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Comparison of Prognostic Factors at Different Ages and Prognostic Significance of Neutrophil-Lymphocyte Ratio in Patients with Gastric Cancer

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Abstract

Background: A number of studies have shown that, to varying degrees, the age affects the prognosis of patients with gastric cancer (GC). This study retrospectively analyzed the clinical and pathologic data of patients with GC to explore the differences in the clinical characteristics and prognostic factors at different ages. Subsequently, since the prognostic significance of neutrophil-lymphocyt(NLR), one of the indicators of systemic inflammation response, remains controversial for GC, we performed a meta-analysis to further evaluate the prognostic role of NLR in GC.

Aim: The aim of our study was to find the prognostic significance of neutrophil-lymphocyte ratio (NLR) within clinicopathological characteristics and prognostic factors in gastric patients.

Methods: In the retrospective study, we analyzed 1037 GC patients admitted to Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine from May 2010 to January 2013. Patients were divided into two groups based on age: the younger group (less than 70 years old), the older group (no less than 70 years old). The clinical features and prognostic factors were analyzed in both groups. Subsequently, in the conduction of meta-analysis, we retrieved relevant research by searching two medical databases, PubMed and EMBASE. Then a random-effects model was used to pool data.

Results: In the retrospective study, the 5-year survival rate for the younger group was 63.4%and only 40.8%for the older group. The mean overall survival time (OS) of the younger group (64.7 months) was significantly longer than that of the older group (48.1 months) (P<0.001). Among patients under 70 years of age, hospitalization time (P<0.001), TNM stage (P<0.001), vascular invasion (P=0.002), and preoperative low pre-albumin (P<0.001) were independently associated with OS, whereas in patients aged 70 and older, TNM stage (P<0.001), oesophageal invasion (P<0.001), histological type (P=0.014), and preoperative NLR (P=0.028) were independent factors for OS. In our meta-analysis, 19 retrieved studies that evaluated the prediction role of NLR included a total of 8312 patients, among whom 3558 patients had elevated NLR values. The results showed that high NLR value was a risk factor for the prognosis of GC. The OS of these older patients was significantly shorter [the pooled hazard ratios (HRs)=1.55; 95%confidence interval (CI):1.41-1.70)].

Conclusion: The OS of elderly patients was significantly worse than that of younger patients. There were significant differences in clinicopathological characteristics and prognostic factors between the two groups. Among them, NLR was a convenient, inexpensive, and reproducible marker that can be used as an important predictor for the prognosis of GC.

Keywords: Gastric cancer; Age; Prognosis; OS; NLR; Meta-analysis

Introduction

GC is one of the most common malignant tumours in the world, with approximately 1 million new cases each year [1,2]. It is the second most lethal worldwide [3], and its 5-year overall survival rate is only 29.7% [2]. Albeit in recent years, tremendous progress has been made in early detection, surgical techniques, and multidisciplinary treatment, including neoadjuvant chemotherapy and radiotherapy, the postoperative OS of GC patients remains extremely low [4]. Therefore, it is essential to identify the most significant independent prognostic factors for GC patients.

Due to the decline of physiological function and poor nutritional status in elderly patients (the cut-off value was 70 years old in this study), radical gastrectomy trauma may readily lead to higher incidence of postoperative complications and, accordingly, increased postoperative mortality rate [5,6]. It is urgent and necessary to accurately identify the pivotal prognostic factors for GC patients at different ages. We firstly performed a retrospective analysis to compare different clinical and pathologic factors and explore their prognostic roles in patients with GC at different ages.

In recent years, the relationship between inflammation and cancer has been widely explored [7-9], in which NLR is one of the inflammatory markers, and its prognostic role has been demonstrated in pancreatic [10], colorectal [11], and lung cancer [12], as well as lymphoma [13]. NLR is neutrophil-lymphocyte ratio, which may affect the prognosis of cancer patients via activation of natural killer cells. But the prognostic role of NLR in GC remains controversial [14] though Hirashima et al. [15] first found its role in GC. Therefore, we secondly conducted a systemic review and meta-analysis to explore the prognostic role of NLR in GC.

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Objective

This is a retrospective study that explored the prognostic factors at different ages and the prognostic significance of neutrophil-lymphocyte ratio in gastric cancer patients. We compared the clinicopathological features of patients in two groups (age<70 and age>70), analyzed the prognostic factors and did a thorough meta-analysis. The findings indicated that the improvement of preoperative nutritional status may be beneficial to the prognosis in younger patients, while the alleviation of inflammatory status should be emphasized for older patients before surgery. The conclusion can provide reliable reference for clinicians to identify and rectify the independent prognostic influencing factors for gastric cancer patients.

Materials and Methods

Patients selection

In the retrospective analysis portion, we investigated the clinical and pathologic data of GC patients admitted to Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine from May 2010 to January 2013. 1037 patients in total were included in our study. The inclusion criteria were as follows:

(1) The postoperative, pathologically confirmed diagnosis of gastric adenocarcinoma with stage I to IV;

(2) The entire set of clinicopathological information; and

(3) The complete follow-up data.

In the meta-analysis portion, we searched all articles through PubMed and EMBASE without limitation of publication time. The following terms were used: ("neutrophil-lymphocyte ratio" or "neutrophil-to-lymphocyte ratio" or NLR) and ("gastric cancer" or "GC" or "gastric adenocarcinoma" or "stomach neoplasms" or "gastric carcinoma") and ("prognosis" or "prognostic value" or "overall survival" or "OS"). We repeatedly executed search strategy to ensure that no other related article was missed. By checking the authors' names and the affiliations for each study, we excluded any article with overlapping or duplicated results with other included articles.

Studies were included if they met the following criteria:

(1) The diagnosis of GC was confirmed pathologically;

(2) The relationship between preoperative NLR and overall survival (OS) was evaluated; and

(3) The sufficient data (HR and 95%CI for OS) were provided.

Exclusion criteria were as follows:

(1) Reviews, case reports, letters, or conference abstracts;

(2) Studies on cancer cells and animal models; and

(3) Studies that failed to raise the cut-off value of NLR elevation.

