Association of the age-adjusted Charlson Comorbidity Index and systemic inflammation with survival in gastric cancer patients after radical gastrectomy

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ABSTRACT

Purpose: To examine the associations of the Age-Adjusted Charlson Comorbidity Index (ACCI) and pre-operative systemic inflammation with survival in gastric cancer (GC) patients who underwent radical gastrectomy.
Methods: Data from patients with GC who underwent radical gastrectomy between January 2009 and December 2014 in Fujian Medical University Union Hospital were retrospectively analyzed. Univariate and multivariate Cox regression analyses were performed to identify the prognostic factors. The relationship between the ACCI and systemic inflammation of the patients was explored, and the prognostic value of a new scoring system based on the ACCI and systemic inflammation (ANLR) was evaluated.
Results: A total of 2257 patients with GC were included. The ACCI and neutrophil to lymphocyte ratio (NLR) were independent prognostic factors for overall survival (both P < 0.001) by multivariate analysis. A higher ACCI was an independent predictor of the increase in preoperative NLR (P < 0.001). Based on the preoperative ACCI and NLR, we established a novel marker, ANLR. Multivariate analysis showed that the ANLR was a significant independent predictor of 5-year OS (P < 0.001). The Harrell's C-statistics (C-index) of a model combining the ANLR and pTNM was 0.744 (95% CI: 0.728–0.760), which was significantly higher than the pTNM stage (0.717, 95% CI: 0.702–0.731; P < 0.001).
Conclusion: The ACCI of patients with gastric cancer was associated with preoperative systemic inflammation. The ACCI combined with the NLR, which are commonly collected biomarkers, could enhance prognostication for GC patients.

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Introduction

Although the incidence and mortality of GC have declined worldwide [1], GC is still the fifth most common malignant tumor in the world and the third most common cause of death related to cancer worldwide (723,000 deaths, accounting for 8.8% of the total) [2]. In addition, with the aging of the population and the increase in life expectancy, the proportion of elderly patients with GC is constantly increasing. Previous study have shown that people over 70 years old account for 30% of patients with GC [3]. However, as the functional reserve of the human body tends to decline with age,

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elderly patients often have more comorbidities [4], leading to the poor prognosis of patients [5—9]. Therefore, this part of the population is increasingly attracting attention. In 1994, Charlson et al. established a new scoring system, the Age-Adjusted Charlson Comorbidity Index (ACCI) [10], which made the preoperative evaluation of patients more convenient.

In 1863, Virchow first found a link between malignancy and inflammation [11]. Systemic inflammation is considered to play a key role in the pathogenesis and development of tumors [12]. The disease progression of malignancy and tumor-specific survival are determined not only by the intrinsic characteristics of the tumor but also by the characteristics of the host, especially the systemic inflammation. Studies have shown that markers of systemic inflammation, including the lymphocyte to monocyte ratio (LMR), NLR and platelet to lymphocyte ratio (PLR), are closely related to the prognosis of various tumors [13—16]. The increase in markers of systemic inflammation often indicates the existence of preoperative comorbidities [17]. Clinically, most patients with preoperative comorbidities are elderly patients. The aging process is often accompanied by immune and endocrine-metabolic disorders in turn [18]. However, the correlation between the ACCI and systemic inflammation in patients with GC and their coeffect on prognosis have not been reported. Therefore, the purpose of this study was to evaluate the association of the ACCI and systemic inflammation with survival in GC patients who underwent radical surgery.

Patients and methods

Database

Data from primary GC patients who underwent radical gastrectomy in the Affiliated Union Hospital of Fujian Medical University from January 2009 to December 2014 were obtained from a prospectively maintained gastric cancer database and retrospectively analyzed. The inclusion criteria were as follows: (1) histologically confirmed primary gastric adenocarcinoma; (2) no distant metastasis; and (3) radical gastrectomy with R0 resection and regional lymphadenectomy. Patients who met the following criteria were excluded from this study: (1) patients with primary GC invading the surrounding organs or metastasis, (2) patients with gastric stump carcinoma, and (3) patients with incomplete/inaccurate medical records. In total, 2257 patients were enrolled. The extent of gastrectomy and the dissection of the lymph nodes around the stomach were in accordance with the fourth edition of the Japanese gastric cancer treatment guidelines [19]. Staging was performed according to the corresponding part of the eighth edition of the AJCC Staging Manual [20].

