Int J Clin Exp Med 2017;10(4):6780-6790
www.ijcem.com /ISSN:1940-5901/IJCEM0044889

Original Article

Clinical value of preoperative inflammatory parameters in advanced node-negative gastric cancer patients following radical gastrectomy

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Received October 20, 2016; Accepted February 23, 2017; Epub April 15, 2017; Published April 30, 2017

Abstract: Background: The cancer-specific outcomes of patients are thought to be associated with the patient's immune status. The aim of this study is to evaluate the value of the various preoperative inflammatory parameters in advanced node-negative gastric cancer patients to identify common clinicopathological factors for the prognosis of these patients. Methods: A total of 190 patients harboring advanced gastric adenocarcinoma with none lymph node and distant metastases, who underwent radical gastrectomy were collected and retrospectively analyzed from database of Zhongshan Hospital of Fudan University between 2006 and 2010. Clinicopathologic findings, preoperative inflammatory parameters, and follow-up status were recorded. Survival analyses were generated according to the Kaplan-Meier method. Univariate and multivariate analyses were carried out by the Cox proportional hazard model. Results: Factors influencing overall survival were degree of tumor differentiation (P = 0.027), T stage (P<0.001), preoperative leukocyte count (P = 0.038), preoperative neutrophil count (P = 0.006), and preoperative neutrophil to lymphocyte ratio (NLR) (P = 0.036). On multivariate analysis, preoperative neutrophil count and preoperative NLR were both recognized as independent prognostic factors for overall survival of advanced node-negative gastric cancer patients (P = 0.030 and P = 0.032, respectively), and the prognosis of these patients with high preoperative neutrophil count and/or preoperative NLR was significantly worse than those with low preoperative neutrophil count and/or preoperative NLR. Based on this condition, a new prognostic model based on T stage and preoperative inflammatory parameters was constructed, which could lead to better prognostic accuracy than did preoperative inflammatory parameters or T stage alone. Conclusions: Preoperative neutrophil count and preoperative NLR significantly and independently predict the clinical outcome in advanced node-negative gastric cancer patients.

Keywords: Inflammatory parameters, node-negative, gastric cancer, radical gastrectomy, overall survival

Introduction

Mortality associated with gastric cancer in many industrialized nations has decreased during recent decades whereas China is still one of the countries with the highest incidence of gastric cancer and accounts for over 40% of all new cases worldwide [1-3]. The ability to predict the precise prognosis of a patient with gastric cancer is critical for the selection of the optimal treatment plan and follow-up strategies [4, 5]. At present, tumor-node-metastasis (TNM) staging of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) is the most important prognostic factor for gastric cancer [6, 7]. However, in the population of advanced node-negative gastric cancer patients without distant metastases, their clinical outcomes are heterogeneous and the prognosis of these patients cannot be stratified by the number of lymph nodes metastases and/or the lymph node metastases ratio [8, 9]. So, there is only one prognostic factor, T stage, for these patients according to TNM staging system; a common clinicopathological factor except for T stage that could significantly and preoperatively influence the clinical outcome and estimate the disease-specific survival of advanced node-negative gastric cancer patients following radical gastrectomy is still unknown. As to such fact, finding a common clinicopathological factor that could significant-

ly influence the clinical outcome of these patients is one of the most important and interesting things that the surgeons have to confront.

The cancer-specific outcomes of patients are thought to be associated with the patient's immune status, such as the local and systemic inflammation, which is a key player in cancer biology and targeting these inflammatory responses might potentially improve patient prognosis [10, 11]. Recent studies have identified the variation of preoperative inflammatory parameters, such as leukocyte, neutrophil, lymphocyte, platelet, neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), as simple and convenient markers for the systemic inflammatory responses and robust prognostic indicators in patients with several types of cancer, including pancreatic cancer [12], ovarian cancer [13], cervical cancer [14], biliary tract cancer [15], lung cancer [16], colorectal cancer [17], gastrointestinal stromal tumor [18], breast cancer [19], bladder cancer [20], non-small cell lung cancer [21], renal cell carcinoma [22], hepatocellular carcinoma [23], multiple myeloma [24], and gastric cancer [25]. However, an extensive analysis of the variation of preoperative inflammatory parameters in correlated to prognosis of advanced node-negative gastric cancer patients without distant metastases following radical gastrectomy has not been performed and awaits further elucidation.