All searches were carried out independently by two authors. The selection of the article was shown in (Figure 1).

Data extraction

In the retrospective analysis portion, all the data were obtained from the inpatient and outpatient records, including demographic information (age and gender), tumour-specific data (tumour size, neural invasion, vascular invasion, oesophageal invasion, histopathologic type, and tumour location), therapeutic modalities (surgical procedures, chemotherapy, and radiotherapy) and survival data. Peripheral blood detection data were collected preoperatively, including blood routine examination, serum albumin, serum pre-albumin, etc.

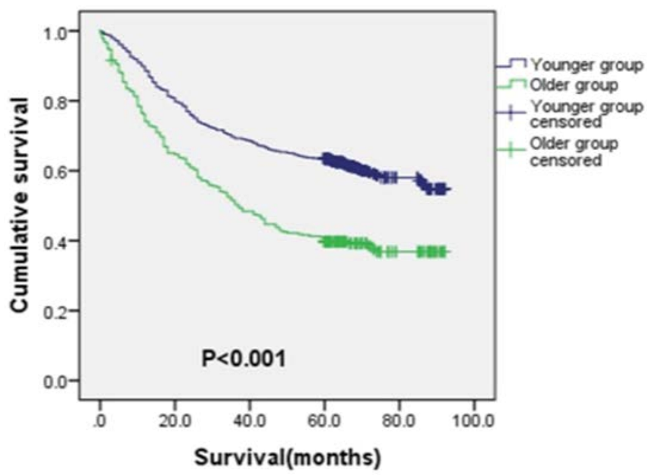

Figure 1: OS based on age in 1037 patients.

All the patients underwent routine assessment after surgery, including physical examination, laboratory examination, CT scan, and upper gastrointestinal endoscopy. The latest follow-up was January 20th, 2018, with a median follow-up duration of 61.3 months (range, 0-92 months). All patients were followed up for at least 5 years except for those who died during the follow-up period. The OS was calculated from the date of surgery until death or final available follow-up.

In the meta-analysis portion, the extracted data were as follows: (1) publication details, including the first author's name, publication year, and origin of population studied; (2) demographic characteristics including sample size, gender distribution, age, and disease stage; (3) HR of NLR for OS and its 95%CI; (4) follow-up time; and (5) cut-off values for elevated NLR. If several estimates were reported in the same article, we chose the most powerful one.

Data processing

In the retrospective analysis portion, according to Onodera, the prognostic nutritional index (PNI) was calculated as follows: 10 × serum albumin (g/dl)+0.005 × total lymphocyte count (per cubic millimetre) [16]. Its cut-off value was defined as 47 according to Youden's index of the receiver operating characteristic (ROC) curve. The optimal cut-off values for hospitalization time and low preoperative pre-albumin were 18 days and 212 mg/L, respectively, based on the Youden's index of the ROC curve. Similarly, the optimal cut-off values for preoperative NLR and platelet lymphocyte ratio (PLR) were 2.6 and 133, respectively. Preoperative anaemia and hypoalbuminemia were defined as 120 g/L and 35 g/L, respectively, according to the normal ranges used in our hospital.

Tumour stage was determined in accordance with tumour–node–metastasis (TNM) staging system (the seventh edition) proposed by the American Joint Committee on Cancer (AJCC) [17]. Histopathologically, papillary and tubular adenocarcinomas were classified as intestinal-type adenocarcinomas, while poorly differentiated signet ring cell and mucinous adenocarcinomas were classified as diffuse-type adenocarcinomas [18]. The size of the tumour was bounded by 4 cm according to the Youden index of the ROC curve.

We used the Youden's index of ROC curve to divide patients into two different groups based on the age of 70 years. We compared the features of patients in two groups in terms of general characteristics, pathologic findings, inflammatory markers, nutritional immune status, and OS. To obtain more information about the younger group (age<70), we further divided the patients in this group into two subgroups, according to the middle-age definition of WHO.

In our study, oral informed consent was performed on the collection of data and follow-up of patients and/or their close relatives given of the retrospective nature of the study.

In the meta-analysis portion, the quality of studies was assessed by the Newcastle-Ottawa Quality Assessment Scale (NOS) [19]. The scale includes three aspects of assessment: selection, comparability, and results of case group and control group. Studies scored over 6 were considered high quality ones.

Statistical Analysis

In the retrospective analysis portion, the patients' quantitative characteristics were defined using descriptive statistics, with their differences analyzed by chi-square test. Univariate and multivariate analyses were performed using the Cox proportional hazard model to explore the major prognostic factors. The ROC curves were plotted, and the optimal cut-off values of hospitalization time, tumour size, pre-albumin, PNI, NLR, and PLR were determined by Youden's index (maximum (sensitivity+specificity)-1). We used Kaplan -Meier methodology to estimate the cumulative survival, and its statistical difference was assessed by the log rank test. All statistical analyses were carried out using the SPSS statistical software package of version 24.0 (IBM Corporation, Armonk, New York, USA).

In the meta-analysis portion, all statistical analyses were performed via Stata 12.0. HRs and their associated 95%CIs from each study were pooled. Cochran's Q test and I-squared statistics were used to evaluate heterogeneity. If I2 values<50% or p value 0.05, indicating that there was no significant heterogeneity, a fixed effects model was used; otherwise, we applied a random effects model. Subsequently, to find potential sources of heterogeneity, we performed meta-regression and subgroup analyses. We also used sensitivity analysis to evaluate the stability of the results. Finally, publication bias of literature was assessed through Begg's funnel plot and Egger's linear regression test. The alpha was set at 0.05, and all tests were two-sided.

