Z-test method, the C-index of ICS (0.794, 95%CI:0.732–0.856) is significantly higher than that of pLMR (0.714, 95CI:0.631–0.797, $P = 0.008$) and cLMR (0.707, 95%CI: 0.622–0.793, $P = 0.005$).

Predictive nomogram based on ICS

To provide a quantitative method for prognosis prediction, the model that incorporated the independent factors from the multivariate analysis including CEA, pTNM stage, and ICS was developed and presented as the nomogram (Figure 3A). The calibration curves of the nomogram for the probabilities of 3-year survival and 5-year survival both demonstrated optimal agreements between nomogram prediction and actual observation in the internal validation (Figure 3B, C). In addition, the C-index of the nomogram based on the ICS, CEA, and pTNM stage (model1; 0.816; 95% CI, 0.778–0.855) was both significantly higher than the prognostic model merely based on pTNM stage and CEA (model2; 0.767; 95% CI 0.713–0.82; $P = 0.008$) and the model based on the pLMR, CEA, and pTNM stage (model3; 0.792; 95% CI, 0.748–0.835; $P = 0.035$).

The decision curves for models 1, 2, and 3 to predict the correct 3-year outcome in patients with AGC were shown in Figure 4. All models were useful between threshold probabilities of 0.45–0.72, and the net benefit of model 1 was better than the other 2 models when the threshold probabilities between 0.26 and 1.

Discussion

It is well accepted that LMR as one of the immunoinflammatory markers was playing an important role in immune surveillance and tumor progression. Previously published data had demonstrated the correlation between survival and LMR from different points in time, especially in the preoperative setting. However, there were no reports concerning the prognostic role of the kinetics of this biomarker during treatment. Indeed, this is the first study to investigate the prognostic value of LMR and its kinetic after gastrectomy and adjuvant chemotherapy in patients with LAGC. We found that LMR increased after treatment was an

independent favorable factor of prognosis. In addition, patients with intestinal Lauren classification or well-differentiated might be more susceptible to enhance immunity after treatment.

As the basis for the adaptive and innate immune system, lymphocytes participate and enhance immune-surveillance, thereby mediating cytotoxic cell and inhibiting tumor cell proliferation, invasion, and metastasis [20]. It has been reported that the presence of tumor-infiltrating lymphocytes was associated with improving the prognosis in a variety of tumors, possibly owing to tumor-infiltrating, lymphocyte-induced, and anti-tumor activity as well as angiogenesis [21]. Therefore, lymphocytopenia weakens the immune response and represents a decrease of anti-tumor ability and a poor outcome in patients with cancer. Inversely, the circulating monocytes may contribute to tumor growth and inhibit immunosurveillance according to the previous finding [22]. Furthermore, tumor-associated macrophages derived from circulating monocytes have been proven to be associated with tumor metastasis, enhanced angiogenesis, and poor outcome [23]. Thus, LMR, which is calculated based on the values of ALC and AMC, can amplify the ability of ALC and AMC to reflect the immune response and play an important role in the prognosis of GC.

Several studies have determined the prognosis value of LMR in the preoperative and postoperative setting [13, 24–26].However, there was an important limitation that the cut-off value for LMR differed among those researches and, thus limited patient stratification. In addition to this, the outcome may be similar even if the patients were at different groups according to pLMR. In our study, the optimal cutoff value for pLMR is 4.53, and the 5-year OS rate between patients in HL group and LG group are indiscrimination. Previous studies focused on the dynamic changes in terms of the LMR after treatment showed that compared with the pretreatment LMR, the LMR elevated at 4 weeks after the start of nivolumab monotherapy was significantly associated with a prolonger progression-free survival and OS in non-small-cell lung cancer [27]. Moreover, LMR increased more than 1.8 from day 15 to day 100 in patients with Hodgkin Lymphoma who underwent autologous stem cell transplantation was correlated with a lower risk of relapse [28]. In this study, we found that increased cLMR was a favorable prognostic factor for A GC. Although the prognostic accuracy of cLMR was not as well as pLMR, the combination of cLMR could further assist pLMR in identifying outcome and selecting the patients who should receive individualized treatment. Additionally, cLMR was an independent prognostic factor and an increased cLMR was associated with a well histological type or intestinal Lauren classification. These data support the notion that cLMR, which reflected a dynamic reaction of immune response caused by treatment and tumor load, was also a meaning measurement. Therefore, we developed a novel prognostic score, called ICS, based on the combination of pLMR and cLMR, and found that the ICS was also an independent prognostic factor for patients with LAGC. Moreover, as an integrated indicator, the clinical value, discrimination and prognostic accuracy of ICS were significantly better than that of pLMR and cLMR. Thus, we recommended that patients with lower ICS should reexamine regularly and try to receive some molecular targeted agents.