The aim of this study is to evaluate the relationship between the various preoperative inflammatory parameters and overall survival of advanced node-negative gastric cancer patients without distant metastases in a large single cohort in an effort to identify simple and convenient clinicopathological factors for the prognosis of these patients and to aid in clinical decision making, and ultimately improve gastric cancer outcome.

Materials and methods

Patients

The data of 1058 patients underwent radical surgical resection (R0 resection according to the UICC/AJCC and D2 lymphadenectomy) of gastric adenocarcinoma in the Department of General Surgery of Zhongshan Hospital of Fudan University (Shanghai, China) between January 2006 and December 2010 was retrospective reviewed. The selected criteria were the patients harboring advanced gastric adenocarcinoma with none lymph node and distant metastases, and excluded criteria were patients with early gastric cancer, infiltration of adjacent structures (T4b), lymph node metastases, distant metastases, gastric stump cancer, and without preoperative complete blood count values. In addition, patients were excluded if they had previously been exposed to any targeted therapy, radiotherapy, chemotherapy, and/or intervention therapy for gastric cancer. As a result, 190 patients were included in the final analysis. The stage of gastric cancer is classified according to the tumor-node-metastasis (TNM) staging system of the seventh UICC/AJCC manual [7]. Ethical approval was granted by the Clinical Research Ethics Committee of Zhongshan Hospital of Fudan University (Shanghai, China), and this research was conducted according to the principles expressed in the Declaration of Helsinki. Signed informed consent was obtained from all patients for the acquisition and use of patient tissue samples and anonymized clinical data.

Data collection

A retrospective review of prospectively maintained data was performed, and the clinicopathological features (patient's gender, age, degree of tumor differentiation, tumor localization, depth of invasion, number of lymph nodes dissection, lymphatic vessel invasion, and tumor size), and the oncological results (overall survival time) were analyzed. In addition, peripheral blood samples were obtained at the time of diagnosis before the surgery, and leukocyte, neutrophil, lymphocyte, and platelet values were recorded. NLR was defined as neutrophil count divided by lymphocyte count, and PLR was defined as platelet count divided by lymphocyte count. The normal range of the inflammatory parameters was as follows: leukocyte count range from 3.5 to 9.5×10^9 cells/L, neutrophil count range from 1.8 to 6.3×10^9 cells/L, lymphocyte count range from 1.1 to 3.2×10^9 cells/L, and platelet count range from 125 to 350×10^9 cells/L.

Statistical analysis

Statistical analysis was performed with MedCalc Software (version 11.4.2.0; MedCalc,

Table 1. Patient demographics and clinicopathological characteristics and correlation with overall survival

Factor	No. of Patients	No. of Deaths	P*
All patients	190	33	
Age (years)†			0.538
≤60	78	13	
>60	112	20	
Gender			0.861
Female	52	9	
Male	138	24	
Localization			0.106
Proximal	37	10	
Middle	39	4	
Distal	114	19	
Differentiation			0.027
Well	11	0	
Moderate	76	8	
Poorly	103	25	
Tumor size (cm)†			0.735
≤3.5	110	20	
>3.5	80	13	
T Stage			<0.001
T2	65	3	
T3	63	10	
T4	62	20	
Lymphatic vessel invasion			0.224
Absent	160	26	
Present	30	7	
No. of LNs			0.081
<15	51	14	
≥15	139	19	
Leukocyte†			0.038
Low	94	11	
High	96	22	
Neutrophil†			0.006
Low	93	9	
High	97	24	
Lymphocyte†			0.900
Low	115	21	
High	75	12	
Platelet†			0.497
Low	96	18	
High	94	15	
NLR†			0.036
Low	86	9	
High	104	24	
PLR†			0.507
Low	95	14	
High	95	19	

Abbreviation: LNs, lymph nodes resected; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio. *P<0.05 was considered statistically significant. †Split at median.