Results

Object characteristics

In the retrospective analysis portion, a total of 1037 patients with GC were included in our study; 728 (70.2%) were males and 309 (29.8%) were females, with a ratio of 2.36: 1. The average age of all patients was 62.9 years (range 19-90 years). All the patients were followed-up for 5 years; 452 patients (43.6%) died and 585 (56.4%) survived. Up to the end of follow-up, 482 (46.5%) patients died, and 555 (53.5%) remained alive. In this study, we divided patients into two groups in accordance with their age: 716 cases (69%) in the younger group (<70 years) with a range of 19-69 years and the average 57 years; and 321 cases (31%) in the older group (≥ 70 years) with a range of 70-90 years and the average 76 years.

The 5-year survival rates were 63.4%for the younger and 40.8%for the elderly, respectively (Figure A). The mean OS (64.7 months) in the younger group was significantly higher than that in the older group (48.1 months) (P<0.001). In addition, the 5-year survival rates for patients with TNM stage I-IV were 94.4%, 78.2%, 36.9%, and 7.5%, respectively (Figure 2). And their OS values were 87.1, 75.5, 46.2, and 19.1 months, respectively (P<0.001) (Table 1).

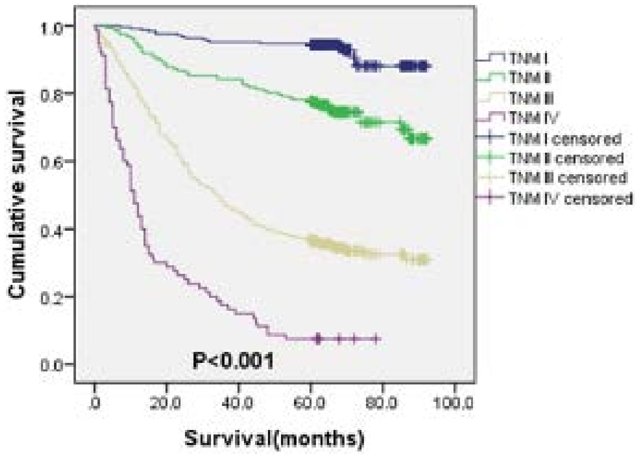

Figure 2: OS based on TNM stage in 1037 patients.

Characteristics	Patients n (%)	Overall survival months (95%CI)	P value
Age (years)			<001
<70	716 (69%)	64.7(62.2-67.3)	
≥70	321 (31%)	48.1(44.1-52.2)	
Sex			0.84
Male	728(70.2%)	59.6(56.9-62.2)	
Female	309(29.8%)	59.7(55.7-63.8)	
Hospitalization(days)			<0.001
<18	494(47.6%)	68.7(65.7-71.6)	
≥18	543(52.4%)	51.5(48.4-54.6)	
Depth of invasion (T)			<0.001
2-Jan	313(30.2%)	84.4(82.0-86.8)	
4-Mar	724(69.8%)	48.9(46.3-51.6)	
Lymph node metastasis(N)			<0.001
0	393(37.9%)	80.6(78.1-83.2)	
3-Jan	644(62.1%)	46.8(44.0-49.6)	
Distant metastasis(M)			<0.001
0	957(92.3%)	62.9(60.7-65.2)	
1	80(7.7%)	19.1(14.5-23.8)	
TNM stage			<0.001
I	251 (24.2%)	87.1(84.9-89.2)	
II	197(19.0%)	75.5(71.4-79.5)	
III	509(49.1%)	46.2(43.1-49.2)	
IV	80(7.7%)	19.1(14.5-23.8)	
Hematological type			<0.001
Intestinal type	555(53.5%)	64.5(61.6-67.4)	
Diffuse type	482(46.5%)	53.9(50.6-57.2)	
Tumor location			<0.001
Cardia	200(19.3%)	50.9(45.9-56.0)	
Non-cardia	837(80.7%)	61.7 (59.2-64.1)	
Tumor size (cm)			<0.001
<4	405(39.1%)	75.2(72.3-78.1)	
≥4	632(60.9%)	49.7(46.8-52.6)	
Neural invasion			<0.001
No	822(74.3%)	63.1(60.7-65.6)	
Yes	215(25.7%)	45.9(41.1-50.7)	

Vessel invasion			<0.001
No	771(74.3%)	65.7(63.2-68.1)	
Yes	266(25.7%)	42.0(37.7-46.3)	
Esophageal invasion			<0.001
No	949(91.5%)	61.6(59.3-63.9)	
Yes	88(8.5%)	38.7(31.5-45.8)	
NLR			<0.001
<2.6	634(61.1%)	64.5(61.8-67.3)	
≥2.6	382(38.9%)	51.8(48.2-55.5)	
HB(g/L)			<0.001
<120	407(39.2%)	53.2(49.6-56.8)	
≥120	630(60.8%)	63.8(61.1-66.6)	
PLR			<0.001
<133	486(46.9%)	64.9(61.8-68.0)	
≥133	551(53.1%)	54.9(51.8-58.0)	
Albumin			<0.001
<35	165(15.9%)	46.4(40.8-52.0)	
≥35	872(84.1%)	62.1(59.8-64.5)	
Pre-albumin			<0.001
<212	354(34.1%)	45.7(41.8-49.5)	
≥212	683(65.9%)	66.9(64.3-69.4)	
PNI			<0.001
<47	387(37.3%)	48.3(44.7-52.0)	
≥47	65-(62.7%)	66.4(63.7-69.0)	

Table 1: General characteristics and overall survival among 1038 gastric cancer patients.

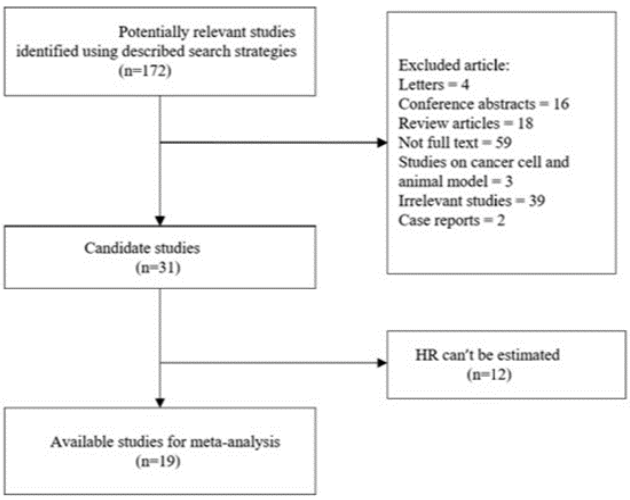

Figure 3: Flow chart of the meta-analysis.