To date, the most important and common predictive systems for GC are the AJCC TNM staging system, which is based on the depth of tumor invasion (T), the number of lymph node metastasis (N), and the distant metastases (M)[15]. However, due to the variety of patient prognosis, it might be ambiguous for patient selection solely depending on the TMM classification. To assist with clinical practice and decision making, a nomogram, currently an accurate and discriminatory tool for predicting prognosis among patients with cancer [29], was built by incorporating ICS into CEA and TNM staging. It is essential to validate the nomogram to avoid overfitting of the model and determine generalizability [30]. In this study, the calibration plots for 3-year and 5-year survival showed a favorable agreement between prediction and actual obversion in the internal validation, which guarantees the reliability of the constructed nomogram. Moreover, the nomogram exhibited better discrimination power and accuracy than that of non-ICS or pLMR based nomogram. Therefore, in clinical practice, the ICS can be used as a supplement to the TNM staging system to identify high-risk subgroups of patients, to assess the individual clinical outcome, and to provide a basis for guiding follow-up and treatment.

Our study does have some limitations and deficiencies. First, we lacked the data to examine all patients at all time points during treatment. Second, this study with a retrospective nature was performed in a single center, that inevitably led to potential biases and a relatively small sample size. However, the sample size of this article is sufficient to effectively show the prognosis value of LMR kinetics on survival. Moreover, due to the patients were consecutively enrolled, some patients had a follow-up period less than five years and no outcome was observed, which may have an impact on the results of the survival analysis. Finally, because the ICS in our nomogram is calculated based on LMR after three cycles of chemotherapy, so it doesn't apply to the prediction of outcomes in the initial three months after surgery. Future studies will need to elucidate the mechanism of changes in immune status of GC patients with different tumor stages after surgery or chemotherapy to deduce whether cLMR can better stratify patients for additional treatment.

Conclusion

Our study is the first to show that immune status change is significantly associated with prognosis for GC patients. Considering that, we developed a novel prognostic score named ICS, which could discriminate the prognosis of patients effectively. Additionally, we established and validated a novel nomogram that incorporates ICS, CEA, and TNM staging system to predict prognosis for LAGC patients. Through this model, clinicians could estimate the effect of treatment, predict the outcome of individual patients, and identify patients who should receive specific treatment strategy more precisely.

Declaration

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration

and its later amendments or comparable ethical standards. Due to the retrospective nature of this study, the Ethics Committee of Lanzhou University Second Hospital approved the study and determined that written informed consent was not required.

Conflict of Interest: All authors declare no conflicts of interest.

*Availability of data and materials:*The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Tables

Table 1: The relationship between change of lymphocyte-monocyte ratio and clinicopathological variables