Mariakerke, Belgium) and SPSS Software (version 17.0; SPSS Inc., Chicago, IL, USA). The follow-up was conducted until the December 31, 2013 or until death, and the median follow-up for the patients was 37 months (range, 1-67 months). No patients had been lost in follow-up. The overall survival was defined as the time between the first day of diagnosis and the date of cancer-related death or the last follow-up visit. The statistical significance of categorical data was evaluated using χ^2 or Fisher's exact test. Cumulative survival rates were calculated by Kaplan-Meier method, and the differences between the subgroups were examined by the log-rank test. Numbers at risk were calculated for the beginning of each time period. The prognostic value of inflammatory parameters was determined by univariate and multivariate analysis. A prognostic model combining inflammatory parameters with T stage was constructed with the logistic regression. Receiver operating characteristic (ROC) analysis was performed to assess the prognostic value of the parameters. The correlation between inflammatory parameters was determined using the Spearman correlation analysis. All *P* values were two sided, and P<0.05 was considered to be statistically significant.

Results

Clinicopathological characteristics

Table 1 summarizes the clinicopathological characteristics of patients collected in this study. Of 190 patients, most were male (72.6%) and old (>60 years, 58.9%), and had a distal-located cancer (60.0%), lymphatic vessel invasion (84.2%), smaller tumor size (≤3.5 cm, 57.9%), poorly differentiation (54.2%), and greater number of lymph nodes resected (≥15, 73.2%). The cut-off values for the preoperative inflammatory parameters were defined using the median values, these parameters that greater than or equal to median values were classified as high and less than median values were classified as low. According to this criterion, all patients were dichotomized into two groups: preoperative leukocyte count (cut-off = 5.8×10^9 cells/L, Low, <5.8×10^9 cells/L; High, ≥5.8×10^9 cells/L), preoperative neutrophil count (cut-off = 3.5×10^9 cells/L, Low, <3.5×10^9 cells/L; High, ≥3.5×10^9 cells/L), preoperative lymphocyte count (cut-off = 1.8×10^9 cells/L, Low, <1.8×10^9 cells/L; High, ≥1.8×10^9 cells/L), preoperative platelet count (cut-off = 216×10^9

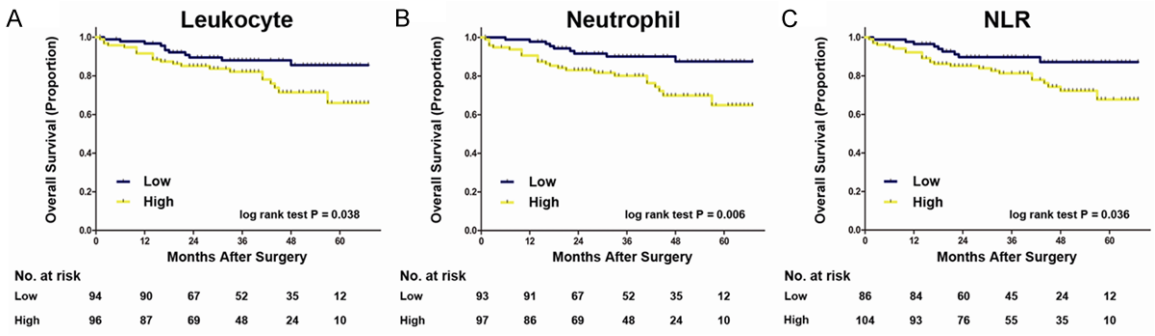

Figure 1. Analyses of overall survival according to the preoperative inflammatory parameters in advanced node-negative gastric cancer patients. Kaplan-Meier analyses of overall survival according to preoperative leukocyte count (A), neutrophil count (B), and NLR (C) in patients with advanced node-negative gastric cancer. *P* value was calculated by log-rank test.