Definition of the ACCI

The ACCI, as defined by Charlson et al., is a combination of the age equivalence index and Charlson Comorbidity Index. Each decade of age over 40 adds 1 point to risk (e.g., 50—59 years, 1 point; 60—69 years, 2 points; and 70—79 years, 3 points), and the points for age are added to the score from the Charlson comorbidity index (e.g., 0, 1, 2, and 3). Conditions that had completely resolved (i.e., history of pneumonia) or a history of operation for currently inactive conditions (i.e., history of cholecystectomy) were not counted as comorbid diseases [21]. The optimal cutoff value of the ACCI was obtained by X-tile (Version 3.6.1, Yale University). Thus, the patients were divided into three groups: a low ACCI group (ACCI = 0—1), a middle ACCI group (ACCI = 2), and a high ACCI group (ACCI = 3—10).

Markers of systemic inflammation

The hematological and laboratory parameters were obtained within 1 week before surgery. These parameters included the neutrophil count, lymphocyte count, platelet count, and albumin (Alb) level. The NLR was defined by dividing the neutrophil count by the lymphocyte count. The PLR was defined by dividing the platelet count by the lymphocyte count. The LMR was defined by dividing the lymphocyte count by the monocyte count. The optimal cutoff values for the NLR, PLR and LMR were calculated by X-tile software (Version 3.6.1, Yale University) as 3.0, 162.5 and 3.2, respectively [22].

Follow-up evaluation

All of the patients were surveyed after surgery by physical examination and laboratory tests, including tests for tumor markers (e.g., carcinoembryonic antigen [CEA] and CA19-9) every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Overall survival (OS) was defined as the time from surgery to death from any cause or to the time of censoring on the date of the last follow-up.

Statistical analysis

The statistical analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize cohort characteristics. Categorical data are presented as proportions and analyzed with a chi-square test or Fisher's exact test. Univariate and multivariate logistical regressions were used to assess the relationship between preoperative ACCI and systemic inflammation. The Kaplan-Meier method was used to calculate the survival rate, and the differences were assessed with log-rank tests. Cancer-specific death and non-cancer-specific death are considered to be two competing events. The Fine and Grey's model was used for proportional risk analysis to evaluate the influence of variables on mortality from other causes and cancer-specific mortality [23]. Differences in survival were calculated using the Cox proportional hazards model. Variables with a p value of <0.05 on univariate analysis were then included in a multivariate Cox regression analysis. Risk scores were computed using the R software system, version 3.4.3. Model performance was assessed by C-index. The predictive accuracy of the ANLR was evaluated both by the integrated area under the ROC curve (iAUC) with $1000 \times$ bootstrap resampling [24] and time-dependent receiver operating characteristic (t-ROC) curves. The performance of risk prediction models was compared using the likelihood ratio p value.

Results

Clinicopathological characteristics

A total of 2257 patients with GC were included in the study, with an average age of 61 years (interquartile range (IQR): 54—69 years). Of the 2257 GC patients, 1702 were male (75.4%), and 555 were female (24.6%). There were 1046 patients (46.4%) with tumors located in the lower third of the stomach, 400 patients (17.7%) with tumors located in the middle of the stomach, 563 patients (24.9%) with tumors located in the upper third, and 247 patients with tumors across more than 2 regions (10.9%). A total of 659 patients had TNM stage I disease (29.2%), 555 patients had TNM stage II disease (24.6%) and 1043 patients had TNM stage III disease (46.2%). According to the cut-off value of the ACCI, there were 644 patients with a high ACCI, accounting for 28.5%; 702 patients with an intermediate ACCI, accounting for 31.1%; and 911 patients with a low

ACCI, accounting for 40.4%. Based on the cut-off values of each marker of systemic inflammation, 542 patients had a high NLR (24.0%); 1715 patients had a low NLR (76.0%); 1668 patients had a high LMR (73.9%); 589 patients had a low LMR (26.1%); 759 patients had a high PLR (33.6%); and 1498 patients had a low PLR (66.4%) (Supplemental Table 1).