Variables	cLMR		*P* value
	≤1	>1	
Case	99	111	
Age (years), n (%)			0.898
≤60	58(58.6)	66(59.5)	
>60	51(41.4)	45(40.5)	
Sex, n (%)			0.705
Male	69(69.7)	80(72.1)	
Female	30(30.3)	31(27.9)	
ECOG, n (%)			0.669
0	37(37.4)	40(36)	
1	51(51.5)	54(48.6)	
2	11(11.1)	17(15.3)	
Lauren classification, n (%)			0.003
Intestinal	27(27.3)	56(50.5)	
Diffuse	43(43.4)	32(28.8)	
Mixed	29(29.3)	23(20.7)	
Histologic type, n (%)			0.014
Well	42(42.4)	66(59.5)	
Poor	57(57.6)	45(40.5)	
Tumor location, n (%)			0.479
Upper third	19(19.2)	29(26.1)	
Middle third	53(53.5)	53(47.7)	
Lower third	27(27.3)	29(26.1)	
Adjuvant chemotherapy, n (%)			0.549
Docetaxel (No)	63(63.6)	75(67.6)	
Docetaxel (Yes)	36(36.4)	36(32.4)	
Vessel invasion, n (%)			0.93
No	21(21.2)	23(20.7)	
Yes	78(78.8)	88(79.3)	

Nerve invasion, n (%)			0.827
No	29(29.3)	31(27.9)	
Yes	70(70.7)	80(72.1)	
Style of operation, n (%)			0.107
Distal gastrectomy	15(15.2)	29(26.2)	
Total gastrectomy	37(37.4)	31(27.9)	
Subtotal gastrectomy	47(47.5)	51(45.9)	
Tumor size (cm), n (%)			0.49
≤4	56(56.6)	68(61.3)	
>4	43(43.4)	43(38.7)	
CA-199 (U/ml), n (%)			0.464
≤27	85(85.9)	99(89.2)	
>27	15(14.1)	12(10.8)	
CEA (ng/ml), n (%)			0.105
≤5.15	74(74.4)	93(83.8)	
>5.15	25(25.3)	18(16.2)	
pTNM, n (%)			0.076
II	37(37.4)	55(49.5)	
III	62(62.6)	56(50.5)	
pLMR n (%)			0.036
≤4.53	34(34.3)	54(48.6)	
>4.53	65(65.7)	57(51.4)	

ECOG: Eastern Cooperative Oncology Group; CA-199: Carbohydrate antigen 199; CEA: Carcinoembryonic Antigen; pTNM: pathological TNM; LMR: lymphocyte-monocyte ratio; pLMR: preoperative lymphocyte-monocyte ratio; cLMR: change of lymphocyte-monocyte ratio.

Table 2 univariate and multivariate analysis for the entire patients with locally advanced gastric cancer

Clinicopathological features	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
≤60	Reference			
>60	1.067(0.737-1.554)	0.732		
Sex				
Male	Reference			
Female	0.672(0.439-1.029)	0.068		
ECOG				
0	Reference			
1	0.996(0.669-1.476)	0.976		
2	0.903(0.494-1.653)	0.742		
Lauren classification				
Intestinal	Reference			
Diffuse	2.361(1.535-3.629)	0.001		0.058
Mixed	1.463(0.884-2.420))	0.139		0.394
Histologic type				
Well	Reference			
Poor	1.269(0.88-1.83)	0.202		
Tumor location				
Upper third	Reference			
Middle third	1.212(0.747-1.966)	0.436		
Lower third	1.478(0.87-2.15)	0.149		
Adjuvant chemotherapy				
Docetaxel (No)	Reference			
Docetaxel (Yes)	0.611(0.404-0.923)	0.019		0.053
Vessel invasion				
No	Reference			
Yes	2.208(1.278-3.814)	0.005		0.278

Nerve invasion				
No	Reference			
Yes	2.445(1.508-3.964)	<0.001		
Style of operation				
Distal gastrectomy	Reference			
Total gastrectomy	1.791(1.049-3.057)	0.033		0.126
Subtotal gastrectomy	1.327(0.781-2.254)	0.295		0.21
Tumor size (cm)				
≤4	Reference			
>4	2.45(1.692-3.549)	<0.001		0.77
CA-199 (U/ml)				
≤27	Reference			
>27	1.958(1.207-3.176)	0.006		0.983
CEA (ng/ml)				
≤5.15	Reference		Reference	
>5.15	2.392(1.61-3.554)	<0.001	1.71(1.705-2.721)	0.024
pTNM				
II	Reference		Reference	
III	3.549(2.303-5.468)	<0.001	2.963(1.817-4.883)	<0.001
pLMR				
≤4.53	Reference		Reference	
>4.53	0.442(0.305-0.639)	<0.001	0.352(0.235-0.528)	<0.001
cLMR				
≤1	Reference		Reference	
>1	0.441(0.303-0.642)	<0.001	0.402(0.269-0.601)	<0.001

