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ABOUT COVER

Editorial board member of *World Journal of Gastrointestinal Oncology*, Adriana Ciocalteu, MD, PhD, is a Researcher at the Research Center of Gastroenterology and Hepatology and a Teaching Assistant in the Department of Gastroenterology of the University of Medicine and Pharmacy, Craiova (Romania). Having received her Bachelor's degree from University of Medicine and Pharmacy of Craiova in 2011, she undertook her postgraduate training at the Clinical Emergency County Hospital Craiova in the Gastroenterology Unit, Copenhagen University Hospital, Herlev and at Aarhus University Hospital (Denmark), receiving her PhD in 2016. Upon return to Craiova, she began her practice as Specialist in Gastroenterology and Teaching Assistant in the Department of Gastroenterology at the University of Medicine and Pharmacy. Her ongoing research interests involve studying malignant pathology of the digestive system using state-of-the-art techniques. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Retrospective Study

Comparison of prognostic factors in different age groups and prognostic significance of neutrophil-lymphocyte ratio in patients with gastric cancer

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Abstract

BACKGROUND

Gastric cancer (GC) is one of the most common malignant tumors in the world. Although in recent years tremendous progress has been made in its early detection, the postoperative overall survival (OS) of GC patients remains extremely low. A number of studies have shown that age, to varying degrees, affects the prognosis of patients with GC. Therefore, this study retrospectively analyzed the clinical and pathologic data of patients with GC to explore the differences in the clinical characteristics and prognostic factors in different age groups.

AIM

To explore the difference in clinicopathological characteristics and prognostic factors in GC patients in different age groups.

METHODS

In this retrospective study, we analyzed 1037 GC patients admitted to Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from May 2010 to January 2013. The patients were divided into two groups based on age: Younger group (less than 70 years old) and older group (no less than 70 years old). In the younger group, we subdivided the patients in two subgroups by a cut-off value of 45 years. The clinical features and prognostic factors were analyzed in both groups. Subsequently, we retrieved studies that evaluated the predictive role of neutrophil-lymphocyte ratio (NLR) by searching two medical databases, PubMed and EMBASE, to conduct a meta-analysis. Random-effects model was used to pool the data.

RESULTS

In the retrospective study, the mean OS time of the younger group (64.7 mo) was

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significantly longer than that of the older group (48.1 mo) ($P < 0.001$). Among patients under 70 years of age, hospitalization time, tumor-node-metastasis (TNM) stage, vascular invasion, and preoperative low pre-albumin were independently associated with OS ($P < 0.005$). In patients aged 70 years and above, TNM stage, esophageal invasion, histological type, and preoperative NLR were independent factors for OS ($P < 0.05$). The OS of these older patients was also significantly shorter ($P < 0.05$). In the meta-analysis, 19 retrieved studies included a total of 8312 patients, among whom 3558 had elevated NLR values. The results showed that high NLR value was a risk factor for the prognosis of GC ($P < 0.01$).

CONCLUSION

The OS of elderly patients is significantly worse than that of younger patients. There are significant differences in clinicopathological characteristics and prognostic factors between younger and older patients. NLR is a convenient, inexpensive, and reproducible marker that can be used as an important predictor of the prognosis of GC.

Key Words: Gastric cancer; Neutrophil-lymphocyte ratio; Age; Prognosis; Overall survival; Meta-analysis

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Core Tip: This is a retrospective study that explored the prognostic factors in different age groups and the prognostic significance of neutrophil-lymphocyte ratio in gastric cancer patients. We compared the clinicopathological features of patients in two age groups (< 70 years and ≥ 70 years), analyzed the prognostic factors, and performed 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 in gastric cancer patients.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors in the world, with approximately 1 million new cases each year^[1,2]. It is the second most lethal malignancy worldwide^[3], with the 5-year overall survival (OS) rate being only 29.7%^[2]. Although in recent years tremendous progress has been made in its 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), trauma due to radical gastrectomy may readily lead to a 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 in different age groups. In the present study, we performed a retrospective analysis to compare different clinical and pathologic factors and explore their prognostic roles in patients with GC in different age groups.

In recent years, the relationship between inflammation and cancer has been widely explored^[7-9], in which neutrophil-lymphocyte ratio (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 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 also conducted a systemic review and meta-analysis to explore the prognostic role of NLR in GC in this study.

MATERIALS AND METHODS

Patient selection

This study was reviewed and unanimously approved by the Ethics Committee of Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. In the retrospective analysis portion, we investigated the clinical and pathologic data of GC patients admitted to the hospital from May 2010 to January 2013. A total of 1037 patients were included in our study. The inclusion criteria were as follows: (1) Postoperative, pathologically confirmed diagnosis of stages I to IV gastric adenocarcinoma; (2) Complete clinicopathological information; and (3) 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 the 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 OS was evaluated; and (3) The sufficient data (hazard ratio [HR] and 95% confidence interval [CI] for OS) were provided. The 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 provide the cut-off value of NLR elevation.

All searches were carried out independently by two authors. The flow chart of selection of the article is 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), tumor-specific data (tumor size, neural invasion, vascular invasion, esophageal invasion, histopathologic type, and tumor location), therapeutic modalities (surgical procedures, chemotherapy, and radiotherapy), and survival data. Peripheral blood detection data were collected preoperatively, including routine blood examination, serum albumin, serum pre-albumin, *etc.*

All the patients underwent routine assessments after surgery, including physical examination, laboratory examination, CT scan, and upper gastrointestinal endoscopy. The latest follow-up date was January 20, 2018, with a median follow-up duration of 61.3 mo (range, 0-92 mo). All patients were followed 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 value 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: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per cubic millimeter)}$ ^[16]. Its cut-off value was defined as 47 according to the 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 d and 212 mg/L, respectively, based on the Youden's index of the ROC curves. Similarly, the optimal cut-off values for preoperative NLR and platelet lymphocyte ratio (PLR) were 2.6 and 133, respectively. Those for preoperative anemia



Figure 1 Flow chart of the meta-analysis.

and hypoalbuminemia were defined as 120 g/L and 35 g/L, respectively, according to the normal ranges used in our hospital.