In the meta-analysis portion, the flow diagram of our literature search was shown in (Figure 3).

A total of 172 items were generated based on search strategy; finally, we retrieved 19 articles that met our inclusion criteria [20-38].

Table 2 summarized the characteristics of the included studies. We collected data from 19 studies with a total of 8312 patients. 4 articles were prospective studies and 15 were retrospective. 12 enrolled studies had less than 400 patients and 7 studies had more than 400 patients. The cut-off value of NLR in 10 studies was less than 3, and that of the remaining 9 was more than 3. HR and 95%CI were reported directly in all included studies.

Characteristic	Younger group n (%)	Older group n (%)	P value
Sex			**0.407**
Male	497(69.4%)	231(72.0%)	
Female	219(30.6%)	90(28.0%)	
Hospitalization(days)			<0.001
<18	369(51.5%)	125(38.9%)	
≥18	347(48.5%)	196(61.6%)	
T stage			<0.001
2-Jan	240(33.5%)	73(22.7%)	
4-Mar	476(66.5%)	248(77.3%)	
N stage			0.021
0	288(40.2%)	105(32.7%)	
3-Jan	428(59.8%)	216(67.3%)	
M stage			0.343
0	657(91.8%)	300(93.5%)	
1	59(8.2%)	21(6.5%)	
TNM stage			0.003
I-II	331(46.2%)	117(36.4%)	
III-IV	385(53.8%)	204(63.6%)	
Histological type			0.001
Intestinal type	359(50.1%)	196(61.1%)	
Diffuse type	357(49.9%)	125(38.9%)	
Tumour location			0.059
Cardia	127(17.7%)	73(22.7%)	
Non-cardia	589(82.3%)	248(77.3%)	
Tumour size (cm)			<0.001
<4	318(44.4%)	87(27.1%)	
≥4	398(55.6%)	234(72.9%)	
Neural invasion			0.358
No	562(78.5%)	260(81%)	
Yes	154(21.5%)	61 (19%)	
Vessel invasion			0.719
No	530(74%)	241(75.1%)	
Yes	186(26%)	80(24.9%)	
Oesophageal invasion			0.855
No	656(91.6%)	293(91.3%)	
Yes	60(8.4%)	28(8.7%)	
NLR			0.003
<2.6	459(64.1%)	175(54.5%)	
≥2.6	257(35.9%)	146(45.5%)	
Anaemia			<0.001
No	499(69.7%)	131(40.8%)	
Yes	217(30.3%)	190(59.2%)	
PLR			0.003
<133	358(50%)	128(39.9%)	
≥133	358(50%)	193(60.1%)	
Low albumin			<0.001
No	650(90.8%)	222(69.2%)	
Yes	t(9.2%)	99(30.8.%)	
Low pre-albumin			<0.001
No	534(74.6%)	149(46.4%)	
Yes	182(25.4%)	172 (53.6%)	
PNI			<0.001
<47	191(26.7%)	196(61.1%)	
≥47	525(73.3%)	125(38.9%)	

Table 2: General Characters of the eligible studies.\

Association of age with characteristics

The clinicopathological features of the two groups were summarized in (Table 3).

There was no significant difference in gender distribution, distant metastasis, neural and vascular invasion, oesophageal invasion, or tumour location between the two groups. Compared with the younger patients, older patients had longer hospitalization, deeper tumour invasion, more advanced TNM stage, larger tumour size, and more lymph node metastasis. And they had higher preoperative NLR and PLR values, and lower preoperative PNI values, being more likely to have anaemia, hypoproteinaemia, and hyperalbuminemia. With regard to pathologic types, more patients in the older group had intestinal-type adenocarcinomas, while more younger patients had diffuse-type adenocarcinomas.

Univariate and multivariate Cox regression analysis for OS

The results of univariate Cox analysis showed that in the younger group, hospitalization time (P<0.001), T (P<0.001), N (P<0.001), M (P<0.001), TNM stage (P<0.001), histological type (P<0.001), tumour location (P=0.001), tumour size (P<0.001), neural invasion (P<0.001), vascular invasion (P<0.001), oesophageal invasion (P<0.001), preoperative NLR (P<0.001), preoperative PLR (P<0.001), preoperative anaemia (P=0.046), preoperative low albumin (P=0.010), preoperative low pre-albumin (P<0.001), and preoperative PNI (P<0.001) were significantly correlated with OS, respectively. The results of multivariate Cox regression analysis indicated that hospitalization time [HR=1.801; 95%CI: (1.394-2.327); P<0.001] , TNM stage [HR=5.418; 95%CI: (3.731-7.869);P<0.001], vascular invasion [HR=1.501; 95%CI: (1.163-1.936); P=0.002], and preoperative low pre-albumin [HR=1.637; 95% CI: (1.254-2.138); P<0.001] were independent prognostic factors for OS, respectively. The 5-year survival rate of patients with low and normal pre-albumin were 46.2%and 69.3%, respectively. The OS of the former (50.7 months) was significantly shorter than that of the latter (69.6 months) (P<0.001) (Figure 4).

Therefore, preoperative nutritional status may affect the survival prognosis of young patients with gastric cancer.