Table 2. Multivariate Cox regression analyses for overall survival

	Overall Survival	
Factor	Hazard Radio (95% CI)	P*
Analysis 1		
Differentiation: Poorly vs Well + Moderate	1.628 (0.665 to 3.982)	0.286
T Stage: T4 vs T2+T3	2.748 (1.238 to 6.098)	0.013
Leukocyte†: High vs Low	1.730 (0.828 to 3.614)	0.145
Analysis 2		
Differentiation: Poorly vs Well + Moderate	1.625 (0.669 to 3.949)	0.284
T Stage: T4 vs T2+T3	2.678 (1.219 to 5.884)	0.014
Neutrophil†: High vs Low	2.357 (1.086 to 5.116)	0.030
Analysis 3		
Differentiation: Poorly vs Well + Moderate	1.471 (0.604 to 3.582)	0.395
T Stage: T4 vs T2+T3	3.319 (1.519 to 7.255)	0.003
NLR†: High vs Low	2.323 (1.075 to 5.022)	0.032

Abbreviation: NLR, neutrophil to lymphocyte ratio; 95% CI, 95% confidence interval.
*P<0.05 was considered statistically significant. †Split at median.

cells/L, Low, <216×10^9 cells/L; High, ≥216×10^9 cells/L), preoperative NLR (cut-off = 2.0, Low, <2.0; High, ≥2.0), and preoperative PLR (cut-off = 126, Low, <126; High, ≥126).

Prognostic factors for overall survival

Kaplan-Meier survival analysis was performed to investigate the prognostic value of clinicopathological factors. Factors influencing the overall survival rate were degree of tumor differentiation (P = 0.027), T stage (P<0.001), preoperative leukocyte count (P = 0.038), preoperative neutrophil count (P = 0.006), and preoperative NLR (P = 0.036) (**Table 1**). As shown in **Figure 1**, preoperative leukocyte count, preoperative neutrophil count, and preoperative NLR are all significant prognostic predictors for patients with advanced node-negative gastric cancer. To evaluate the robustness of the prognostic value of preoperative leukocyte count, preoperative neutrophil count, and preoperative NLR, Cox multivariate regression analyses were performed. As listed in **Table 2**, after adjusting for degree of tumor differentiation and T stage, we found that preoperative neutrophil count and preoperative NLR were both independently associated with overall survival (preoperative neutrophil count, HR (hazard ratio) = 2.357, 95% CI (95% confidence interval): 1.086 to 5.116, P = 0.030; preoperative NLR, HR = 2.323, 95% CI: 1.075 to 5.022, P = 0.032) except for T stage (HR = 2.678, 95% CI: 1.219 to 5.884, P = 0.014; HR = 3.319, 95% CI: 1.519 to 7.255, P = 0.003; respectively).

Prognostic model based on T stage and preoperative inflammatory parameters

In order to develop a more sensitive predictive method for patients with advanced node-negative gastric cancer, a new prognostic model combining T stage and preoperative inflammatory parameters was constructed based on the independent prognostic factors of multivariate