ECOG: Eastern Cooperative Oncology Group; CA-199: Carbohydrate antigen 199; CEA: Carcinoembryonic Antigen; pTNM: pathological TNM; LMR: lymphocyte-monocyte ratio; pLMR: preoperative lymphocyte-monocyte ratio; cLMR: change of lymphocyte-monocyte ratio; HR, hazard ratio; CI, confidence interval.

Table 3: The relationship between the immunity change score and clinicopathological variables

Variables	ICS			*P* value
	1	2	3	
Case	34(16.19)	119(56.67)	57(27.14)	
Age (years), n (%)				0.368
≤60	20(58.8)	66(55.5)	38(66.7)	
>60	14(41.2)	53(44.5)	19(33.3)	
Sex, n (%)				0.126
Male	29(85.3)	82(68.9)	38(66.7)	
Female	5(14.7)	37(31.1)	19(33.3)	
ECOG, n (%)				0.72
0	15(44.1)	43(36.1)	77(36.7)	
1	15(44.1)	62(52.1)	105(50)	
2	4(11.8)	14(11.8)	28(13.3)	
Lauren classification, n (%)				0.001
Intestinal	5(14.7)	48(40.3)	30(52.6)	
Diffuse	22(64.7)	38(31.9)	15(26.3)	
Mixed	7(20.6)	22(27.7)	12(21.1)	
Histologic type, n (%)				0.055
Well	12(35.3)	61(51.3)	35(61.4)	
Poor	22(64.7)	58(48.7)	22(38.6)	
Tumor location, n (%)				0.178
Upper third	9(26.5)	20(16.8)	19(33.3)	
Middle third	16(47.1)	65(54.6)	25(43.9)	
Lower third	9(26.5)	34(28.6)	13(22.8)	
Adjuvant chemotherapy, n (%)				0.083
Docetaxel (No)	12(35.3)	34(28.6)	26(45.6)	
Docetaxel (Yes)	22(64.7)	85(71.4)	31(54.4)	
Vessel invasion, n (%)				0.264
No	4(11.8)	29(24.4)	11(19.3)	
Yes	30(88.2)	90(75.6)	46(80.7)	

Nerve invasion, n (%)				0.058
No	4(11.8)	37(31.1)	19(33.3)	
Yes	30(88.2)	82(68.9)	38(66.7)	
Style of operation, n (%)				0.348
Distal gastrectomy	4(11.8)	25(21)	15(26.3)	
Total gastrectomy	15(44.1)	35(29.4)	18(31.6)	
Subtotal gastrectomy	15(44.1)	59(49.6)	24(42.1)	
Tumor size (cm), n (%)				0.002
≤4	11(32.4)	75(63)	38(66.7)	
>4	23(67.6)	44(37)	19(33.3)	
CA-199 (U/ml), n (%)				0.242
≤27	27(79.4)	105(88.2)	52(91.2)	
>27	7(20.6)	14(11.8)	5(8.8)	
CEA (ng/ml), n (%)				0.589
≤5.15	25(73.5)	95(79.8)	47(82.5)	
>5.15	9(26.5)	24(20.2)	10(17.5)	
pTNM, n (%)				0.313
II	11(32.4)	56(47.1)	25(43.9)	
III	23(67.6)	63(52.9)	32(56.1)	

ECOG: Eastern Cooperative Oncology Group; CA-199: Carbohydrate antigen 199; CEA: Carcinoembryonic Antigen; pTNM: pathological TNM;