In the older group, however, univariate analysis showed that T (P<0.001), N (P<0.001), M (P<0.001) , TNM stage(P<0.001), histological type (P<0.001), tumour size(P<0.001), neural invasion (P<0.001), vascular invasion (P<0.001), oesophageal invasion (P<0.001), preoperative NLR (P=0.002), preoperative low albumin (P=0.019), preoperative low pre-albumin (P<0.001), and preoperative PNI (P=0.002) were correlated with OS, respectively. In the same way, these factors were tested by a multivariate Cox regression analysis: TNM stage [HR=3.873; 95%CI: (2.571-5.836); P<0.001], pathohistological type [HR=1.441; 95%CI: (1.078-1.928); P=0.014], oesophageal invasion [HR=2.330; 95%CI: (1.505-3.607); P<0.001], and preoperative NLR [HR=1.396; 95%CI: (1.038-1.880); P=0.028] were identified as the independent prognostic factors for OS, respectively. The 5-year survival rates of patients with preoperative NLR ≥ 2.6 and <2.6 were 32.2%and 48%, respectively. The OS values were 41.3 months and 53.8 months, respectively, and the difference was statistically significant (Figure 5). These results of univariate and multivariate analyses were shown in Table 4 and Table 5, respectively.

We further made univariate and multivariate analysis in the younger group by age sub-stratification. The results were shown in supplemental materials. In the subgroup A (45 ≤ age<70), univariate analysis demonstrated that hospitalization (P=0.01), T (P<0.001), N (P<0.001), M (P<0.001), TNM stage (P<0.001), histological type (P<0.001), location (P=0.007), tumour size (P<0.001), neural invasion (P<0.001), vascular invasion (P<0.001), oesophageal invasion (P<0.001), preoperative NLR (P=0.001), PLR (P=0.002), preoperative low albumin (P=0.002), preoperative low pre-albumin (P<0.001), and preoperative PNI (P<0.001) were all statistically significant in

First author	Year	Country	Study design	Treatment	No(m/F,n)	Age (median and range)	Cuttoff value(<CV/≥CV)	Summary Results	TNM stage	Study Period	Follow up(m) (median and range)	NOS Score
Jin et al.	2017	china	R	ML	119(87/32)	59(34-78)	2.23(56/63)	Positive	I-III	2004-2007	84	8
I.R.Cho et al.	2014	Korea	R	C	268(175/93)	55.4	3(130/138)	Positive	III-IV	2006-2009	11(2-60)	7
Deng et al.	2015	China	R	S	389(282/107)	65(29-62)	2.36(132/257)	Negative	I- IV	2007-2009	24(3-60)	8
Lma et al.	2014	Egypt	P	C	70(47/23)	53(30-70)	3(30/40)	Positive	III-IV	2010-2014	NR	6
GONDA et al.	2017	Japan	R	C	110(56/54)	66.2(35-80)	3(53/47)	Positive	IV	2013-2015	NR	6
Qu et al.	2017	China	R	S	436(312/124)	58(26-82)	2.51(326/110)	Positive	I- II	2007-2013	29(6-67)	8
Jeong et al.	2012	Korea	R	C	104(69/35)	52.5(28-82)	3(49/55)	Positive	IV	2002-2009	11.9(10.2-11.9)	8
Jung et al.	2011	Korea	R	S	293(193/100)	62(27-96)	2(138/155)	Positive	III-IV	2004-2007	38.2(4.2-65.5)	7
E.Y.Kim et al.	2015	Korea	P	S	1986(1317/669)	59(23-88)	2(1247/739)	Positive	I-III	2000-2009	NR	6
J H Kim et al.	2015	Korea	R	S	601(401/200)	59.5	1.7(280/321)	Positive	I-III	2005-2011	49(2.4-104.4)	7
Lee DY et al.	2013	Korea	R	S	220(149/71)	57(23-89)	2.15(164/56)	Negative	I- IV	2002-2006	NR	6
Lieto et al.	2017	Italy	P	S	401(236/165)	NR	3.22(215/82)	Positive	I- IV	2000-2015	23.3(9.3-59.7)	8
Liu et al.	2017	china	R	S	1056(714/342)	58(19-89)	2(505/551)	Positive	I-III	2000-2012	33(1-97)	8
MAO et al.	2017	china	R	S	337(237/100)	59(19-89)	3.41(258/79)	Positive	I- IV	2010	29.77(0.43-59.7)	7
Mohri et al.	2014	Japan	P	ML	123(85/38)	66(18-94)	3.1(64/59)	Positive	IV	1999-2011	29.4(12.2-60.2)	7
C.Y.Ock et al.	2017	Korea	R	S	745(534/211)	60(20-89)	2.42(372/373)	Positive	NR	2004-2014	37.8(1.6-117)	7
Qiu et al.	2015	China	R	S	706(481/225)	59(24-83)	3(497/209)	Positive	I- IV	2001-2008	48.0(3.0-175.0)	7
Tanaka et al.	2014	Japan	R	S	191(122/69)	64	2.5(94/97)	Negative	IV	1997-2010	NR	6
Ubukata	2010	Japan	R	S	157(108/49)	65.27(29-84)	5(70/87)	Positive	I- IV	1996-2003	NR	7

Table 3: Comparison of clinical characteristics between 716 younger patients and 321 older patients with gastric cancer.

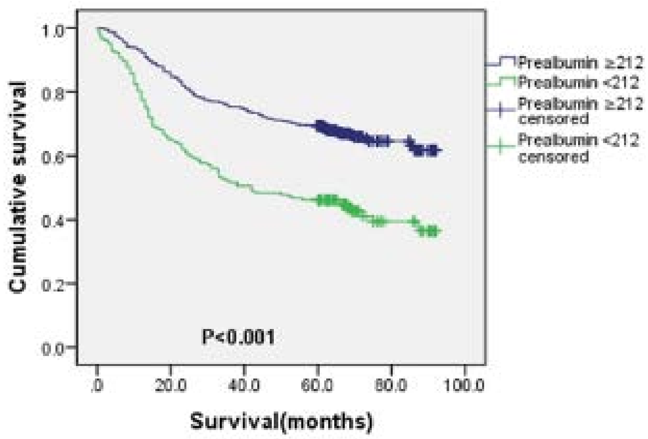

Figure 4: OS based on preoperative pre-albumin in 716 younger patients.