Survival analysis

The median follow-up period was 50 months (IQR: 31–71 months). The 5-year OS was 66.0% in all patients. The univariate Cox regression analysis revealed that the NLR, PLR, LMR and Alb were statistically significant (all P < 0.05, Supplemental Table 2). In addition, other clinical and pathological variables, including BMI, ASA score, tumor location, tumor size, pTNM staging, lymphovascular invasion, and adjuvant chemotherapy, were also statistically significant for 5-year OS (all P < 0.05, Supplemental Table 2). In addition to TNM staging, the preoperative NLR and ACCI were still independent prognostic factors for 5-year OS by further multivariate analysis (P < 0.05, Table 1). A high NLR (NLR≥3.0) was closely associated with poor prognosis. Therefore, we included the NLR in this study as the representative of systemic inflammation.

Correlations between the ACCI and systemic inflammation

The interrelationships between gender, the ACCI, BMI, pTNM stage, ASA score, tumor location, tumor size, histologic type, lymphovascular invasion and the representative systemic inflammation NLR are shown in Table 2. The univariate logistic regression analysis showed that all factors, except gender and histologic type, were significantly related to the increase in the preoperative NLR (all P < 0.05). Further multivariate logistic regression analysis showed that the ACCI was an independent risk factor for increasing

the preoperative NLR. In addition, other variables, including BMI, Alb and tumor size, were also independently significant (all P < 0.05).

Establishment of the Prognostic Score Based on the ACCI and NLR (ANLR).

As observed in the Kaplan-Meier curves, we combined the preoperative ACCI and NLR, and based on these results, we divided all patients into 6 groups (Fig. 1).

Survival analysis showed no significant difference between the survival of subgroup 2 (NLR≥3.0 and ACCI = 0–1) and subgroup 3 (NLR<3.0 and ACCI = 2). The survival of subgroup 4 (NLR≥3.0 and ACCI = 2), subgroup 5 (NLR<3.0 and ACCI = 3–10) and subgroup 6 (NLR≥3.0 and ACCI = 3–10) was similar (all P > 0.05, Fig. 1A). However, the survival of the latter and the former groups were significantly different (P < 0.05, Fig. 1A). There was a significant difference between subgroup 1 (NLR<3.0 and ACCI = 1) and the other groups (P < 0.05, Fig. 1A). Thus, we established a new prognostic score system (ANLR) based on the ACCI and systemic inflammation (NLR). Subgroup 1 was assigned to the low ANLR group; subgroups 2 and 3 were assigned to the intermediate ANLR group; and subgroups 4, 5 and 6 were assigned to the high ANLR group. Of the whole cohort, there were 737 patients in the low ANLR group (32.6%), 704 patients in the intermediate ANLR group (31.2%), and 816 patients in the high ANLR group (36.2%).

Influence of the ANLR on OS

The relationship between the ANLR and clinicopathological data was compared (Table 3). The high ANLR group was dominated by patients with higher ASA scores, larger tumor sizes, and more advanced staging, and patients who were prone to lymphovascular invasion (all P < 0.05, Table 3).

Kaplan-Meier curves showed significant differences in the 5-year OS among the three ANLR groups (the 5-year OS: low ANLR group: 75.2%, intermediate ANLR group: 67.9%, high ANLR group: 55.6%, P < 0.001, Fig. 1B). Multivariate Cox regression analysis showed that the ANLR was an independent prognostic factor for 5-year OS. Other independent risk factors included tumor size and TNM staging (all P < 0.001, Table 4).