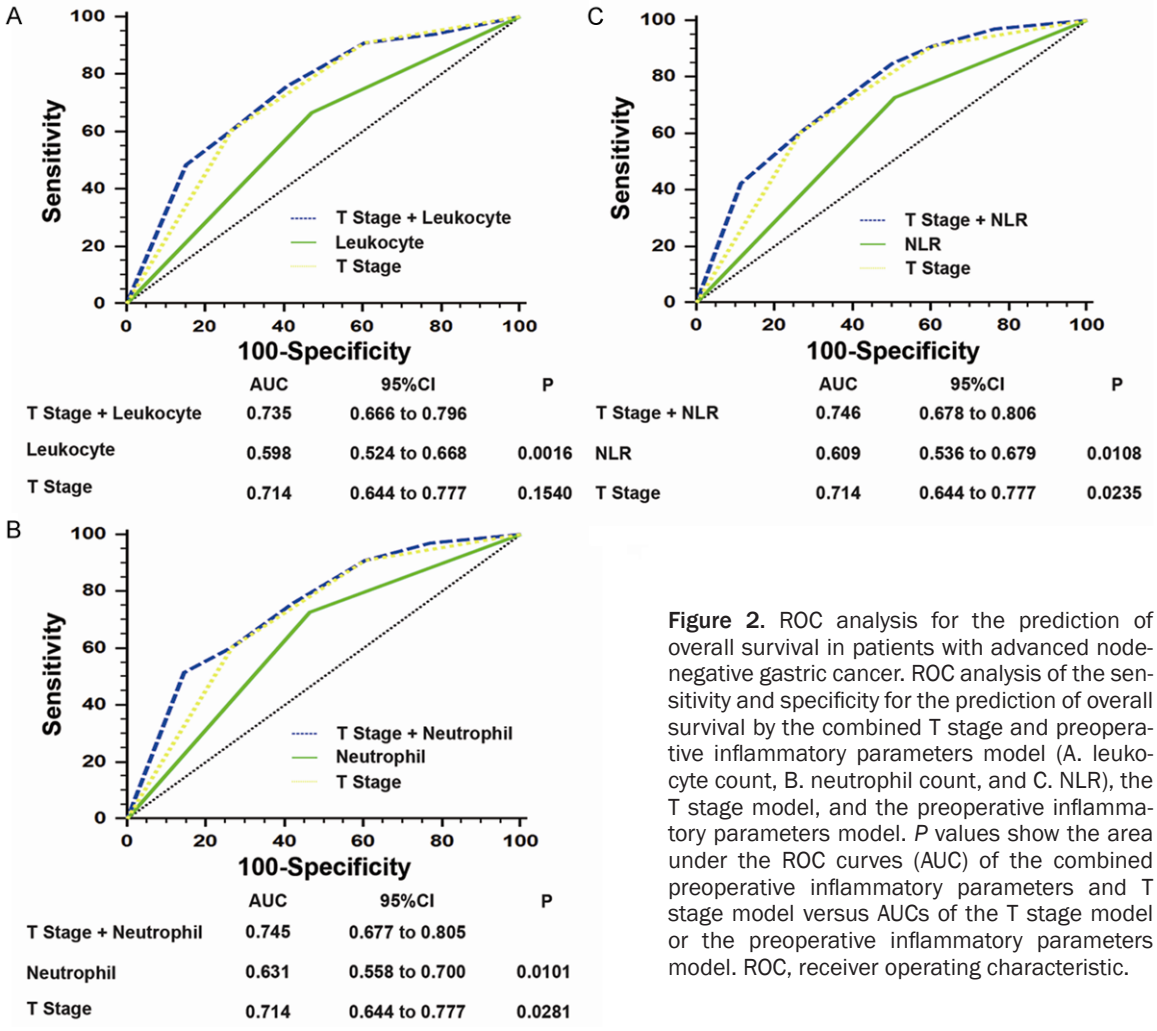

Figure 2. ROC analysis for the prediction of overall survival in patients with advanced node-negative gastric cancer. ROC analysis of the sensitivity and specificity for the prediction of overall survival by the combined T stage and preoperative inflammatory parameters model (A. leukocyte count, B. neutrophil count, and C. NLR), the T stage model, and the preoperative inflammatory parameters model. *P* values show the area under the ROC curves (AUC) of the combined preoperative inflammatory parameters and T stage model versus AUCs of the T stage model or the preoperative inflammatory parameters model. ROC, receiver operating characteristic.

analysis. ROC analysis was performed to compare its prognostic ability. As shown in **Figure 2**, prognostic model of T stage plus preoperative inflammatory parameters, including T stage plus preoperative leukocyte count (AUC (area under the ROC curves) [95% CI], 0.735 [0.666-0.796]), T stage plus preoperative neutrophil count (AUC [95% CI], 0.745 [0.677-0.805]), and T stage plus preoperative NLR (AUC [95% CI], 0.746 [0.678-0.806]), exhibited better prognostic values than did preoperative inflammatory parameters (preoperative leukocyte count, AUC [95% CI], 0.598 [0.524-0.668], P = 0.0016; preoperative neutrophil count, AUC [95% CI], 0.631 [0.558-0.700], P = 0.0101; preoperative NLR, AUC [95% CI], 0.609 [0.536-0.679], P = 0.0108; respectively) or T stage (AUC [95% CI], 0.714 [0.644-0.777], P = 0.1540, P = 0.0281, and P = 0.0235, respectively) alone.