Tumor stage was determined in accordance with the tumor-node-metastasis (TNM) staging system (the seventh edition) proposed by the American Joint Committee on Cancer^[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 tumor was bounded by 4 cm according to the Youden index of the ROC curve.

We used the Youden's index of the ROC curve to divide patients into two different groups based on the age of 70 years. We compared the features of patients in the 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 years), we further divided the patients in this group into two subgroups, according to the middle-age definition of the World Health Organization (WHO).

Informed consent was approved by the Ethics Committee of Renji Hospital. This study design and protocol were thoroughly reviewed and unanimously approved by the Ethics Committee of Renji Hospital (Microsoft1).

In the meta-analysis portion, the quality of studies was assessed by the Newcastle-Ottawa Quality Assessment Scale^[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, tumor size, pre-albumin, PNI,

NLR, and PLR were determined by the 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 version 24.0 (IBM Corporation, Armonk, NY, United States).

In the meta-analysis portion, all statistical analyses were performed *via* Stata 12.0. HRs and their associated 95%CI from each study were pooled. Cochran's Q test and I-squared statistics were used to evaluate heterogeneity. If I^2 values < 50% or $P \geq 0.05$, which indicates 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 the 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

Subject characteristics

In the retrospective analysis portion, a total of 1037 patients with GC were included in our study (Table 1); 728 (70.2%) were male and 309 (29.8%) were female, with a male-to-female ratio of 2.36: 1. The patients ranged in age from 19 to 90 years, with an average age of 62.9 years. All the patients were followed 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 an age range of 19-69 years and an average of 57 years; and 321 cases (31%) in the older group (≥ 70 years) with an age range of 70-90 years and an average of 76 years.

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

In the meta-analysis portion, the flow chart of our literature search is shown in Figure 1. A total of 172 articles were obtained based on the search strategy; finally, we retrieved 19 articles that met our inclusion criteria^[20-38].

Supplementary Table 1 summarizes the characteristics of the included studies. We collected data from 19 studies with a total of 8312 patients. Four studies were prospective and 15 were retrospective. Twelve enrolled studies had less than 400 patients and seven had more than 400 patients. The cut-off value of NLR in ten studies was less than 3, and that of the remaining nine was more than 3. HR and 95%CI were reported directly in all included studies.

Association of age with characteristics

The clinicopathological features of the two groups are summarized in Table 2. There was no significant difference in gender distribution, distant metastasis, neural or vascular invasion, esophageal invasion, or tumor location between the two groups. Compared with younger patients, older patients had longer hospitalization, deeper tumor invasion, more advanced TNM stage, larger tumor size, and more lymph node metastasis ($P < 0.005$). And they had higher preoperative NLR and PLR values, and lower preoperative PNI values, being more likely to have anemia, hypoprealbuminemia, and hypoalbuminemia ($P < 0.005$). With regard to pathologic type, more patients in the older group had intestinal-type adenocarcinomas, while more younger patients had diffuse-type adenocarcinomas ($P < 0.005$).

Univariate and multivariate Cox regression analysis for OS

The results of univariate Cox analysis (Table 3) showed that in the younger group (less than 70 years old), hospitalization time ($P < 0.001$), TNM stage ($P < 0.001$), tumor location ($P = 0.001$), histological type ($P < 0.001$), neural invasion ($P < 0.001$), vascular invasion ($P < 0.001$), esophageal invasion ($P < 0.001$), preoperative NLR ($P < 0.001$), preoperative PLR ($P < 0.001$), preoperative anemia ($P = 0.046$), preoperative low albumin ($P = 0.010$), preoperative low pre-albumin ($P < 0.001$), and preoperative PNI (

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

Characteristic	Patients <i>n</i> (%)	Overall survival months (95%CI)	<i>P</i> value
Sex			0.864
Male	728 (70.2%)	59.6 (56.9-62.2)	
Female	309 (29.8%)	59.7 (55.7-63.8)	
Age (yr)			< 0.001
< 70	716 (69%)	64.7 (62.2-67.3)	
≥ 70	321 (31%)	48.1 (44.1-52.2)	
Hospitalization (d)			< 0.001
< 18	494 (47.6%)	68.7 (65.7-71.6)	
≥ 18	543 (52.4%)	51.5 (48.4-54.6)	
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)	
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)	
Lymph node metastasis (N)			< 0.001
0	393 (37.9%)	80.6 (78.1-83.2)	
1-3	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)	
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)	
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)	
Depth of invasion			< 0.001
1-2	313 (30.2%)	84.4 (82.0-86.8)	
3-4	724 (69.8%)	48.9 (46.3-51.6)	
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)	

TNM: Tumor-node-metastasis; NLR: Neutrophil-lymphocyte ratio; HB: Hemoglobin; PLR: Platelet lymphocyte ratio; PNI: Prognostic nutritional index.

$P < 0.001$) were significantly correlated with OS. The results of multivariate Cox regression analysis (Table 3) indicated that hospitalization time ($P < 0.001$), TNM stage ($P < 0.001$), vascular invasion ($P = 0.002$), and preoperative low pre-albumin ($P < 0.001$) were independent prognostic factors for OS, respectively. The 5-year survival rates of patients with low and normal pre-albumin were 46.2% and 69.3%, respectively; the OS of the former (50.7 mo) was significantly shorter than that of the latter (69.6 mo) ($P < 0.001$) (Figure 3A). Therefore, preoperative nutritional status may affect the survival prognosis of young patients with gastric cancer.

In the older group, however, univariate analysis (Table 4) showed that TNM stage ($P < 0.001$), histological type ($P < 0.001$), neural invasion ($P < 0.001$), vascular invasion ($P < 0.001$), esophageal 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 significantly correlated with OS. In the same way, these factors were tested by a multivariate Cox regression analysis (Table 4): TNM stage ($P < 0.001$), pathohistological type ($P = 0.014$), esophageal invasion ($P < 0.001$), and preoperative NLR ($P = 0.028$) were identified as the independent prognostic factors for OS. 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 mo and 53.8 mo, respectively, and the difference was statistically significant (Figure 3B).