We further compared the predictive accuracy of the model combining the ANLR and pTNM staging with that containing pTNM staging only for prediction of OS by establishing the time-ROC curves (Fig. 2A). The results showed that the prognostic model incorporating the ANLR and pTNM was superior to the model with simple pTNM staging during the follow-up period. The C-index of the model combining the ANLR with pTNM was 0.744 (95% CI: 0.728–0.760), which was significantly higher than the model with only the pTNM stage (0.717, 95% CI: 0.702–0.731; P < 0.001). The clinical performance of the combination of the ANLR and pTNM exceeded that of pTNM staging alone (Fig. 2B, likelihood ratio P < 0.001).

Discussion

In recent years, the proportion of elderly patients with gastric cancer has been increasing due to the extension of human life expectancy [25]. Age has been identified as an independent prognostic factor for the survival of many malignant diseases [26–29]. The functional reserve of the human body tends to decline with age. Furthermore, elderly patients are prone to have more comorbidities, leading to decreased quality of life and increased risk of death [4]. Inflammation has been implicated in the pathogenesis of several of the major age-related diseases, including cardiovascular disease, type 2 diabetes, and dementia, and this condition is associated with increased mortality [30]. Cancer-related inflammation

Table 1
Multivariate analysis of clinicopathologic variables in relation to OS in patients undergoing potentially curative resection for gastric cancer.

Clinicopathological features	Mutivariate analysis		P
	HR	(95% CI)	
BMI			0.110
<18.5			
18.5–25			0.626
>25			0.246
ACCI			<0.001
0-1			
2	1.324	(1.100–1.594)	0.003
3-10	1.894	(1.612–2.382)	<0.001
NLR (<3.0/>3.0)	1.199	(1.023–1.405)	0.025
LMR (<3.2/>3.2)			0.278
PLR (<162.5/>162.5)			0.132
ALB (<35/>35)			0.114
ASA			0.643
1			
2			0.691
3			0.352
Tumor Location			<0.001
Upper			
Middle	0.908	(0.733–1.125)	0.378
Lower	0.792	(0.660–0.950)	0.012
Mixed	1.271	(1.011–1.597)	0.040
Tumor Size(mm) (<40/>40)	1.627	(1.297–2.042)	
pTNM stage			<0.001
I			
II	2.285	(1.623–3.217)	<0.001
III	6.684	(4.853–9.206)	<0.001
Lymphovascularinvasion(Negative/Positive)			0.646
Adjuvant chemotherapy(Yes/No)			0.111
Postoperative complication(Yes/No)			0.092

Table 2
The relationship between systemic inflammation and other clinicopathological parameters.