Relation between clinical characteristics and preoperative inflammatory parameters

The relationship between preoperative inflammatory parameters (preoperative leukocyte count, preoperative neutrophil count, and preoperative NLR) and clinicopathological factors of patients and tumor was further measured. As shown in **Table 3**, preoperative leukocyte count, preoperative neutrophil count, and preoperative NLR were all significantly correlated with T stage (P = 0.027, P = 0.034, and P = 0.003, respectively). Patients with higher T stage had elevated preoperative inflammatory parameters. Besides, preoperative neutrophil count and preoperative NLR were also correlated with tumor size significantly (P = 0.007 and P = 0.007, respectively). In addition, we analyzed the correlation between preoperative leukocyte count, preoperative neutrophil count,

Table 3. Relation between clinical characteristics and Leukocyte, Neutrophil, and NLR

	Leukocyte†			Neutrophil†			NLR†		
Factor	High	Low	P*	High	Low	P*	High	Low	P*
All patients	96	94		97	93		104	86	
Age (years)†			0.290			0.958			0.092
≤60	43	35		40	38		37	41	
>60	53	59		57	55		67	45	
Gender			0.086			0.071			0.145
Female	21	31		21	31		24	28	
Male	75	63		76	62		80	58	
Localization			0.239			0.145			0.275
Proximal	20	17		24	13		23	14	
Middle	15	24		17	22		24	15	
Distal	61	53		56	58		57	57	
Differentiation			0.084			0.226			0.260
Well	3	9		3	8		4	7	
Moderate	39	37		38	38		39	37	
Poorly	55	48		56	47		61	42	
Tumor size (cm)†			0.101			0.007			0.007
≤3.5	50	60		47	63		51	59	
>3.5	46	34		50	30		53	27	
T Stage			0.027			0.034			0.003
T2	29	36		28	37		27	38	
T3	27	36		29	34		45	18	
T4	40	22		40	22		32	30	
Lymphatic vessel invasion			0.950			0.785			0.570
Absent	81	79		81	79		89	71	
Present	15	15		16	14		15	15	
No. of LNs			0.940			0990			0.763
<15	26	25		26	25		27	24	
≥15	70	69		71	68		77	62	

Abbreviation: NLR, neutrophil to lymphocyte ratio. *P<0.05 was considered statistically significant. †Split at median.

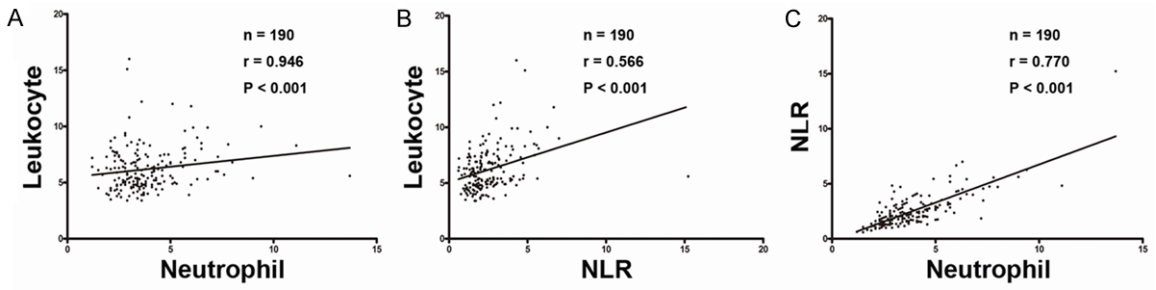

Figure 3. Analyses of the correlation between the preoperative inflammatory parameters in advanced node-negative gastric cancer patients. Spearman correlation analysis between preoperative leukocyte count and neutrophil count (A), preoperative neutrophil count and NLR (B), preoperative leukocyte count and NLR (C) in patients with advanced node-negative gastric cancer.