Figures

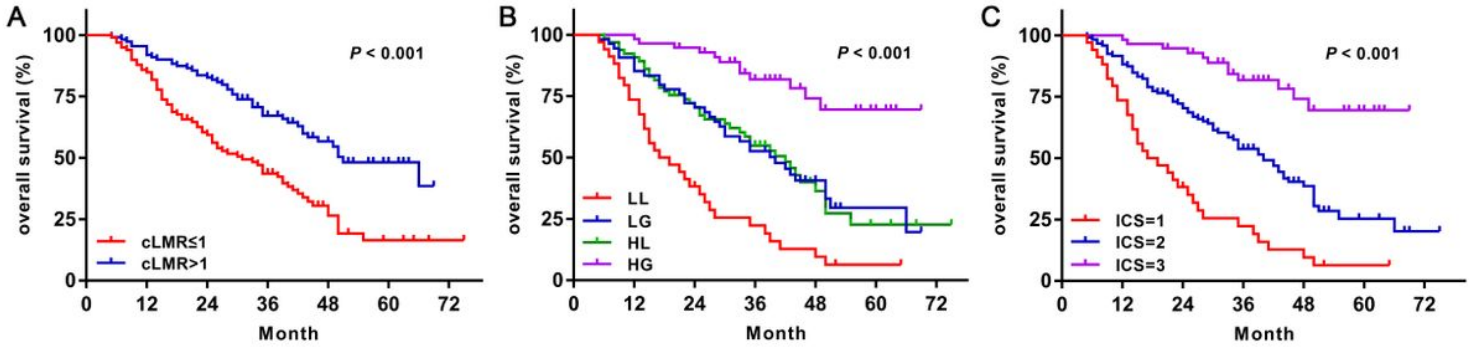

Figure 1

Kaplan–Meier curve of the overall survival in (A) patients with different values of cLMR, (B) four groups according to the preoperative LMR and cLMR. HL represent pLMR > 4.53 and cLMR ≤ 1; HG represent pLMR > 4.53 and cLMR > 1; LL represent pLMR ≤ 4.53 and cLMR ≤ 1, LG represent pLMR ≤ 4.53 and cLMR > 1, (C) different score of ICS. Abbreviation: LMR: lymphocyte-monocyte ratio; pLMR: preoperative lymphocyte-monocyte ratio; cLMR: change of lymphocyte-monocyte ratio; ICS: immunity change score.