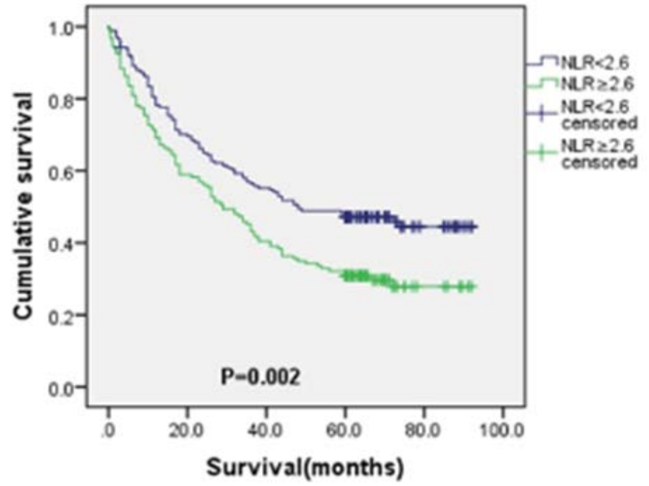

Figure 5: OS based on preoperative NLR in 321 older patients.

Characteristics	Univariate	Analysis	Multivariate	Analysis
	HR (95%CI)	P value	HR (95%CI)	P value
Sex (Male /Female)	1.016(0.742-1.392)	0.92		
Hospitalization (≥ 18/<18)	1.328(0.991-1.780)	0.058		
T stage (3+4/1+2)	4.356(2.709-7.003)	<0.001		
N stage (1-3/0)	3.690(2.544-5.352)	<0.001		
M stage (1/0)	5.142(3.210-8.237)	<0.001		
TNM (III-IV/I-II)	5.462(3.723-8.001)	<0.001	3.873(2.571-5.836)	<0.001
Histo (Diffuse /Intestinal)	1.67(1.264-2.220)	<0.001	1.441(1.078-1.928)	0.014
Location (Cardia/non)	1.314(0.955-1.807)	0.094		
Tumor size (≥ 4/<4)	2.711(1.854-3.963)	<0.001	1.468(0.965-2.232)	0.073
Neural invasion(Y/N)	1.928(1.392-2.671)	0.001	1.191(0.828-1.713)	0.347
Vessel invasion(Y/N)	1.983(1.464-2.684)	<0.001	1.299(0.927-1.822)	0.129
Oesophageal invasion(Y/N)	2.602(1.716-3.944)	<0.001	2.330(1.505-3.607)	<0.001
NLR (≥ 2.6/<2.6)	1.554(1.174-2.056)	0.002	1.396(1.038-1.880)	0.028
Anemia(Y/N)	1.336(0.999-1.785	0.051		
PLR (≥ 133/<133)	1.221(0.913-1.633)	0.179		
Low albumin(Y/N)	1.420(1.060-1.904)	0.019	1.121(0.792-1.587)	0.519
Low prealbumin(Y/N)	1.781(1.336-2.374)	<0.001	1.190(0.857-1.653)	0.299
PNI (<47/ ≥ 47)	1.589(1.179-2.142)	0.002	0.962(0.659-1.404)	0.84

Table 4: Univariate and multivariate analyses of overall survival of 716 gastric cancer patients in younger group.

their respective differences. In multivariate analysis, TNM stage (P<0.001), vascular invasion (P<0.001), and preoperative low pre-albumin (P<0.001) were indicated to be independent factors (Table 2). And survival curve of preoperative low pre-albumin was also shown in Sfigure a. In the subgroup B (age<45), univariate analysis demonstrated that hospitalization (P=0.022),T (P<0.015), N (P=0.01), M (P<0.001), TNM stage (P<0.001), location (P=0.011), tumour size (P=0.004), vascular invasion (P<0.001), preoperative NLR (P=0.012), PLR (P=0.025), and pre-operative PNI (P=0.019) were all significant in their respective differences.TNM stage (P<0.001) and vascular invasion (P=0.013) were indicated to be only two significant factors in the multivariate analysis mode (Table 1).

The correlation between NLR and OS

In the 19 studies included, there was no significant heterogeneity (I-squared=9.1%; P=0.345). Thus, we applied a fixed-effects model for analysis. The results showed that the pooled HR was 1.55 with 95%CI 1.41-1.70, indicating that patients with elevated NLR had shorter OS (Figure 6).

Subsequently, meta-regression analyses showed that the treatment method, study design, NLR threshold, sample size, and proportion of males were not the sources of heterogeneity, and their P values were all more than 0.05 (Table 6).

Then subgroup analyses showed that, regardless of surgery, chemotherapy, or comprehensive therapy, there was a significant correlation between elevated NLR and poor prognosis with pooled HRs [Surgery 1.49, 95%CI: (1.34-1.67); Chemotherapy 1.55, 95%CI: (1.29-1.86); and Multiple therapy 1.95, 95%CI: (1.46-2.60)], respectively. When performing subgroup analyses stratified by study design, high NLR value indicated poor prognosis in prospective studies [HR=1.61, 95%CI: (1.31–1.98)] and retrospective studies [HR=1.54, 95%CI: (1.39–1.70)], respectively. In the subgroup analyses by sample size, the results showed that high NLR value remained to be a worse prognostic indicator regardless of sample size from the pooled HRs [1.54, 95%CI: (1.34-1.77) for studies with over 400 cases and 1.56, 95%CI: (1.38-1.76) for studies with less than 400 cases]. When performing subgroup analyses stratified by the cut-off value<3 and ≥ 3, we found that elevated

Characteristics	Univariate	Analysis	Multivariate	Analysis
	HR (95%CI)	P value	HR (95%CI)	P value
Sex (Male /Female)	1.016(0.742-1.392)	0.92		
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PNI (<47/ ≥ 47)	1.589(1.179-2.142)	0.002	0.962(0.659-1.404)	0.84

Table 5: Univariate and multivariate analyses of overall survival of 321 gastric cancer patients in older group.