| Clinicopathological features	Odds Ratio for Systemic Inflammation (95%CI)				
	Univariate analysis		P value	Multivariate analysis		P value
Gender						
Female						
Male	1.116	(0.889–1.402)	0.344			
BMI			<0.001			0.019
<18.5						
18.5–25	0.613	(0.464–0.809)	0.001	0.727	(0.545–0.969)	0.030
>25	0.494	(0.343–0.711)	<0.001	0.590	(0.406–0.857)	0.006
ACCI			<0.001			0.001
0–1						
2	1.375	(1.083–1.745)	0.009	1.310	(1.027–1.673)	0.030
3–10	1.853	(1.464–2.345)	<0.001	1.594	(1.247–2.037)	<0.001
ALB						
<35						
>35	0.443	(0.355–0.553)		0.563	(0.445–0.711)	<0.001
ASA			<0.001			0.107
1						
2	1.401	(1.143–1.717)	0.001			0.220
3	2.068	(1.245–3.433)	0.005			0.152
Tumor Location			0.016			0.197
Upper						
Middle	1.104	(0.828–1.472)	0.500			0.073
Lower	0.750	(0.591–0.953)	0.019			0.102
Mixed	0.900	(0.636–1.242)	0.549			0.581
Tumor Size(mm)						
<40						
>40	1.913	(1.552–2.357)	<0.001	1.659	(1.335–2.061)	<0.001
pTNM stage			<0.001			0.077
I						
II	1.571	(1.185–2.083)	0.002			0.620
III	1.966	(1.539–2.510)	<0.001			0.179
Histologic type						
Undifferentiated						
Differentiated	0.975	(0.753–1.264)	0.850			
Lymphovascular invasion						
Negative						
Positive	1.338	(1.092–1.640)	0.005			0.190
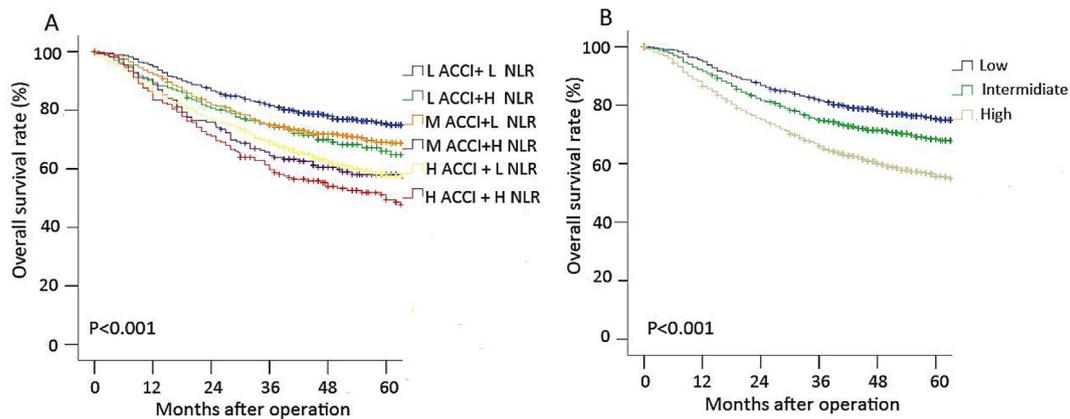
Fig. 1. Kaplan–Meier analysis for OS of GC patients according to preoperative NLR and ACCI–Meier analysis for OS according to (A) combination of preoperative NLR and ACCI, and (B) ANLR.

has been recognized as one of the hallmarks of cancer [31] with a crucial role in regulating the tumor microenvironment. Therefore, there may be a strong correlation between age, comorbidity and systemic inflammation. However, no relevant studies have been reported so far.

In this study with a large cohort, we found that both the ACCI and the marker of systemic inflammation, NLR, were independent risk factors for the prognosis of GC. The NLR, a measure of the proportion of systemic neutrophils and lymphocytes, has been proposed as an indicator of cancer-related inflammation and has been shown to have prognostic relevance across a large variety of tumor types [32–34]. Lymphocytes are basic components of the innate and adaptive immune system and are the cellular basis of immunosurveillance and immunoediting [35]. Previous studies have found that the presence of tumor-infiltrating lymphocytes was associated with improved outcomes in a variety of cancers, which may be due to tumor infiltration, lymphocyte induction, antitumor activity and the inhibition of angiogenesis [36]. Kazuo

Table 3
The relationship between the ANLR and clinicopathological characteristics in patients undergoing potentially curative resection for gastric cancer.

