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Neutrophil-lymphocyte ratio is a predictor of venous thromboembolism in gastric cancer patients.

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Abstract

Background: The Neutrophil-lymphocyte Ratio (NLR) reflects the inflammatory state. Elevated NLR has been reported to be a prognostic indicator in some malignancies. The aim of this study was to determine whether NLR is a prognostic factor in the response to anticoagulation and survival in patients with gastric cancer and Venous Thromboembolism (VTE) treated with anti-VTE.
Methods: We retrospectively recruited 73 patients with gastric cancer who had VTE, among 539 patients with pathologically proven gastric cancer between January 2008 and December 2016. Univariate and multivariate analyses were performed to identify clinicopathological predictors of anticoagulant response and overall survival.
Results: Patients with high NLR had more late tumor stage (p=0.046), deeper tumor depth (p=0.033), and worse histologic grade (p=0.045) than did the low NLR group. There was a statistically significant association between poor NLR (p=0.001) and low albumin (p=0.016) and anticoagulant therapy. Multivariate analysis showed that high levels of NLR (hazard ratio, 1.56, 95% CI: 1.32-1.87, p=0.032) and late tumor stage (hazard ratio, 2.11, 95% CI: 1.29-3.44, p=0.043) were independent risk factors for poor prognosis for gastric cancer patients with VTE.
Conclusions: The results suggest that NLR may be a useful biomarker in predicting the response to anticoagulation and survival in patients with gastric cancer with VTE.

Keywords: Neutrophil-lymphocyte ratio, Gastric cancer, Venous thromboembolism.

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Introduction

Venous Thromboembolism (VTE), including deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), is a common complication of cancer patients and is one of the major causes of morbidity and mortality [1,2]. Studies have shown that about 20% of patients who underwent VTE for the first time had cancer, and cancer patients had a 7-fold risk of developing VTE [3-5]. Gastric cancer is the fourth most common cancer in the world and the second most common cause of cancer-related death [6]. Recently, emerging studies have shown that VTE is relatively frequent in gastric cancer. The incidence of VTE in patients with gastric cancer was 3.5% to 24.4%, and VTE showed an adverse effect on the survival of cancer patients, even after adjustment for comorbidity [7,8]. The main mechanism of thrombosis in cancer patients is associated with abnormal vessel wall, blood flow and blood components [9]. In addition, inflammation is associated with prothrombotic state [10,11]. Inflammatory cells and mediators are an essential part of the tumor microenvironment [12].

Various biomarkers have been used to assess the inflammatory status of cancer patients. Among them, the neutrophil-lymphocyte ratio (NLR), which is a systemic inflammatory index, is an easily available and low-cost biomarker used in clinical practice, which has been associated with relapse [13,14] and survival [15-17] in various cancers. NLR has been reported to not only be of prognostic value in patients with gastric cancer, but also be a useful predictor of the depth of invasion of the gastric wall in these patients with gastric cancer [18]. Although NLR has been extensively studied in prognostic significance of cancer survival, [19-21] more and more studies have shown the clinical value between thrombosis and NLR, mainly in non-cancer patients [22]. However, there is currently no study of the association between NLR and cancer-related thrombosis. We therefore performed this study to assess the clinical impact of NLR on VTE diagnosis as a prognostic factor for anticoagulation and survival, as well as clinical features of patients with gastric cancer treated with anticoagulant VTE.

Materials and Methods

Patients

We retrospectively analyzed patients with newly diagnosed VTE based on imaging examination (computed tomography [CT] or Doppler ultrasonography) in patients with gastric cancer diagnosed by pathology in Zhangjiagang traditional Chinese medicine hospital in January 2008 and December

2016. This study included 539 patients with complete medical records of gastric cancer. In patients with gastric cancer, the incidence of VTE was calculated and data from patients diagnosed with VTE were collected. All VTE patients were treated with warfarin, low molecular weight heparin, or both. Patients with arterial thrombosis without VTE or those without evidence of VTE imaging were excluded from the analysis. Exclusion criteria were as follows: Patients had active inflammation, such as infection; patients had a blood system disorder; and a history of blood transfusions over the past three months; Patients had other types of cancer.

Clinical data

Baseline patient characteristics were collected through a medical record review, including demographics, histology, and medical history. The stage of cancer TNM depends on the sixth edition of the International Union of Cancer Control (UICC) standards and is available at the time of VTE diagnosis. Clinical signs and anticancer treatment at VTE diagnosis were also evaluated. The anticoagulant response was assessed in patients who underwent at least one follow-up CT scan or Doppler ultrasound. Responses are categorized as "resolution" and "no resolution". Resolution refers to the absence of evidence of VTE in one or more subsequent imaging examinations. The cases in subsequent imaging showed partial improvement, and unaltered or aggravated in VTE were considered to be no resolution. The relationship between anticoagulant response and clinical variables was analyzed and the effect of response on survival was also evaluated.

We investigated the clinical value of NLR as a prognostic factor in patients with VTE. Complete and differential blood cell counts were assessed in an anticoagulated whole blood of EDTA using an automated blood cell analyzer (Bayer Advia2120). The NLR was calculated as the neutrophil count divided by the lymphocyte count from the diagnosis of VTE. 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. The cut-off value for ‘‘high versus low’’ NLR has not been unified currently. Thus, in the present study, the cut-off value for ‘‘high versus low’’ PLR value was defined as previously reported. A NLR>3.0 was considered elevated according to the published literature [23].