We further made univariate and multivariate analyses in the younger group (less than 70 years old) by age sub-stratification. In the subgroup A ($45 \leq \text{age} < 70$), univariate analysis (Table 5) demonstrated that hospitalization ($P = 0.01$), T stage ($P < 0.001$), N stage ($P < 0.001$), M stage ($P < 0.001$), TNM stage ($P < 0.001$), histological type ($P < 0.001$), tumor location ($P = 0.007$), tumor size ($P < 0.001$), neural invasion ($P < 0.001$), vascular invasion ($P < 0.001$), esophageal 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 significantly correlated with OS. In the multivariate analysis (Table 5), TNM stage ($P < 0.001$), vascular invasion ($P < 0.001$), and preoperative low pre-albumin ($P < 0.001$) were indicated to be independent factors. The survival curve of preoperative low pre-albumin is shown in Figure 3C ($P < 0.001$). In the subgroup B ($\text{age} < 45$), univariate analysis demonstrated that hospitalization ($P = 0.022$), T stage ($P < 0.015$), N stage ($P = 0.01$), M stage ($P < 0.001$), TNM stage ($P < 0.001$), tumor location ($P = 0.011$), tumor size ($P = 0.004$), vascular invasion ($P < 0.001$), preoperative NLR ($P = 0.012$), PLR ($P =$

Table 2 Comparison of clinical characteristics between 716 younger patients (age < 70 yr) and 321 older patients (age > 70 yr) with gastric cancer

Characteristic	Younger group <i>n</i> (%)	Older group <i>n</i> (%)	<i>P</i> value
Sex			0.407
Male	497 (69.4%)	231 (72.0%)	
Female	219 (30.6%)	90 (28.0%)	
Hospitalization (d)			< 0.001
< 18	369 (51.5%)	125 (38.9%)	
≥ 18	347 (48.5%)	196 (61.6%)	
TNM stage			0.003
I-II	331 (46.2%)	117 (36.4%)	
III-IV	385 (53.8%)	204 (63.6%)	
T stage			< 0.001
1-2	240 (33.5%)	73 (22.7%)	
3-4	476 (66.5%)	248 (77.3%)	
N stage			0.021
0	288 (40.2%)	105 (32.7%)	
1-3	428 (59.8%)	216 (67.3%)	
M stage			0.343
0	657 (91.8%)	300 (93.5%)	
1	59 (8.2%)	21 (6.5%)	
Tumor size (cm)			< 0.001
< 4	318 (44.4%)	87 (27.1%)	
≥ 4	398 (55.6%)	234 (72.9%)	
Tumor location			0.059
Cardia	127 (17.7%)	73 (22.7%)	
Non-cardia	589 (82.3%)	248 (77.3%)	
Histological type			0.001
Intestinal type	359 (50.1%)	196 (61.1%)	
Diffuse type	357 (49.9%)	125 (38.9%)	
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%)	
Esophageal 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%)	
Anemia			< 0.001

No	499 (69.7%)	131 (40.8%)	0.003
Yes	217 (30.3%)	190 (59.2%)	
PLR			
< 133	358 (50%)	128 (39.9%)	< 0.001
≥ 133	358 (50%)	193 (60.1%)	
Low albumin			
No	650 (90.8%)	222 (69.2%)	< 0.001
Yes	66 (9.2%)	99 (30.8%)	
Low pre-albumin			
No	534 (74.6%)	149 (46.4%)	< 0.001
Yes	182 (25.4%)	172 (53.6%)	
PNI			
< 47	191 (26.7%)	196 (61.1%)	< 0.001
≥ 47	525 (73.3%)	125 (38.9%)	

TNM: Tumor-node-metastasis; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNI: Prognostic nutritional index.

Table 3 Univariate and multivariate analyses of overall survival of 716 gastric cancer patients in younger group (age < 70 yr)

Characteristic	Univariate HR (95%CI)	Analysis P value	Multivariate HR (95%CI)	Analysis P value
Sex (Male/Female)	0.983 (0.765-1.263)	0.893		
Hospitalization (≥ 18/< 18 mo)	2.439 (1.909-3.115)	< 0.001	1.801 (1.394-2.327)	< 0.001
T stage (3 + 4/1 + 2)	9.948 (6.242-15.855)	< 0.001		
N stage (1-3/0)	6.841 (4.797-9.756)	< 0.001		
M stage (1/0)	5.799 (4.278-7.860)	< 0.001		
TNM (III-IV/I-II)	7.791 (5.586-10.867)	< 0.001	5.418 (3.731-7.869)	< 0.001
Location (Cardia/non-cardia)	1.567 (1.190-2.064)	< 0.001	1.042 (0.753-1.441)	0.804
Tumor size (≥ 4/< 4 cm)	2.962 (2.267-3.871)	< 0.001	1.123 (0.831-1.517)	0.452
Histological type (Diffuse/Intestinal)	1.661 (1.311-2.105)	< 0.001	1.249 (0.973-1.604)	0.081
Neural invasion (Y/N)	2.024 (1.573-2.604)	< 0.001	0.987 (0.758-1.286)	0.925
Vessel invasion (Y/N)	2.865 (2.260-3.632)	< 0.001	1.501 (1.163-1.936)	0.002
Esophageal invasion(Y/N)	2.197 (1.566-3.082)	< 0.001	1.214 (0.814-1.810)	0.341
NLR (≥ 2.6/< 2.6)	1.602 (1.267-2.024)	< 0.001	1.151 (0.881-1.505)	0.303
Anemia (Y/N)	1.282 (1.004-1.637)	0.046	0.746 (0.559-0.995)	0.046
PLR (≥ 133/< 133)	1.540 (1.217-1.948)	< 0.001	1.102 (0.835-1.453)	0.493
Low albumin (Y/N)	1.585 (1.117-2.249)	0.010	0.781 (0.515-1.183)	0.243
Low prealbumin (Y/N)	2.149 (1.688-2.735)	< 0.001	1.637 (1.254-2.138)	< 0.001
PNI (< 47/≥ 47)	1.839 (1.444-2.343)	< 0.001	1.226 (0.896-1.679)	0.203

TNM: Tumor-node-metastasis; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNI: Prognostic nutritional index.