Clinicopathological features	ANLR			P value
	Low	Intermediate	High	
Case	737	704	816	
Age(y)				<0.001
<65	737(100.0%)	493(70.0%)	176(21.6%)	
>65	0(0.0%)	211 (30.0%)	640(78.4%)	
Gender				<0.001
Male	519(70.4%)	534(75.9%)	649(75.4%)	
Female	218(29.6%)	170(24.1%)	167(24.6%)	
ALB				<0.001
<35	88(11.9%)	133(18.9%)	238(29.2%)	
>35	649(88.1%)	571(81.1%)	578(70.8%)	
ACCI				<0.001
0-1	737(100.0%)	174(24.7%)	0(0.0%)	
2	0(0.0%)	530(75.3%)	172(21.1%)	
3-10	0(0.0%)	0(0.0%)	644(78.9%)	
NLR				<0.001
<3.0	737(100.0%)	530(75.3%)	448(54.9%)	
>3.0	0(0.0%)	174(24.7%)	368(45.1%)	
BMI (km/cm^2)				0.005
<18.5	71(9.6%)	75(10.7%)	125(15.4%)	
18.5—25	552(75.0%)	512(73.4%)	554(68.4%)	
>25	113(15.4%)	111(15.9%)	131(16.2%)	
ASA score				<0.001
1	582(79.8%)	489(70.1%)	344(42.5%)	
2	145(19.9%)	202(28.9%)	405(50.1%)	
3	2(0.3%)	7(1.0%)	60(7.4%)	
Tumor Location				<0.001
Upper	131(17.8%)	186(24.9%)	246(30.1%)	
Middle	130(17.6%)	126(20.3%)	144(17.6%)	
Lower	396(53.7%)	305(44.2%)	346(42.2%)	
Mixed	80(10.9%)	87(12.4%)	80(9.8%)	
Tumor size (mm)				<0.001
<40	358(48.7%)	381 (40.5%)	266(32.8%)	
>40	377(51.3%)	739(59.5%)	596(67.2%)	
Histologic type				<0.001
Differentiated	579(78.6%)	597(84.8%)	708(86.8.%)	
Undifferentiated	158(21.4%)	107(15.2%)	108(15.1%)	
Lymphovascular invasion				0.001
Positive	200(27.1%)	218(31.0%)	292(35.8%)	
Negative	537(72.9%)	486(69.0%)	524(64.2%)	
pTNM stage				<0.001
I	255(34.6%)	201 (28.6%)	203(24.9%)	
II	182(24.7%)	161(22.9%)	212(26.0%)	
III	300(40.7%)	342(48.6%)	401(49.1%)	
Postoperative complication				0.003
Yes	99(13.4%)	106(15.1%)	159(19.5%)	
No	638(86.5%)	598(84.9%)	657(80.5%)	
Adjuvant chemotherapy				<0.001
Yes	385(52.5%)	383(54.4%)	359(44.0%)	
No	352(47.8%)	321 (45.6%)	457(56.0%)	

Table 4
Multivariate analysis of clinicopathologic variables in relation to OS in patients undergoing potentially curative resection for gastric cancer.

Clinicopathological features	Multivariate analysis[a]	
	HR (95% CI)	P
Tumor size (cm)		<0.001
<40	Reference	
>40	1.597(1.245—2.049)	
pTNM stage		<0.001
I	Reference	
II	1.614(1.004—2.596)	
III	6.193(4.114—9.325)	
ANLR		<0.001
0	Reference	
1	1.191(0.973—1.459)	
2	1.885(1.567—2.268)	

[a] Adjusted for the following variables: ASA score, tumor location, tumor size, Lymphovascular invasion, BMI, Adjuvant chemotherapy, pTNM stage, NLR, PLR, ALb and postoperative complication.

et al. found that the number of peripheral blood circulating lymphocyte is closely related to the state of tumor infiltrating lymphocytes [37]. Peripheral lymphocyte count reduction could herald a tumor infiltrating cells decreased, thus affecting the prognosis of patients with tumor. Studies have shown that the potential role of the NLR in carcinogenesis and tumor aggressiveness may be due to an increased number of neutrophils, which were shown to interact with other cell populations to produce cytokines and effector molecules [38]. Neutrophils are high motility cells with antitumor or protumor phenotypes depending on microenvironmental factors [39].