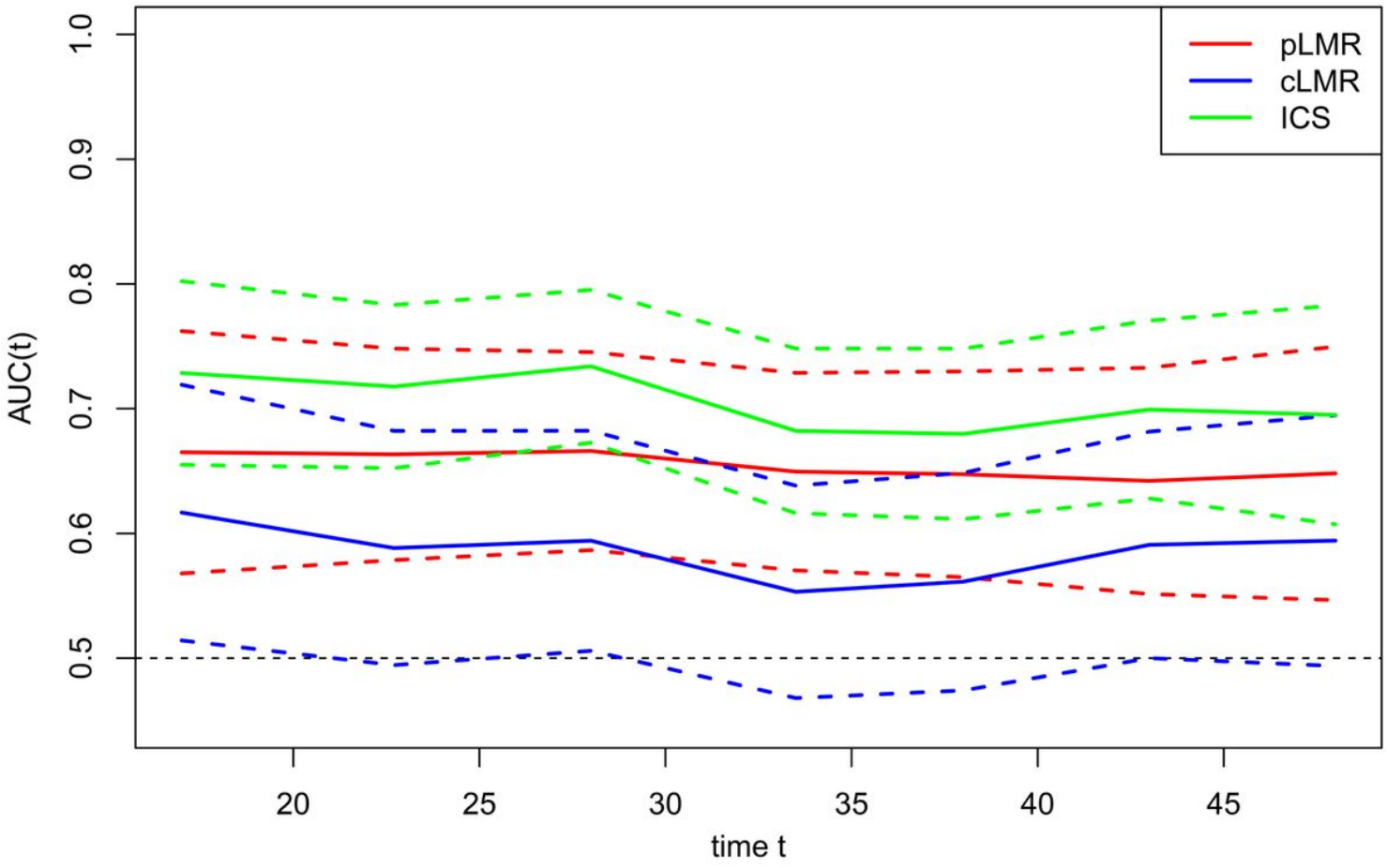

Figure 2

Time-dependent ROC curves for the pLMR, cLMR, and ICS. The x-axis represents year after diagnosis, whereas the y-axis represents the estimated AUC at a single point in time. The red, blue, and green full lines represent the AUCs for the pLMR, cLMR, and ICS, and dash lines represent the 95% confidence intervals for each AUC. Abbreviation: ROC: receiver operating characteristic; AUC: area under the curve; pLMR: preoperative lymphocyte-monocyte ratio; cLMR: change of lymphocyte-monocyte ratio; ICS: immunity change score.