0.025), and preoperative PNI ($P = 0.019$) were significantly correlated with OS. TNM stage ($P < 0.001$) and vascular invasion ($P = 0.013$) were indicated to be the only significant factors in the multivariate analysis (Table 6).

Table 4 Univariate and multivariate analyses of overall survival of 321 gastric cancer patients in older group (age > 70 yr)

Characteristic	Univariate HR (95%CI)	Analysis P value	Multivariate HR (95%CI)	Analysis P value
Sex (Male/Female)	1.016 (0.742-1.392)	0.920		
Hospitalization (≥ 18 / < 18 mo)	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
Location (Cardia/non-cardia)	1.314 (0.955-1.807)	0.094		
Tumor size (≥ 4 / < 4 cm)	2.711 (1.854-3.963)	< 0.001	1.468 (0.965-2.232)	0.073
Histological type (Diffuse/Intestinal)	1.675 (1.264-2.220)	< 0.001	1.441 (1.078-1.928)	0.014
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
Esophageal 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)	0.840

TNM: Tumor-node-metastasis; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNI: Prognostic nutritional index.

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 [95%CI: (1.41-1.70)], indicating that patients with an elevated NLR had a shorter OS (Figure 4).

Subsequently, meta-regression analyses (Table 7) showed that treatment method, study design, NLR threshold, sample size, and proportion of males were not the sources of heterogeneity ($P > 0.01$). Subgroup analyses showed that, regardless of surgery, chemotherapy, or comprehensive therapy, there was a significant correlation between elevated NLR and poor prognosis (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). When performing subgroup analyses stratified by study design, we found that a high NLR value was associated with a poor prognosis in both prospective [HR = 1.61, 95%CI: (1.31-1.98)] and retrospective studies [HR = 1.54, 95%CI: (1.39-1.70)]. When performing subgroup analyses stratified by the cut-off value < 3 and ≥ 3 , we found that elevated NLR value was still an indicator for poor OS in both prospective [HR = 1.46, 95%CI: (1.29-1.66)] and retrospective studies [HR = 1.65, 95%CI: (1.45-1.88)] (Table 7).

The results of the sensitivity analysis, as shown in Figure 5A, indicated that 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 the literature. As shown in Figure 5B, 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.

Table 5 Univariate and multivariate analyses of overall survival of 65 gastric cancer patients in younger group (age < 45 yr)

Characteristic	Univariate HR (95%CI)	Analysis P value	Multivariate HR (95%CI)	Analysis P value
Sex (Male/Female)		0.555		
Hospitalization (≥ 18 / < 18 mo)	2.698 (1.153-6.312)	0.022		0.072
T stage (3 + 4/1 + 2)	60.674 (2.194-1677.654)	0.015		
N stage (1-3/0)	8.062 (2.361-27.534)	0.01		
M stage (1/0)	6.437 (2.599-15.946)	< 0.001		
TNM (III-IV/I-II)	10.933 (3.217-37.162)	< 0.001	9.253 (2.644-32.377)	< 0.001
Location (Cardia/non-cardia)	3.684 (1.344-10.092)	0.011		0.301
Tumor size (≥ 4 / < 4 cm)	4.293 (1.599-11.527)	0.004		0.271
Histological type (Diffuse/Intestinal)		0.161		
Neural invasion (Y/N)		0.63		
Vessel invasion (Y/N)	4.518 (1.988-10.266)	< 0.001	2.898 (1.249-6.723)	0.013
Esophageal invasion (Y/N)		0.31		
NLR (≥ 2.6 / < 2.6)	2.878 (1.257-6.588)	0.012		0.445
Anemia (Y/N)		0.094		
PLR (≥ 133 / < 133)	3.083 (1.148-8.276)	0.025		0.958
Low albumin (Y/N)		0.295		
Low prealbumin (Y/N)		0.051		
PNI (< 47 / ≥ 47)	2.760 (1.178-6.466)	0.019		0.244

TNM: Tumor-node-metastasis; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNI: Prognostic nutritional index.

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. 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].

The WHO defines “elderly” as older than 65 years old^[41]. In previously published studies in older patients with GC, 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 GC, and found that the optimal cut-off age was 70 years old. Therefore, the patients were divided into either a younger group (69 years and younger) or an older group (70 years and older) in the present study based on the cutoff value of 70 years. In the younger group, 716 patients were included and their age distribution was from 19 to 69 years old. Given 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 the 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 also found that advanced age was closely associated with longer hospitalization time, advanced tumor stage, poor nutrition, and severe 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 identified

Table 6 Univariate and multivariate analyses of overall survival of 651 gastric cancer patients in middle-age group ($45 \leq \text{age} < 70$).

Characteristic	Univariate HR (95%CI)	Analysis P value	Multivariate HR (95%CI)	Analysis P value
Sex (Male/Female)		0.953		
Hospitalization ($\geq 18 / < 18$ mo)	1.546 (1.210-1.976)	0.01		0.127
T stage (3 + 4 / 1 + 2)	8.995 (5.635-14.358)	< 0.001		
N stage (1-3 / 0)	6.752 (4.659-9.786)	< 0.001		
M stage (1 / 0)	5.792 (4.186-8.013)	< 0.001		
TNM (III-IV / I-II)	7.558 (5.348-10.682)	< 0.001	5.994 (4.183-8.590)	< 0.001
Histological type (Diffuse/Intestinal)	0.598 (0.468-0.764)	< 0.001		0.104
Location (Cardia / non-cardia)	1.481 (1.111-1.973)	0.007		0.947
Tumor size ($\geq 4 / < 4$ cm)	2.859 (2.165-3.776)	< 0.001		0.302
Neural invasion (Y/N)	2.075 (1.596-2.696)	< 0.001		0.723
Vessel invasion (Y/N)	2.749 (2.146-3.523)	< 0.001	1.603 (1.242-2.069)	< 0.001
Esophageal invasion (Y/N)	2.209 (1.559-3.130)	< 0.001	1.431 (1.285-2.130)	0.046
NLR ($\geq 2.6 / < 2.6$)	1.541 (1.206-1.970)	0.001		0.335
Anemia (Y/N)		0.157		
PLR ($\geq 133 / < 133$)	1.486 (1.163-1.898)	0.002		0.436
Low albumin (Y/N)	1.721 (1.216-2.438)	0.002		0.484
Low prealbumin (Y/N)	2.128 (1.656-2.735)	< 0.001	1.654 (1.285-2.130)	< 0.001
PNI ($< 47 / \geq 47$)	1.806 (1.404-2.323)	< 0.001		0.265

TNM: Tumor-node-metastasis; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet lymphocyte ratio; PNI: Prognostic nutritional index.

to be 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 esophageal invasion, pathohistological type, and preoperative NLR could independently predict OS for the older group.

