

## ORIGINAL ARTICLE

# Neutrophil-Lymphocyte Ratio is a Predictor of Venous Thromboembolism in Gastric Cancer Patients

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### SUMMARY

**Background:** The neutrophil-lymphocyte ratio (NLR) reflects inflammatory status. An elevated NLR has been reported to be a prognostic indicator in some malignant tumors. The aim of this study was to determine whether NLR at the time of venous thromboembolism (VTE) diagnosis is a prognostic factor for the response to anticoagulation and survival in gastric cancer patients treated with anticoagulation for VTE.

**Methods:** We retrospectively enrolled 73 gastric cancer patients newly diagnosed with VTE, from among 597 patients pathologically confirmed for gastric cancer between January 2008 and December 2013. Univariate and multivariate analyses were performed to identify clinicopathological predictors in respect to the response to anticoagulation and overall survival.

**Results:** Compared with the low NLR group, patients with high NLR presented more frequently with advanced tumor stage ( $p = 0.046$ ) and deeper tumor depth ( $p = 0.033$ ). Patients with poor histology differentiation ( $p = 0.045$ ), high NLR ( $p = 0.001$ ), and low albumin ( $p = 0.016$ ) were statistically correlated with the poor response to anticoagulation. Multivariate analysis revealed that a high level of NLR (hazard ratio, 1.56, 95% CI: 1.32 - 1.87,  $p = 0.032$ ) and advance cancer stage (hazard ratio, 2.11, 95% CI: 1.29 - 3.44,  $p = 0.043$ ) were independent poor prognostic factors for OS in gastric cancer patients with VTE.

**Conclusions:** The results demonstrated that the NLR at the time of VTE diagnosis could be a useful biomarker for predicting the response to anticoagulation and survival in gastric cancer patients with VTE.

(Clin. Lab. 2019;65:xx-xx. DOI: 10.7754/Clin.Lab.2018.181005)

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#### KEY WORDS

neutrophil-lymphocyte ratio, gastric cancer, venous thromboembolism

#### INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication and a major cause of morbidity and mortality in patients with cancer [1,2]. Research showed that approximately 20% of patients experiencing a first occurrence of VTE had cancer and cancer patients had a 7-fold increased risk of developing VTE [3-5].

Gastric cancer is the fourth most common cancer worldwide and the second most frequent cause of cancer-related death [6]. Recently, emerging research showed

that VTEs are found relatively frequently in gastric cancer. The incidence of VTE in patients with gastric cancer ranged from 3.5% to 24.4%, and VTE indicated a detrimental effect on survival in patients with cancer, even after adjusting for comorbid conditions [7,8].

The main mechanisms of thrombosis in cancer patients are correlated with abnormal vessel walls, blood flow, and blood constituents [9]. Additionally, inflammation is associated with a pro-thrombotic state [10,11]. Inflammatory cells and mediators are fundamental components of the tumor microenvironment [12].

Various biomarkers have been used to evaluate the inflammatory state in patients with cancer. Among these, the neutrophil-lymphocyte ratio (NLR) as an indicator of systemic inflammation, is an easily-obtained and low-cost biomarker used in clinical practice that has been associated with recurrence [13,14] and survival [15-17] in various cancers. Furthermore, NLR has been reported to not only be of prognostic value in patients with gastric cancer, but also to be a useful predictor of the depth of invasion of the gastric wall in these patients with gastric cancer [18].

Despite the NLR having been widely studied in terms of the prognostic significance on cancer survival outcomes [19-21], a growing number of studies have indicated the clinical value between thrombosis and NLR, mainly in non-cancer patients [22]. However, there are no data regarding the association between NLR and cancer-related thrombosis in patients with gastric cancer at present. Therefore, we conducted this study to assess the clinical impact on the NLR at the time of VTE diagnosis as a prognostic factor for response to anticoagulation and survival, as well as the clinical characteristics of gastric cancer patients treated with anticoagulation for VTE.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed patients who were newly diagnosed with VTE based on imaging examination (computed tomography [CT] or Doppler ultrasound) among those with pathologically confirmed gastric cancer at Sichuan Cancer Hospital, between January 2008 and December 2013. A total of 597 gastric cancer patients with complete medical records were included in the study. The incidence of VTE was calculated among the patients with gastric cancer, and data on patients diagnosed with VTE were collected. All patients with VTE were treated with either warfarin, low-molecular weight heparin, or both. Patients with arterial thrombosis without VTE or those who received anticoagulation without imaging evidence of VTE were excluded from the analysis.

### Clinical data

Baseline patient characteristics, including demographics, histology, and medical history were collected by medical record review. Cancer TNM stage was based

on the sixth edition of the Union for International Cancer Control (UICC) standard and obtained at the time of VTE diagnosis. Clinical signs and anticancer treatment at the time of VTE diagnosis were also reviewed.