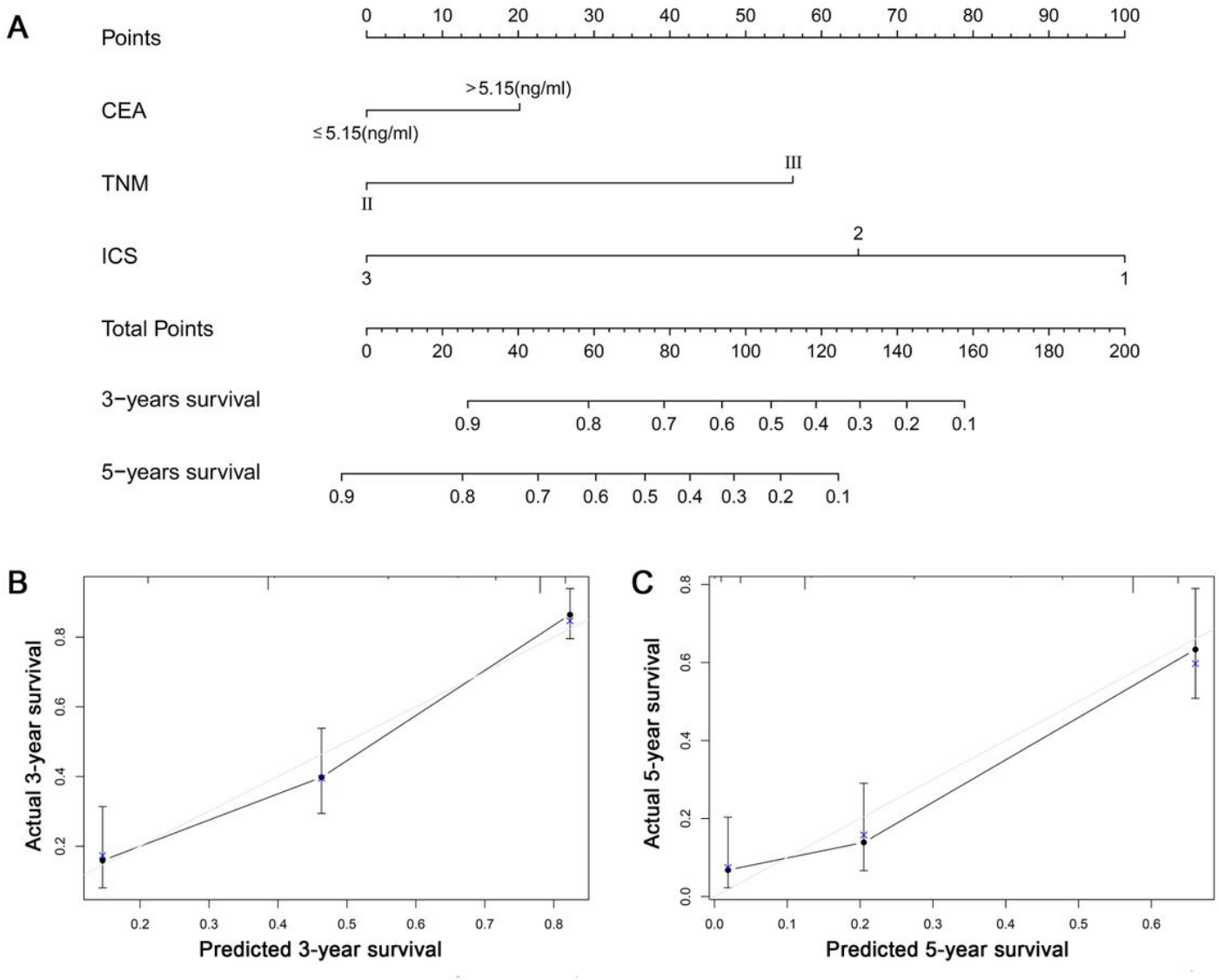

Figure 3

Developed predictive nomogram and Calibration curves. (A) The nomogram, incorporated the CEA, TNM stage, and ICS, was developed to predict the 3- and 5-year overall survival of patients with locally advanced gastric cancer; (B) Calibration curve of the nomogram for predicting the 3-year survival; (C) Calibration curve of the nomogram for predicting the 5-year survival. The y-axis represents the actual overall survival, and the nomogram-predicted overall survival is plotted on the x-axis. The prediction probability of the nomogram is turn out to be prefect compared with the actual outcome if the plot can coincide with the 45° line. Abbreviation: ICS: immunity change score. CEA: Carcinoembryonic Antigen.