It is easy to understand that TNM stage can serve as a prognostic factor^[46], but its prognostic value is limited because it can only be used after surgery^[17]. Similarly, vascular invasion, esophageal 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 focused 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 and preoperative NLR in the older group should be stressed.

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. First, malnutrition weakens human immune defense system, including cellular and humoral immunity and phagocytic functions, resulting in increased risks of postoperative infection and metastasis^[51]. Second, 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 tumor 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 d) is shorter than albumin and it is a negative acute phase protein synthesized by the liver. Therefore, the pre-albumin level is highly sensitive in identifying the body's metabolic status and immune function. Han *et al*^[56] also showed that pre-albumin was an independent predictor of postoperative survival outcome^[56]. The finding is consistent with that in our study. Therefore, we propose that younger GC patients' nutritional status should be ameliorated considerably before surgery,

Table 7 Summary of meta-regression and the subgroup analysis

Subgroup	¹ P value	n	HR	95%CI	P	² P value
Design	0.715					
Retrospective		15	1.54	1.39-1.70	14.8	0.287
Prospective		4	1.61	1.31-1.98	9.1	0.345
Sample size	0.879					
< 400		12	1.56	1.38-1.76	2	0.424
≥ 400		7	1.54	1.37-1.77	29.8	0.201
Cut-off value	0.223					
< 3		10	1.46	1.29-1.66	33.2	0.142
≥ 3		9	1.65	1.45-1.88	0	0.798
Male/all	0.225					
< 0.7		14	1.50	1.36-2.66	0	0.469
≥ 0.7		5	1.75	1.43-2.13	25.6	0.251
Treatment	0.162					
Surgery		13	1.49	1.34-1.67	25.1	0.190
Chemotherapy		4	1.55	1.29-1.86	0	0.982
Multiple		2	1.95	1.46-2.60	0	0.375

¹P value of meta-regression.²P value of subgroup analysis.

especially for those with low pre-albumin.

It is often taken for granted that age is an important factor when clinicians choose the optimal therapeutic modality for GC patients. It is self-evident that the operation risk of senile GC patients is much higher than that of young counterparts. We also found significant differences in clinicopathological characteristics and prognostic factors between different age groups of GC patients. However, there is increasing evidence that the senile GC patients with radical gastrectomy have a relatively longer OS than those without^[57,58]. Therefore, according to the findings in our study, the preoperative alleviation of inflammatory status should be emphasized for elderly GC patients after their surgical benefits have been evaluated to prevail over their surgical risks. Certainly, if elder patients cannot bear the risk of surgery, palliative chemotherapy can be an alternative therapeutic method.

It is well known that chronic inflammation induces carcinogenesis and promotes the development of cancers^[59]. 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 NLR and poor prognosis in GC patients. First, an increase in the number of neutrophils around the tumor may inhibit the anti-tumor responses of natural killer cells and activated T cells^[60]. Furthermore, neutrophils promote tumor progression by producing cytokines such as tumor necrosis factor, IL-1, IL-6, angiogenic factors, and vascular endothelial growth factor^[61]. Finally, the decrease of lymphocyte counts attenuates lymphocyte-mediated anti-tumor cellular immune responses. 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. Therefore, we conducted a meta-analysis on the prognostic value of NLR for GC. The results showed that elevated NLR was significantly associated with a shorter OS.

Certainly, some potential limitations may exist in our study. The retrospective analysis was a single-institution study. Moreover, we lacked the data on progression-