and preoperative NLR. As shown in **Figure 3**, there is a significantly correlation between these preoperative inflammatory parameters (preoperative leukocyte count and neutrophil

count, r = 0.946, P<0.001; preoperative neutrophil count and NLR, r = 0.566, P<0.001; preoperative leukocyte count and NLR, r = 0.770, P<0.001; respectively).

Discussion

China is still one of the countries with the highest incidence of gastric cancer although that in many industrialized nations has decreased during recent decades, as more than 80% patients arrive to medical attention with an advanced stage disease [1, 3, 26]. Currently, TNM staging system of UICC/AJCC is the most important prognostic factor for gastric cancer [6, 7]. However, in the population of advanced node-negative gastric cancer patients without distant metastases, there is only one prognostic factor according to TNM staging system, T stage. Because of the heterogeneous of the clinical outcomes and lack of prognostic factors of these patients, finding simple and convenient markers that could refine risk-stratification is important and meaningful things to clinical decision making [5, 9]. Our previous research had demonstrated that greater number of lymph nodes dissection was an independent prognostic factor for advanced node-negative gastric cancer patients following radical gastrectomy (data not shown). In this study, we evaluated the association between six preoperative inflammatory parameters (leukocyte, neutrophil, lymphocyte, platelet, NLR, and PLR) and clinical outcomes of patients with advanced node-negative gastric cancer, and found that preoperative neutrophil count and preoperative NLR were both independent prognostic factors for overall survival of these patients expect for T stage, and the prognosis of the patients with high preoperative neutrophil count and/or preoperative NLR was significantly worse than those with low, which suggested that preoperative neutrophil count and preoperative NLR may be simple, convenient, reproducible, and inexpensive predictors of oncologic outcomes and may aid in the clinical decision-making process because of the blood routine examination is commonly conducted in hospitals of different regions. In addition, patients with higher T stage had elevated preoperative inflammatory parameters. Based on this condition, we constructed a new prognostic model based on T stage and preoperative inflammatory parameters, which could statistically exhibit a better prognostic value than did preoperative inflammatory parameters or T stage alone.

Virchow first found that the tissues of malignant tumors were always infiltrated with a large amount of immune cells, and inferred that carcinogenesis and metastasis might be associated with chronic inflammation in the 19th century [27]. Nowadays, the cancer-specific outcomes of patients with malignant tumors are thought to be associated with the patient's immune status or host-related factors, in particular local and systemic inflammatory response, which is deemed to be a crucial enabling process for cells to acquire essential "hallmarks of carcinogenesis" that constitute the foundation and progression of malignant tumors [10, 11, 28]. The milieu of localized and systemic inflammatory is a key determinant of tumor biology, and the cross-talk between cancer cells and their microenvironment is thought of as a pro-oncogenic influence resulting from an intricate tumor-host interface [29-31]. Previous studies have proved that multiple preoperative inflammatory parameters, such as circulating leukocyte, neutrophil, lymphocyte, NLR, and PLR, were emerging as surrogate markers for the cancer-related local and systemic inflammatory responses, and prognostic indicators in patients with various types of malignant tumors [18-22]. Recently, the preoperative NLR has also been demonstrated as an independent prognostic factor of patients with gastric cancer following radical gastrectomy or receiving chemotherapy [32-39]. However, the patients with advanced node-negative gastric cancer are heterogeneous and the prognosis of these patients cannot be simply and arbitrarily stratified by the same factor used in early gastric cancer and/or advanced gastric cancer with lymph nodes metastases. So, there should be a new research on the prognostic factors for this population. In the light of these considerations, the principle aim of this study is to evaluate the clinical significance of the variation of preoperative inflammatory parameters in advanced node-negative gastric cancer patients to identify common clinicopathological factors to refine risk-stratification of these patients. In the present study, the results indicated that there was a significantly correlation between the local and systemic inflammatory state, as broadly represented by preoperative neutrophil count and preoperative NLR, and oncologic out-