Aging is accompanied by the development of low-grade systemic inflammation, termed 'inflammaging', which is characterized by raised serum C-reactive protein (CRP) and pro-inflammatory cytokines [30]. Studies have shown that the increase of CRP is closely related to the rise of peripheral neutrophils [40]. However, CRP in patients won't be preoperatively monitored until elevated
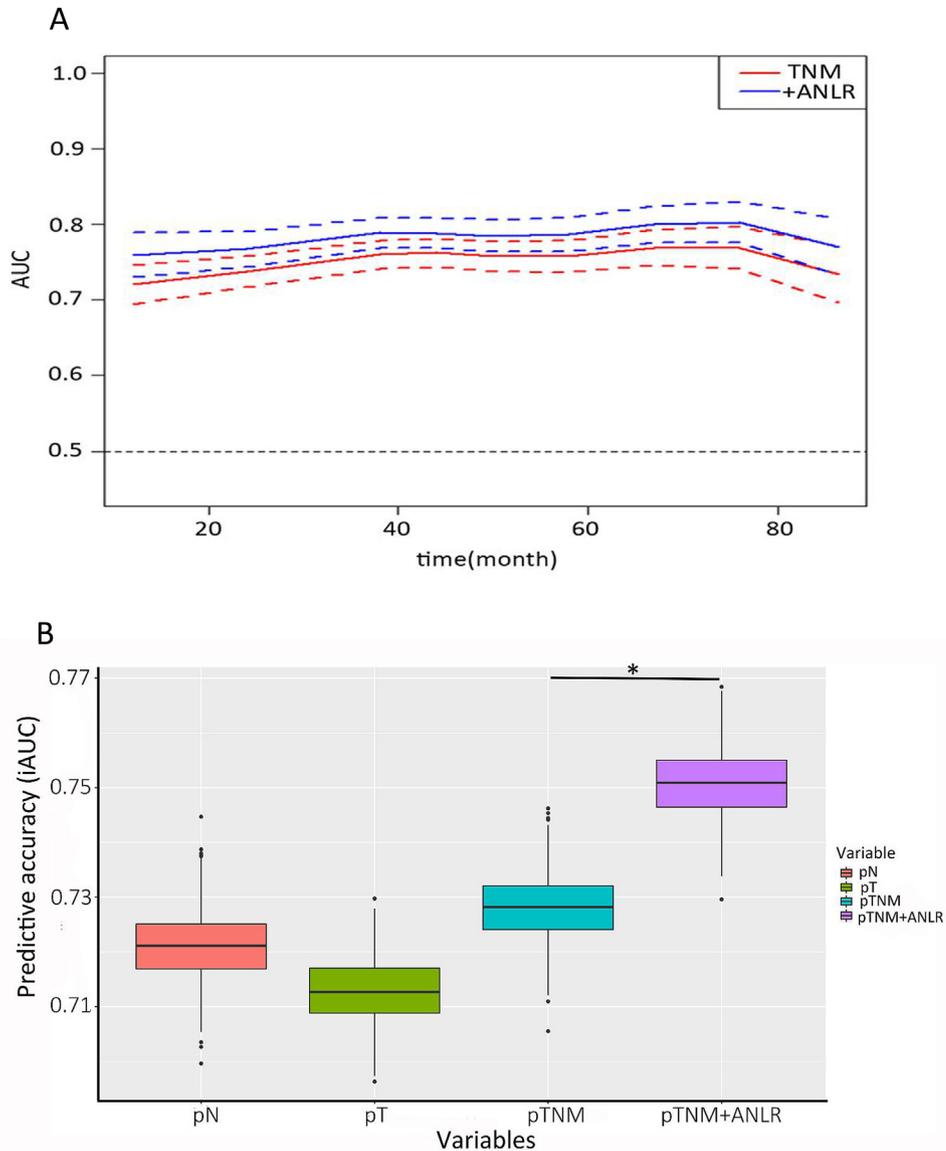
Fig. 2. Predictive accuracy of the model combining the ANLR and pTNM staging with that containing pTNM staging only for prediction of OS: A.Time-dependent ROC curves of pTNM and new model (pTNMN + ANLR) for the prediction of OS. B.Clinical performance of independent prognostic factors parameters. (The predictive accuracy for 5-year overall survival based on the iAUC with 1000 × bootstrap resampling for each parameter is shown in a box plot. Median values of 1000 × bootstrap resampling are shown with thick lines).