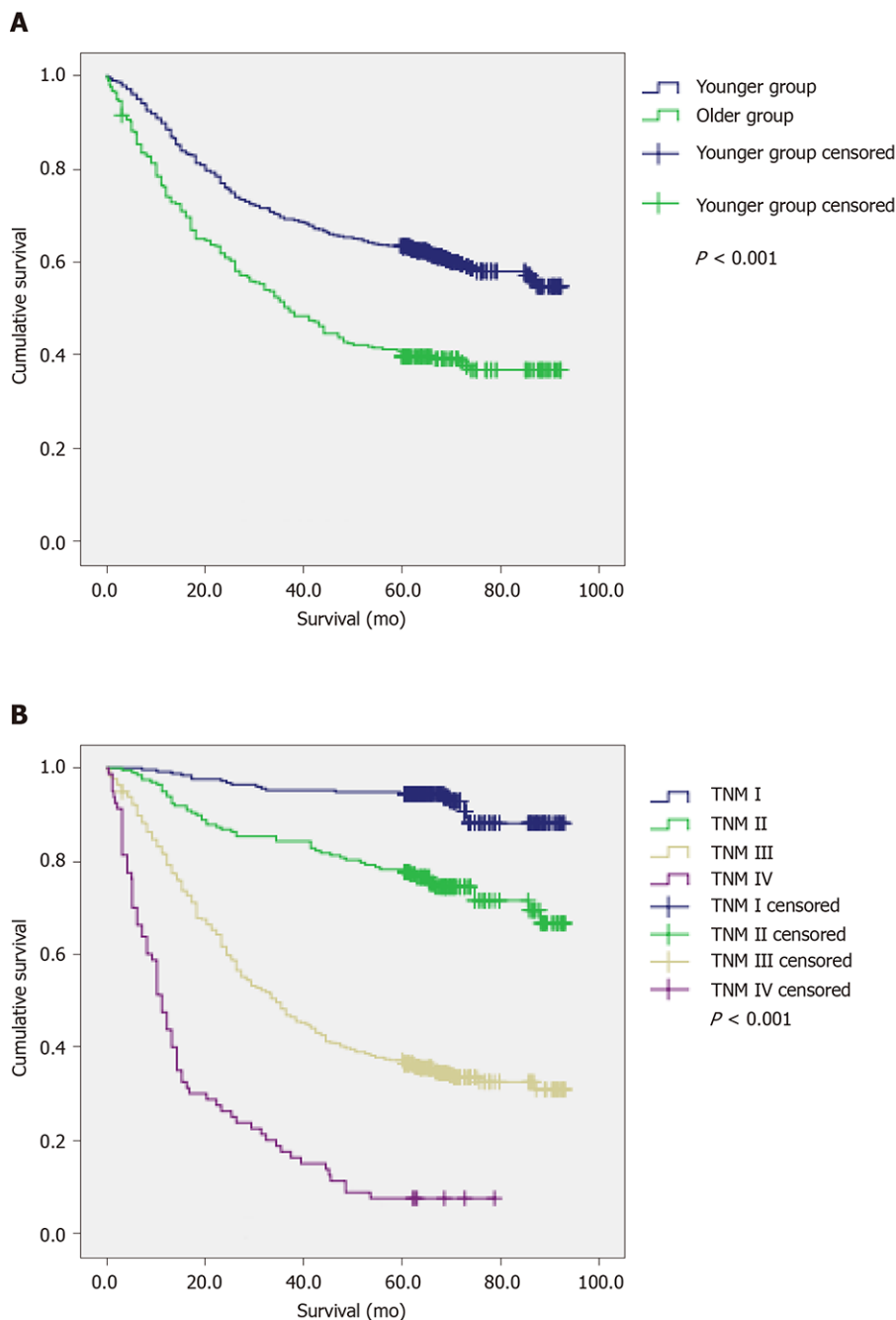


Figure 2 Overall survival. A: Overall survival based on age in 1037 patients ($P < 0.001$); B: Overall survival based on tumor–node–metastasis stage in 1037 patients ($P < 0.001$).

free survival, although 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 was aimed at the elderly patients, and the meta-analysis was aimed at the whole GC patients, which cannot be divided into age groups. Considering the limitations of this study, if possible, we will perform a larger scale, multi-center, and prospective study to validate our findings.

CONCLUSION

The OS of elderly patients is significantly worse than that of younger patients. There are significant differences in clinicopathological characteristics and prognostic factors between younger and older patients. NLR is a convenient, inexpensive, and

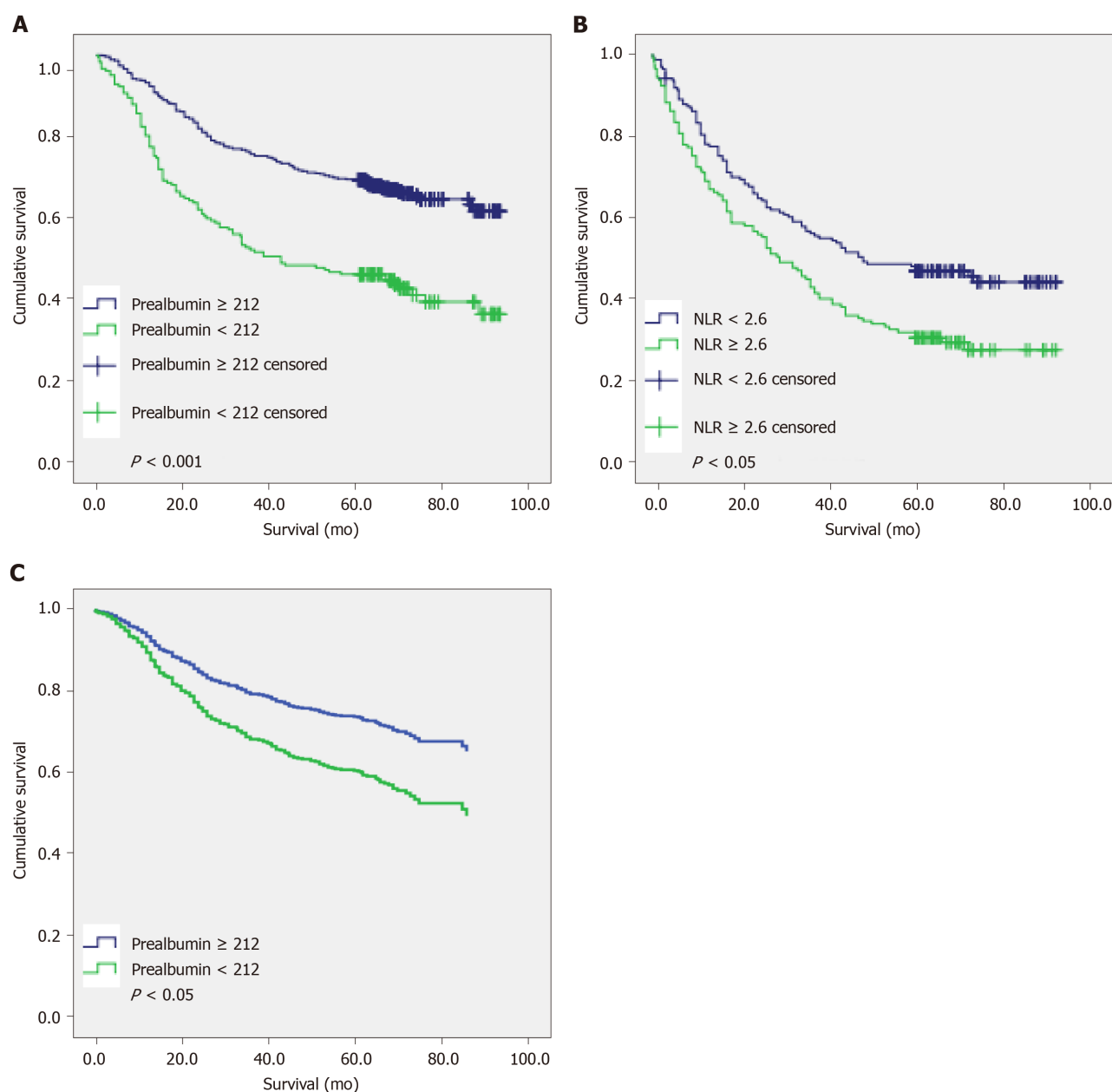


Figure 3 Overall survival. A: Overall survival based on preoperative pre-albumin in 716 younger patients ($P < 0.001$); B: Overall survival based on preoperative neutrophil-lymphocyte ratio in 321 older patients ($P < 0.05$); C: Overall survival based on preoperative pre-albumin in 651 middle age patients ($45 \leq \text{age} < 70$) ($P < 0.05$).