Anticoagulation response was assessed in patients who received at least one follow-up CT scan or Doppler ultrasound. The response was classified as "resolution" and "no resolution". Resolution refers to those cases in which there was no evidence of VTE in one or more subsequent imaging examinations. Cases in the subsequent imaging showing partial improvement and unchanged or aggravations in VTE were considered as no resolution. The relationship between anticoagulation response and clinical variables was analyzed, and the impact of the response on survival was evaluated.

We investigated the clinical value of the NLR as a prognostic factor in patients with VTE. Complete and differential blood cell counts were assessed on EDTA anticoagulated whole blood using an automatic blood cell analyzer (Bayer Advia 2120). The NLR was calculated as the neutrophil count divided by the lymphocyte count from the whole blood differential counts at the time of VTE diagnosis.  $NLR \geq 3$  was considered elevated. Patients, tumors, and VTE characteristics, laboratory data at the time of VTE diagnosis, results of anticoagulant therapy, and survival conditions of the patients were compared according to the NLR status.

### Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics 21.0. Patients' characteristics were detailed using descriptive statistics. The categorical variables were presented as the number of patients and percentages and compared using the chi-square or Fisher's exact tests. Survival probability analyses were performed using the Kaplan-Meier method. Survival was calculated as the time from the date of VTE onset after diagnosis of gastric cancer to the date of death or date of most recent follow-up. Significant differences between the groups were assessed using the log-rank test. Multivariate analysis of survival was analyzed using the Cox proportional hazards model. A p-value less than 0.05 was considered significant for all statistical analyses.

## RESULTS

### Incidence of VTE and patients' characteristics according to the neutrophil-lymphocyte ratio (NLR) status at the time of VTE diagnosis

Of all the 597 patients diagnosed with gastric cancer, 73 (12.22%) were diagnosed with VTE and treated with anticoagulation therapy. The characteristics of the 73 patients are shown in Table 1. The median age at VTE diagnosis was 68 years and 46 (63.01%) patients were over 60 years old. The majority of patients were male (67.13%). Nearly a half of patients were at stage III and IV according to UICC staging system. The result indicated that 38 patients had high NLR levels ( $NLR \geq 3.0$ ).

Table 1. Distribution of cancer patients with VTE.

Variables	Total (n = 73)	NLR $\geq$ 3.0 (n = 38)	NLR < 3.0 (n = 35)	p
<b>Age (year, n, %)</b>				
< 60	27 (36.99%)	13 (34.21%)	14 (40.00%)	<b>0.609</b>
$\geq$ 60	46 (63.01%)	25 (65.79%)	21 (60.00%)	
<b>Gender (n, %)</b>				
Male	49 (67.13%)	26 (68.42%)	23 (65.71%)	<b>0.806</b>
Female	24 (32.87%)	12 (31.58%)	12 (34.29%)	
<b>UICC stage</b>				
I, II	37 (50.68%)	15 (39.47%)	22 (62.86%)	<b>0.046</b>
III, IV	36 (49.32%)	23 (60.53%)	13 (37.14%)	
<b>Tumor depth</b>				
T1, T2	17 (23.29%)	5 (13.16%)	12 (34.29%)	<b>0.033</b>
T3, T4	56 (76.71%)	33 (86.84%)	23 (65.71%)	
<b>N factor</b>				
N0	31 (42.47%)	14 (36.84%)	17 (48.57%)	<b>0.311</b>
N1, N2, N3	42 (57.53%)	24 (63.16%)	18 (51.43%)	
<b>Distant metastasis</b>				
M0	63 (86.30%)	31 (81.58%)	32 (91.43%)	<b>0.221</b>
M1	10 (13.70%)	7 (18.42%)	3 (9.57%)	
<b>Histology</b>				
Differentiated	21 (28.77%)	10 (26.32%)	11 (31.43%)	<b>0.631</b>
Poorly differentiated	52 (71.23%)	28 (73.68%)	24 (68.57%)	

Table 2. Response of anticoagulant therapy according to variables.