neutrophils were observed obviously, which makes preoperative CRP difficult to be obtained. What's more, the test price of CRP is relatively higher. Therefore, we use NLR, an inexpensive, widely available, and reproducible index, combining ACCI to predict the prognosis of patients with gastric cancer. And further analysis found that the ACCI is significantly correlated with the marker of systemic inflammation, NLR, which is an independent risk factor for increasing the preoperative NLR. This result is consistent with a previous hypothesis on "inflammation" in aging. Therefore, this study established a new prognostic scoring system, the ANLR, by combining the ACCI with the preoperative NLR. This study showed that the ANLR was an independent prognostic factor in patients with GC. As a combination of the ACCI and preoperative NLR, the ANLR can better reflect the coeffect of the ACCI and systemic inflammation on tumor progression.

According to previous studies, most patients with gastric cancer die of cancer. Therefore, we further analyzed the impact of ACCI, NLR and ANLR on cancer-specific death and death from other

causes, respectively. During the follow-up period of 112 months, a total of 756 patients died, of whom 688/2257(30.5%) died of cancer, and only 68/2257(3.0%) died of other causes. Among the patients with high ACCI, 245 cancer-specific deaths (10.9%) and 43 non-cancer-specific deaths (1.9%) were observed. We found that taking the low ACCI group as the reference group, the high ACCI group had a 0.7 fold increased risk of death due to cancer and a 6.8 fold increased risk of death due to other diseases after considering competitive event (all P < 0.01, Supplemental Fig. 1). However, high NLR only had a significant effect on cancer-specific death (Supplemental Fig. 2). ANLR had a similar effect with ACCI on cancer-specific death and other causes of death (Supplemental Fig. 3). Nevertheless, the overall impact of ANLR on the survival of GC patients is remarkable.

The American Joint Committee on Cancer (AJCC) TNM staging system has been recognized as the most important prognostic factor and the basis of treatment in GC. However, heterogeneities in the prognosis of individual patients with the same stage still exist.

In this study, a new prognostic model was established by combining the new ANLR maker and pTNM staging. Compared with the predictive accuracy of traditional TNM staging, the predictive accuracy of the new model combining the ANLR with pTNM was significantly better, which suggested that the ANLR could improve the accuracy of prognosis assessment of GC. Therefore, in clinical practice, the ANLR can be used as a supplement for TNM staging in preoperative risk stratification to effectively guide the treatment strategy and postoperative follow-up of GC patients.

This study had some limitations. First, as a retrospective study, it is inevitable that there may be selection bias. Second, some unavoidable confounding factors may exist in this study, such as education level, diet or alcohol intake, which may affect the evaluation of the preoperative NLR and ACCI. Third, the consistency of the condition of the patients before preoperative blood drawing may not be guaranteed. Nevertheless, this study found that the ACCI is significantly related to the preoperative NLR in a large cohort. Based on these findings, we established a novel prognostic model, the ANLR. The ANLR combined with the ACCI and preoperative NLR can effectively improve the predictive accuracy of the prognosis of patients with GC. In clinical practice, the ANLR could be considered a supplement to the traditional staging system to improve the prognosis evaluation of GC patients and guide individualized treatment strategies.

Author contributions

Lin JX, Huang YQ, Zheng CH, Huang CM and Li P conceived of the study, analyzed the data, and drafted the manuscript; Tu RH, Li P, Xie JW, Wang JB, and Li P helped revise the manuscript critically for important intellectual content; Lu J, Chen QY, Cao LL, and Lin M helped collect data and design the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.07.010.

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Conflict of interest

There are no conflicts of interest or financial ties to disclose from any of author.

Ethical approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients for being included in the study.

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