reproducible marker that can be used as an important predictor of the prognosis of GC. In particular, elderly patients should be focused more on the improvement of inflammatory status preoperatively if NLR values are high, whereas preoperative nutritional status improvement may be especially beneficial for the prognosis of younger patients.

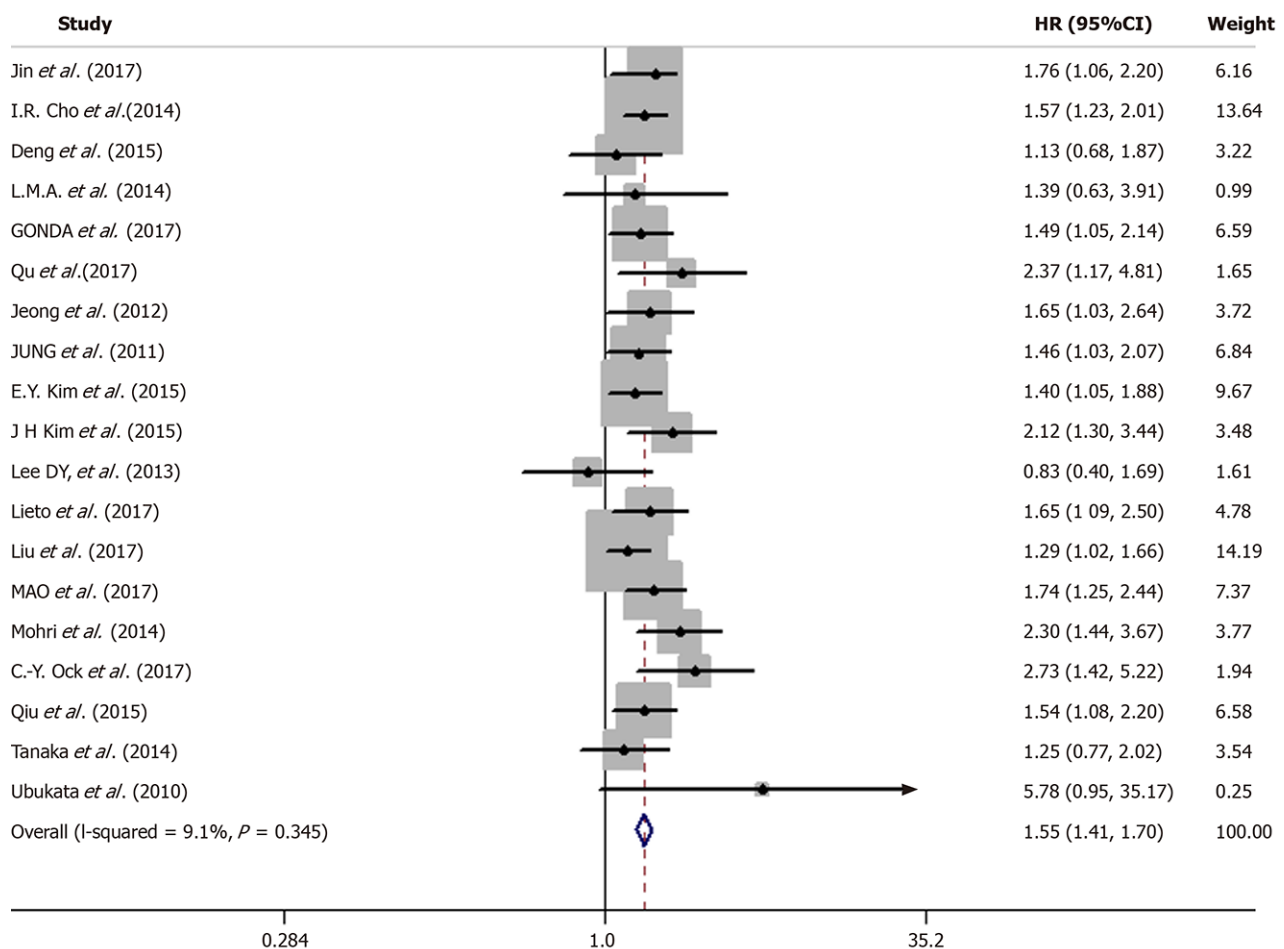


Figure 4 Forest plots of relationship between neutrophil-lymphocyte ratio and overall survival in patients with gastric cancer.