Variables	Resolution (n = 45)	No resolution (n = 28)	p
<b>Histology</b>			
Differentiated	14 (82.35%)	3 (17.65%)	<b>0.045</b>
Poorly differentiated	31 (55.36%)	25 (44.64%)	
<b>NLR</b>			
< 3.0	34 (77.27%)	10 (22.73%)	<b>0.001</b>
$\geq$ 3.0	11 (37.93%)	18 (62.07%)	
<b>Platelet count (<math>\times 10^9/L</math>)</b>			
< 300	10 (71.43%)	4 (28.57%)	<b>0.402</b>
$\geq$ 300	35 (60.34%)	24 (39.66%)	
<b>Albumin</b>			
< 35	13 (44.83%)	16 (55.17%)	<b>0.016</b>
$\geq$ 35	32 (72.73%)	12 (27.27%)	
<b>CRP</b>			
< 20.5	28 (71.79%)	11 (28.23%)	<b>0.056</b>
$\geq$ 20.5	17 (50.00%)	17 (50.00%)	

Table 3. Cox proportional hazards model for overall survival.

Variables	H.R	95% CI	p
<b>NLR at VTE diagnosis</b>			
< 3.0	1		
≥ 3.0	1.56	1.32 - 1.87	0.032
<b>UICC stage</b>			
I, II	1		
III, IV	2.11	1.29 - 3.44	0.043
<b>Response to anticoagulation</b>			
Resolution	1		
No resolution	1.65	0.86 - 3.32	0.162

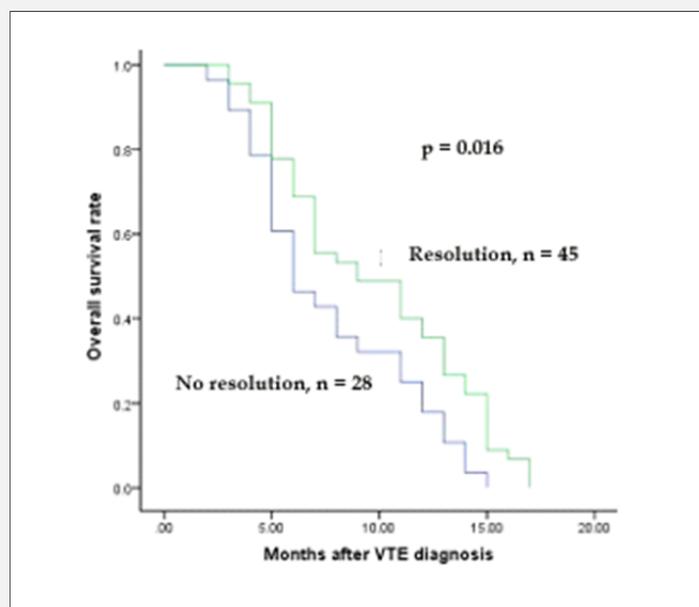


Figure 1. Kaplan-Meier survival curves of gastric cancer patients newly diagnosed with VTE.

The patients were divided into resolution group and no resolution group. Patients who achieved VTE resolution had better OS than patients who failed to achieve VTE resolution ( $p = 0.016$ , log-rank).

The distributions of age, gender, and clinical variables including UICC stage, tumor depth, N factor, distant metastasis and histology at VTE diagnosis according to NLR status are shown in Table 1. The distributions of age and gender were similar in the low and high NLR groups. Patients with high NLR presented more frequently with UICC stage III and IV disease and T3 and T4 tumor depth than patients with low NLR. No statistically significant differences were found between low

and high NLR groups in N factor, distant metastasis, and histology.

**Response to anticoagulant therapy**

The anticoagulation response evaluation was possible in all patients. Forty-five patients (61.64%) showed resolution of VTE, whereas 28 patients (38.36%) did not achieve resolution of VTE. Table 2 shows the relationship between response to anticoagulation and several

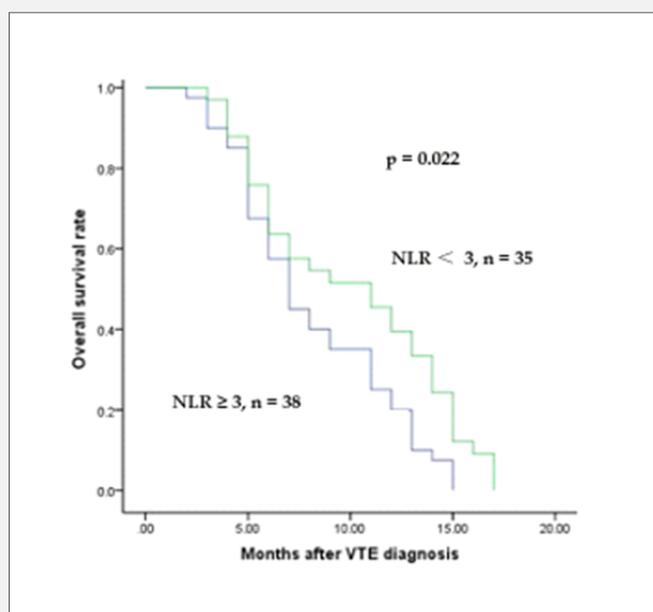


Figure 2. Kaplan-Meier survival curves of gastric cancer patients newly diagnosed with VTE.