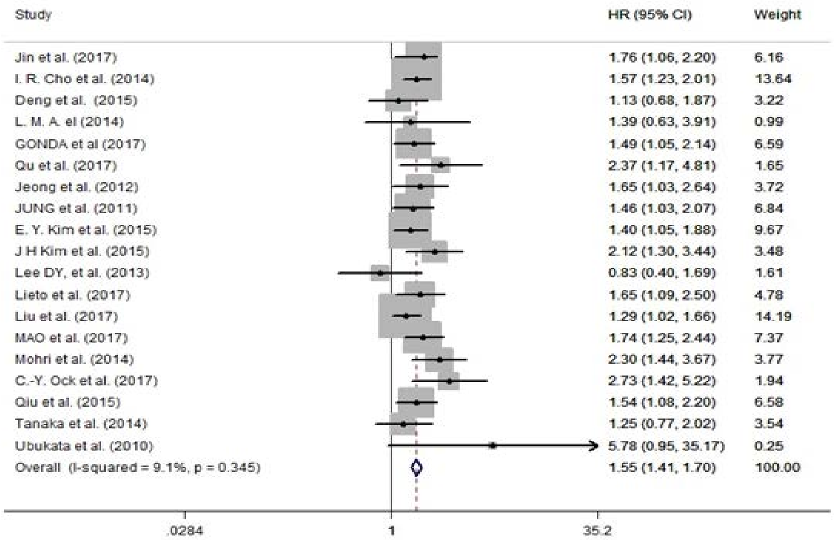

Figure 6: Forest plots of the relationship between NLR and the OS in patients with GC.

NLR value was still an indicator for poor OS, in prospective studies [HR=1.46, 95%CI: (1.29–1.66)] and retrospective studies [HR=1.65, 95%CI:(1.45-1.88)], respectively (Table 6).

The results of the sensitivity analysis, as shown in Figure 7, indicated that there was no single literature can significantly affect the entire result, confirming that the results of this meta-analysis were stable.

We applied Begg's funnel plot and Egger's test to assess publication bias of literature. As shown in Figure 8, no obvious asymmetry was found in the funnel plot shape. Thus, the publication bias in this meta-analysis was not evident. The P values for Begg's test and Egger's test were 0.248 and 0.134, respectively.

Discussion

In general, the 5-year survival rate of GC is still low worldwide, especially in Asian countries such as China, South Korea, and Japan [39], probably due to late diagnosis and inadequate management. Early diagnosis of GC can be achieved through popular science education and endoscopic screening, while appropriate management is a complex task involving many considerations. As in patients with other cancers, the quantitative evaluation of postoperative survival in patients with GC relies on a complex mathematical function, determined by the interactions of various known and unknown factors [40].

WHO defines "elderly" as older than 65 years old [41]. In previously published studies in older patients with gastric cancer, age thresholds ranged from 65 to 85 years old, so 65 years old may not be best suitable for "elderly" patients with GC [42-45]. In our study, we used a survival ROC curve in terms of OS to determine the borderline age in patients with gastric cancer and found that the optimal cut-off age was 70 years old. Therefore, patients were divided into two groups: the younger group (69 years and younger) and the older group (70 years and older). In the younger group, 716 patients were included, and age distribution

Subgroup	N	Model	HR	95%CI	I2	P Value	PMetareg
Treatment							0.162
Surgery	13	Fixed	1.49	1.34-1.67	25.1	0.19	
Chemotherapy	4	Fixed	1.55	1.29-1.86	0	0.982	
Multiple	2	Fixed	1.95	1.46-2.60	0	0.375	
Design							0.715
Retrospective	15	Fixed	1.54	1.39-1.70	14.8	0.287	
Prospective	4	Fixed	1.61	1.31-1.98	9.1	0.345	
Sample size							0.879
＜400	12	Fixed	1.56	1.38-1.76	2	0.424	
≥ 400	7	Fixed	1.54	1.37-1.77	29.8	0.201	
Cut-off value							0.223
＜3	10	Fixed	1.46	1.29-1.66	33.2	0.142	
≥ 3	9	Fixed	1.65	1.45-1.88	0	0.798	
Male/all							0.225
＜0.7	14	Fixed	1.5	1.36-2.66	0	0.469	
≥ 0.7	5	Fixed	1.75	1.43-2.13	25.6	0.251	

Table 6: Summary of the subgroup meta-analysis and Metareg results for OS.

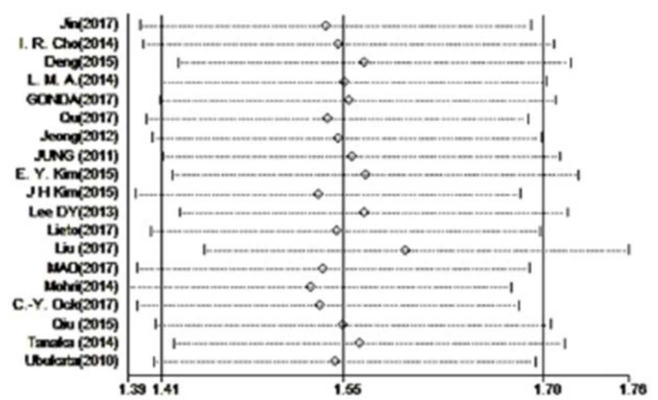

Figure 7: Sensitivity analysis of NLR for OS in patients with GC.

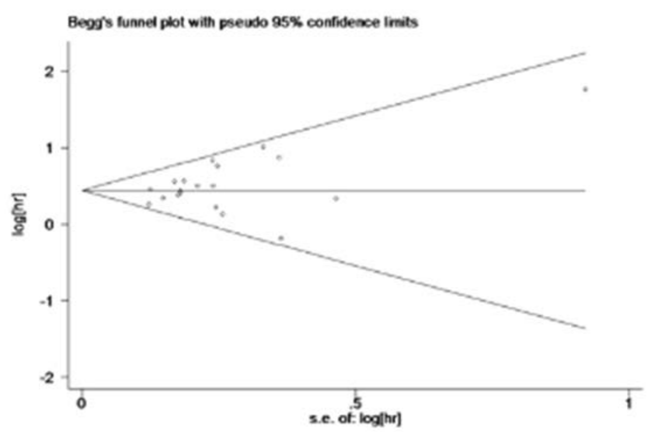

Figure 8: Begg ‘s funnel plot for OS in patients with GC.

was from 19 years old to 69 years old. Given of the large amount of data available, this group can be considered for further subgroup analysis. Accordingly, we stratified the younger group into two subgroups (cut off value was 45 years old) according to the middle age definition of WHO.