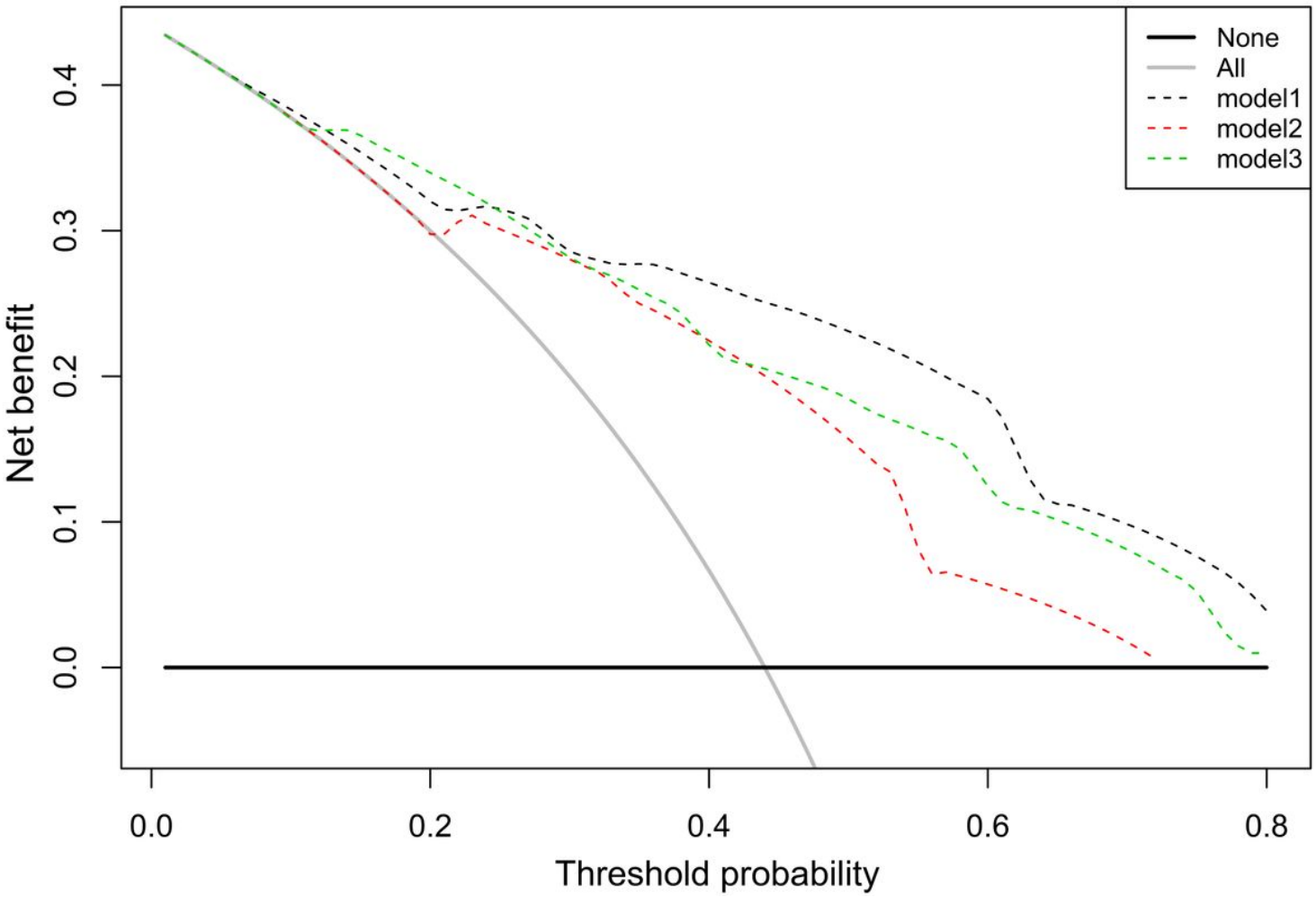

Figure 4

Decision curve analysis for the three nomograms had different components for the prediction of 3-year survival. Model 1 represent the nomogram based on the ICS, CEA, and pTNM stage; Model 2 represent the nomogram based on the CEA and pTNM stage; Model 3 represent the nomogram based on the pLMR, CEA, and pTNM stage. The y-axis measures the net benefit. The horizontal line represents no one died and the blue line represents all patients died. The proportion of patients showing false positive results is subtracted from the proportion showing true positive results, and the relative hazards of false positive and false negative results are weighed. Here, the formula for calculating net benefit was as following: Net benefit = True positives/n – Pt/(1-Pt) ×False positives/n. “Pt” represents threshold probability and “n” represents the number of patients in this study.

Supplementary Files

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- SupportingInformationfigure4.jpg
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- SupportingInformationfigure2.jpg
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