come of advanced node-negative gastric cancer patients following radical gastrectomy. Preoperative neutrophil count and preoperative NLR significantly and independently predict the clinical outcome of these patients. Additionally, preoperative platelet count is also an important index of local and systemic inflammation triggered by the malignant tumors [40]. Along with the continually release of platelet-derived proangiogenic and antiangiogenic factors, platelet degranulation within the microenvironment of the tumor could be a key determinant of tumor progression [40-42]. Nonetheless, there are no positive results available on the significance of tumor-platelet interactions. To our knowledge, this is the first report about the association of preoperative inflammatory parameters and prognosis of advanced node-negative gastric cancer patients. However, this work should be validated in the prospective randomized controlled clinical studies in the future.

Cancer-related local and systemic inflammation is very complex in nature and increasingly recognized as a pivotal multifaceted player in tumor foundation and progression [10]. Nonetheless, the biology underlying the association between elevated preoperative inflammatory parameters and poor survival in patients with various types of malignant tumors has not been clearly interpreted until now. Recently, several studies have provided some potential molecular mechanisms to explain this phenomenon. Firstly, the antitumor responses of activated T cells and natural killer cells might be suppressed by elevated number of neutrophils. Increased preoperative neutrophils and NLR reflected a decreased lymphocyte mediated antitumor immune reaction, which may weaken the lymphocyte-mediated antitumor activity [41]. Secondly, cancer-specific cytokines and chemokines generated by circulating tumor-associated neutrophils, such as interleukin-18, vascular endothelial growth factor (VEGF), and tumor necrosis factor (TNF), may play a pivotal role in remodeling the tumor microenvironment and resulting in the tumor progression [43]. Finally, neutrophil-derived reactive oxygen species (ROS) may decrease the adhesion-promoting properties of the extracellular matrix via the regulation of matrix metalloproteinases (MMPs) and inhibit apoptosis of the tumor cells [33]. However, the exact mechanisms remain poorly understood and await further investigation.

There are several limitations of this study. Firstly, this study is limited by the retrospective nature of the analysis and the selection biases cannot be totally eliminated although we collected the data from a prospectively maintained database. Secondly, there might be some heterogeneity in the thresholds used to determine elevated preoperative inflammatory parameters in this research. The median values were the most consistently used, however a variety of thresholds other than median values have been reported [35, 40]. Thirdly, there is not including the data of disease free survival in this study. There are many factors, such as the follow-up examinations and the postoperative treatment, might influence the disease free survival of gastric cancer patients. And the disease free survival data should be collected in the future researches. Fourthly, this study did not consider the situation of stage migration resulting from lymph nodes micrometastases. The seventh TNM staging system for gastric cancer of UICC/AJCC manual pointed out that micrometastases should be included in the staging of disease [7]. However, the clinical significance of lymph nodes micrometastases is still debated [44, 45]. Finally, the number of patients included in this study is relatively small. Large prospective randomized controlled clinical studies are needed to identify the prognostic value of preoperative inflammatory parameters in the patients with advanced node-negative gastric cancer.

In conclusion, our results demonstrate that, besides T stage, preoperative neutrophil count and preoperative NLR were both significant and independent prognostic factors for advanced gastric cancer patients with none lymph node and distant metastases and following radical gastrectomy. Moreover, the new constructed prognostic model combining T stage and preoperative inflammatory parameters could statistically refine prognostic stratification of these patients. Based on these results, the advanced node-negative patients with elevated preoperative neutrophil count and/or preoperative NLR should be considered as candidates for more intensive postoperative treatment and closer follow-up.

Acknowledgements

This work was supported by grants from Science and Technology Commission of Shanghai Municipality (16DZ1930602).

Disclosure of conflict of interest

None.

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