The patients were divided into NLR  $\geq 3$  group and NLR  $< 3$  group by the optimal cutoff value of NLR. Overall survival of patients with NLR  $\geq 3$  was also shorter than those with NLR  $< 3$  ( $p = 0.022$ , log-rank).

other factors. Patients with poorly differentiated vs. differentiated (55.4 vs. 82.4%,  $p = 0.045$ ), high NLR vs. low NLR level (37.4 vs. 77.3%,  $p = 0.001$ ), and low albumin vs. high albumin level (44.8 vs. 72.7%,  $p = 0.016$ ) tended to show a poorer response to anticoagulant therapy. However, patients with a high CRP level and platelet count were not associated with the response to anticoagulation.

### Survival

Overall survival (OS) after the VTE diagnosis was compared according to the variables. Patients who achieved VTE resolution had better OS than patients who failed to achieve VTE resolution (median OS, 9.2 vs. 6.0 months,  $p = 0.016$ , Figure 1). Among the factors associated with the response to anticoagulation, high NLR was associated with poor OS (Figure 2).

In addition, multivariate analysis by Cox regression revealed that high level of NLR (hazard ratio, 1.56, 95% CI: 1.32 - 1.87,  $p = 0.032$ ) and UICC stage III and IV (hazard ratio, 2.11, 95% CI: 1.29 - 3.44,  $p = 0.043$ ) were independent poor prognostic factors for OS of patients while the other parameters failed to reach statistical significance (Table 3).

### DISCUSSION

In the present study, a high preoperative NLR value in patients with gastric cancer was found to be associated with tumor progression. Patients with high NLR presented more frequently with UICC stage III and IV disease and T3 and T4 tumor depth than patients with low NLR. Cancer growth may cause consecutive systemic inflammatory responses and the host inflammatory response to cancer cells is also associated with tumor progression [23]. The NLR, which has been shown as an indicator of systemic inflammation [24], may be related to the prognosis of cancer patients. For example, the NLR has been shown to be associated with the prognosis of gastric cancer [25] and many different types of carcinoma [17,26-27]. These results suggested the existence of a close relationship between NLR and cancer progression. Furthermore, an increase of the neutrophil count may suppress the immune reactions of the hosts and stimulate and facilitate tumor progression [28-29]. Meanwhile, the immune response of the hosts to tumors depends on the lymphocytes which may reflect the defense activity of the host against tumor progression [21, 30]. Since an increase in the neutrophil count and decrease of the lymphocyte count in the peripheral blood have been shown to be related to tumor progression

[25], the NLR, calculated based on both the neutrophil and lymphocyte counts, may be a good index reflecting the degree of tumor progression.

In this study, we retrospectively investigated the clinical significance of NLR and other factors for newly diagnosed VTE during follow-up for gastric cancer patients. The results demonstrated that a high level of NLR was associated with a lower VTE resolution rate. Moreover, low serum albumin also significantly correlated with the poor response with anticoagulant therapy in the present study. NLR and serum albumin are two acute phase reactant markers that may reflect inflammation and poor general conditions, which are sometimes linked to increased risk for VTE [31,32]. Additionally, NLR at the time of VTE diagnosis might be helpful for predicting the anticoagulation resistant patients among those with gastric cancer and VTE.

We showed that NLR was associated with survival from the time of the VTE diagnosis, and statistical significance still existed after adjusting for tumor stage and response to anticoagulation in the multivariate analysis. The results indicated that patients with high NLR had shorter survival compared with patients with low NLR. Meanwhile, the finding also indicates that high NLR predicts poor prognosis in patients with gastric cancer [19,25]. Numerous studies demonstrated that biomarkers associated with inflammation or thrombosis, such as albumin, CRP, and FDP, were also risk factors related to survival [33]. Based on these findings, we suggest that inflammatory markers, including NLR, may be predictive for survival in cancer patients with VTE. However, further studies are warranted to determine how inflammatory and coagulable states affect survival in patients with cancer.

Nevertheless, this study had a few limitations. First, the sample size was relatively small for generalizing our findings in gastric cancer patients with VTE treated with anticoagulation. Second, the present study was evaluated retrospectively. Thus, a prospective study is needed to validate our results, even though there is little information about the relationship between NLR and thrombosis in patients with cancer.

## CONCLUSION

In summary, we demonstrated that NLR at the time of VTE diagnosis could be a useful biomarker for predicting response and prognosis following anticoagulation in gastric cancer patients with VTE. However, further large prospective studies are warranted to validate our findings.

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## Prognostic Significance of the Neutrophil-Lymphocyte Ratio

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