Our retrospective analysis showed that the OS of elderly patients was significantly worse than that of younger patients. The reason may be that elderly patients are more likely to exhibit some organ dysfunction, making them more difficult to overcome operative stress. We can also see that advanced age is closely associated with longer hospitalization time, advanced tumour stage, poor nutrition, and severely inflammatory state.

As for the analyses of prognostic factors, in the younger group, hospitalization time, TNM stage, vascular invasion, and preoperative low pre-albumin level were independently associated with OS. In the older group, TNM stage was also the independent risk factor for OS; however, the length of stay, vascular invasion, and preoperative low pre-albumin level were not related to OS, but oesophageal invasion, pathohistological type, and preoperative NLR could independently predict OS for the old.

It is easy to understand that TNM stage serves as a recognized prognostic factor [46], but its prognostic value is limited because it can only be used after surgery [17]. Similarly, vascular invasion, oesophageal invasion, and histological types are also determined by the patient's postoperative pathologic features, so their prognostic values for GC are also limited. Therefore, we mainly focus on some indicators that are easy to measure as well as inexpensive and convenient to perform, and objective to evaluate preoperatively. From the above results, preoperative pre-albumin in the younger group should be paid attention to, whereas preoperative NLR in the older group should be paid equally heed to.

There is increasing evidence that cancer-related malnutrition is a common but often unrecognized problem [47], and the prognosis of cancer is closely linked to nutritional status [48-50]. Several potential mechanisms have been hypothesized for their relationship. Firstly, malnutrition weakens human immune defence system, including cellular and humoral immunity and phagocytic functions, resulting in increased risks of postoperative infection and metastasis [51]. Secondly, malnutrition, as a subacute or chronic state, accompanied by varying degrees of nutritional deficiencies and increased inflammatory responses, contributes to body compositional changes and functional decline [52,53], and thus diverse postoperative complications and reduced therapeutic efficacy of drugs [54]. Finally, malnutrition can also promote tumour development by inhibiting immunity [55]. At present, pre-albumin, as a marker of nutritional status, has become the research focus owing to the fact that its half-life (about 1.9 days) is shorter than albumin and a negative acute phase protein synthesized by the liver. Therefore, the pre-albumin level is highly sensitive to identify the body's metabolic status and immune function. Han et al. also showed that pre-albumin was an independent predictor for postoperative survival outcome [56], the finding consistent with that in our study. Therefore, we propose that younger GC patient's nutritional status should be ameliorated considerably before surgery, especially for those with low pre-albumin.

It is well known that chronic inflammation induces carcinogenesis and promotes the development of cancers [57]. NLR reflects the patient's inflammatory status and is known to have prognostic value in patients with cancer. Some possible mechanisms may account for the relationship between poor prognosis and NLR in GC patients. Firstly, an increase in the number of neutrophils around the tumour may inhibit the anti-tumour responses of natural killer cells and activated T cells [58]. Furthermore, neutrophils promote tumour progression by producing cytokines such as tumour necrosis factor (TNF), IL-1, IL-6, angiogenic factors, and vascular endothelial growth factor [59]. Finally, the decrease of lymphocyte counts attenuates lymphocyte-mediated anti-tumour cellular immune responses [60]. Consequently, preoperative NLR should be given a high priority in elderly patients. For those with high NLR, it is essential to find out whether there is acute or chronic inflammation, and effective anti-inflammatory treatment should be recommended to cut down NLR to a suitable level before surgery, which, to a large extent, may improve the prognosis of GC.

To further verify our results in retrospective analysis portion, we attempted to conduct a comprehensive meta-analysis based on previous studies. Nevertheless, there were few studies for the prognostic significance of pre-albumin, its related meta-analysis was not performed. Therefore, we conducted only a meta-analysis on the prognostic value of NLR for GC. The results showed that elevated NLR was significantly associated with shorter OS.

Certainly, some potential limitations may exist in our study. In the retrospective analysis portion, it was a single-institution study. Moreover, we are short of the data on progression-free survival, though OS has widely been considered to be the gold end-point standard for prognostic studies on cancer. In the meta-analysis portion, due to the lack of sufficient data, the correlation between NLR and disease-free survival cannot be explored. For the whole study, in terms of the prognostic significance of NLR for GC, our retrospective analysis is aimed at the elderly patients, but the meta-analysis is aimed at the whole GC patients, which cannot be divided into age groups.

Considering the limitations of this study, if conditions permit, we need a larger scale, multi-Center, and prospective performance to validate our findings.

Conclusion

The OS of elderly patients was significantly worse than that of younger patients. There were significant differences in clinicopathological characteristics and prognostic factors between the two groups. We concluded that preoperative nutritional status improvement may be particularly beneficial for the prognosis of younger patients, whereas elderly patients should need to focus more on the improvement of inflammatory status. There is still little research to assess the significance of pre-albumin in the prognosis of GC, which needs to be paid more attention to in the future. NLR was a widely used, inexpensive and reproducible marker that can be used as an important predictor for the prognosis of GC. In a word, clinicians should attach great importance to the impact of objective indicators on the prognosis of GC, identifying high-risk patients as many as possible, and improving their overall prognosis as much as possible.

Author contributions

Huiping Xue is the corresponding author of the article. Qiong Li and Linyi Huang equally contributed to the article. Qiong Li collected data, did statistical analysis, and wrote the manuscript; LinYi Huang did further statistical analysis, supplemented the manuscript, and completed the revision version required of the editor and peer reviewers; Huiping Xue designed and supervised the research and revised both the draft and the final version of the article. All authors read and approved the final manuscript. The authors declare that they have no conflict of interest.

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