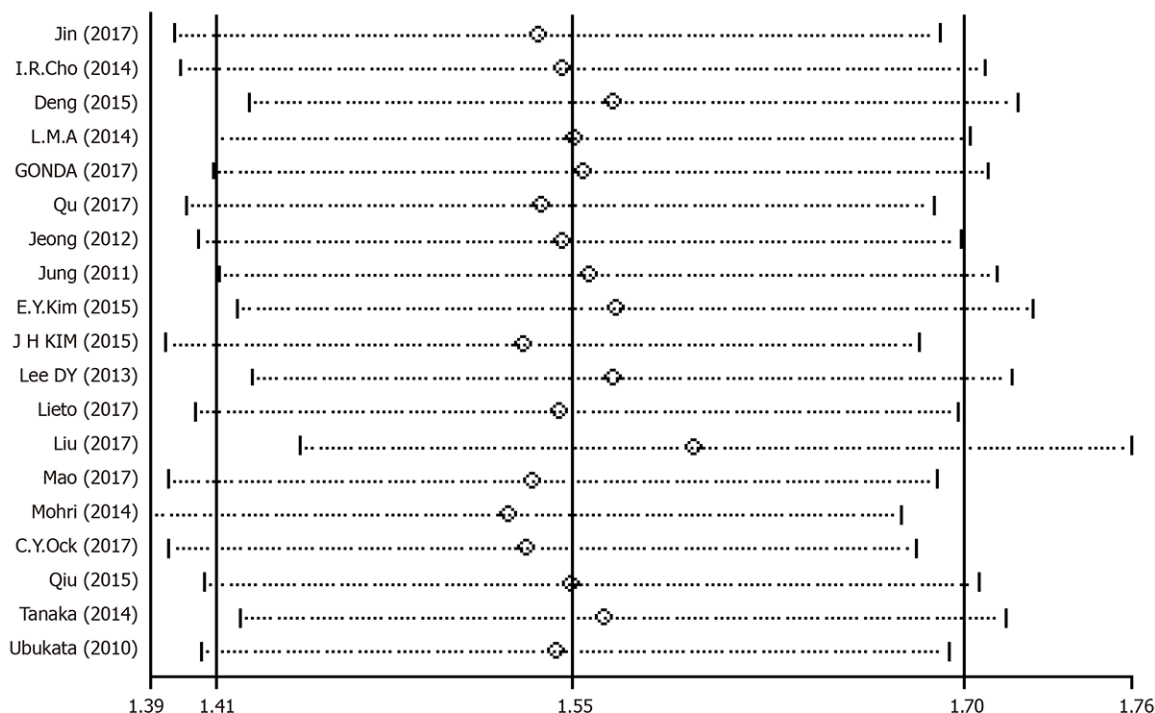
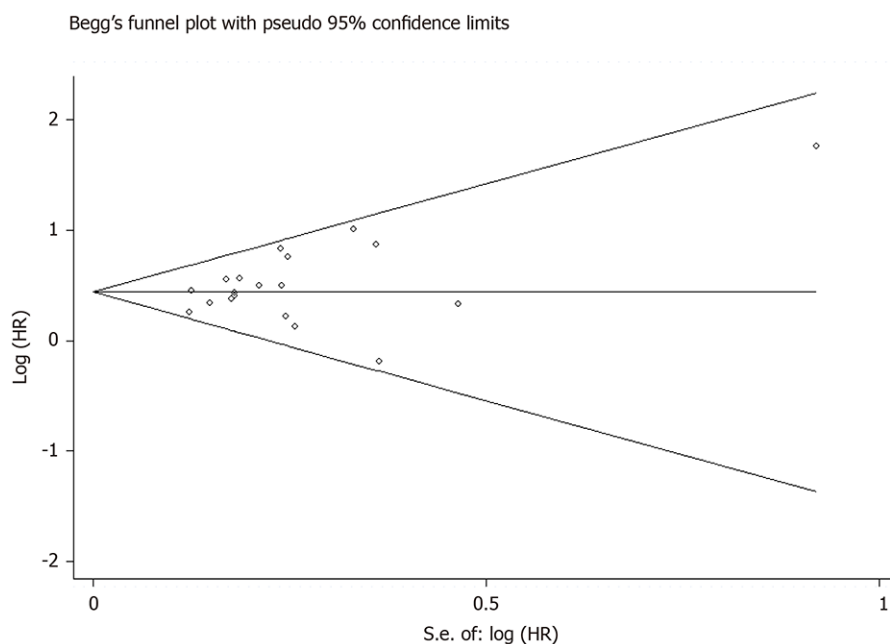
A**B**

Figure 5 Results of sensitivity analysis and Begg's funnel plot. A: Sensitivity analysis of neutrophil-lymphocyte ratio for overall survival in patients with gastric cancer; B: Begg's funnel plot for overall survival in patients with gastric cancer.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is one of the most common malignant tumors in the world. The postoperative overall survival (OS) of GC patients remains extremely low. Therefore, we attempted to analyze the clinical and pathologic data of GC patients in different age groups to explore the differences in the clinical characteristics and prognostic factors.

Research motivation

We attempted to provide reliable reference for clinicians to identify and rectify the independent prognostic influencing factors for GC patients in different age groups.

Research objectives

We designed this retrospective study to analyze the clinical and pathologic data of patients with GC, and explore the differences in the clinical characteristics and prognostic factors between different age groups.

Research methods

We analyzed 1037 GC patients admitted to Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from May 2010 to January 2013. The patients were divided into two groups based on age: Younger group (less than 70 years old) and older group (no less than 70 years old). The clinical features and prognostic factors were analyzed in both groups. Further, a meta-analysis was conducted to explore the prognostic significance of neutrophil-lymphocyte ratio (NLR) in GC patients.

Research results

In the retrospective study, the mean OS of the younger group (64.7 mo) was significantly longer than that of the older group (48.1 mo; $P < 0.001$). Among patients under 70 years of age, hospitalization time, TNM stage, vascular invasion, and preoperative low pre-albumin were independently associated with OS ($P < 0.005$), whereas in patients older than 70 years, TNM stage, esophageal invasion, histological type, and preoperative NLR were independent factors for OS ($P < 0.005$). The OS of these older patients was significantly shorter ($P < 0.005$). In meta-analysis, the results showed that high NLR value was a risk factor for the prognosis of GC.

Research conclusions

There are significant differences in clinicopathological characteristics and prognostic factors between the two age groups of GC patients. NLR is a convenient, inexpensive, and reproducible marker that can be used as an important predictor of the prognosis of GC. The OS of elderly patients is significantly worse than that of younger patients. Elderly patients should focus more on the improvement of inflammatory status, whereas preoperative nutritional status improvement may be particularly beneficial for the prognosis of younger patients. There is still little research to assess the significance of pre-albumin in the prognosis of GC, which needs to be stressed in the future.

Research perspectives

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. NLR is a widely used, inexpensive, and reproducible marker that can be used as an important predictor of the prognosis of GC. In particular, elderly patients should be focused more on the improvement of inflammatory status preoperatively if NLR values are high, whereas preoperative nutritional status improvement may be especially beneficial for the prognosis of younger patients.

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