Statistical analysis

All statistical analyzes were performed using IBM SPSS Statistics 21.0. Descriptive statistics are used to characterize the patient. Categorical variables were expressed as the number and percentage of patients and were compared using a chi-square or Fisher exact test. Kaplan-Meier method was used for survival probability analysis. Survival was calculated as the time from the onset of VTE to the date of death or the most recent follow-up date after diagnosis of gastric cancer. Significant differences between the groups were assessed using the log rank test. Survival multivariate analysis was analyzed using the Cox proportional hazards model. For all statistical analyzes, p values less than 0.05 were considered significant.

Results

The incidence of VTE and patient characteristics according to the neutrophil-lymphocyte ratio (NLR) status at diagnosis of VTE

Of 539 patients diagnosed with gastric cancer, 73 (13.54%) were diagnosed with VTE and received anticoagulant therapy. The characteristics of 73 patients are shown in Table 1. The median age at diagnosis of VTE was 68 years and forty-six patients (63.01%) were over 60 years of age. The majority of patients were men (67.13%). According to the UICC staging system, nearly half of the patients are in phases III and IV. Thirty-eight patients had high NLR levels (NLR $\geq$ 3.0). According to the NLR status, the distribution of VTE-diagnosed age, sex, and clinical variables included UICC staging, tumor depth, N factor, distant metastasis, and histology, was shown in Table 1. Age and sex distribution were similar in the low and high NLR groups. Patients with high NLR exhibited more frequent UICC stage III and IV disease, T3 and T4 tumor depths than patients with low NLR. No statistically significant differences were found between low and high NLR groups in N staging, distant metastasis, and histological grade.

Table 1. *Distribution of cancer patients with VTE*

Variables	Total (N=73)	NLR ≥ 3.0 (n=38)	NLR<3.0 (n=35)	p
Age (year, n, %)				
<60	27	13	14	0.609
≥ 60	46	25	21	
Gender (n, %)				
Male	49	26	23	0.806
Female	24	12	12	
UICC stage				
I,II	37	15	22	0.046
III,IV	36	23	13	
Tumor depth				
T1,T2	17	5	12	0.033
T3,T4	56	33	23	
N factor				
N0	31	14	17	0.311
N1,N2,N3	42	24	18	
Distant metastasis				
M0	63	31	32	0.221
M1	10	7	3	

Histology				
Differentiated	21	10	11	0.631
Poorly differentiated	52	28	24	

Response to anticoagulant therapy

All patients were eligible for anticoagulant evaluation. Forty-five patients (61.64%) showed a resolution of VTE, while 28 patients (38.36%) did not achieve VTE resolution. Table 2 shows the relationship between anticoagulation and several other factors. Patients with poor differentiation (*vs.* good differentiation 55.4 *vs.* 82.4%, p=0.045), high NLR (*vs.* low NLR, 37.4 *vs.* 77.3%, p=0.001), and low albumin (*vs.* high albumin, 44.8*vs.* 72.7%, p=0.016) showed poor response to anticoagulation therapy. However, patients with high CRP levels and platelet counts were not associated with response to anticoagulation.

Table2. *Response of anticoagulant therapy according to variables*

Variables	Resolution (n=45)	No resolution (n=28)	p
Histology			
Differentiated	14	3	0.045
Poorly differentiated	31	25	
NLR			
<3.0	34	10	0.001
≥ 3.0	11	18	
Platelet count(x109/L)			
<300	10	4	0.402
≥ 300	35	24	
Albumin			
<35	13	16	0.016
≥ 35	32	12	
CRP			
<20.5	28	11	0.056
≥ 20.5	17	17	

Survival

The Overall Survival (OS) after VTE diagnosis was compared according to the variables. Patients with VTE resolution were superior to those who did not achieve VTE resolution (median OS, 9.2 *vs.* 6.0 months, p=0.016, Figure 1). Among the factors associated with anticoagulation, high NLR was significantly associated with poor OS (Figure 2).

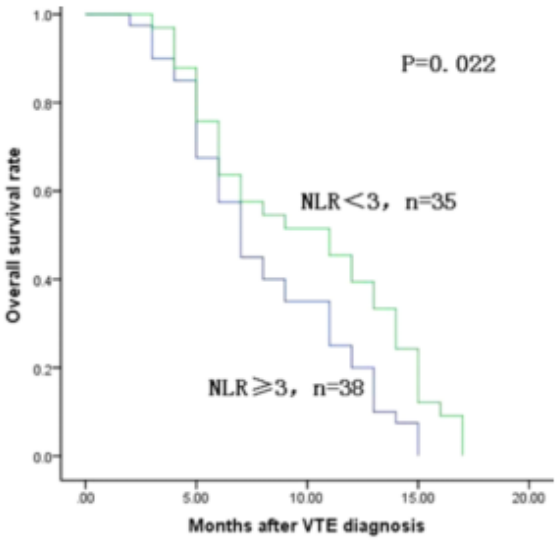

Figure 1. *Kaplan-Meier survival curves of gastric cancer patients newly diagnosed with VTE. The patients were divided into NLR ≥ 3 group and NLR<3 group by the optimal cut-off value of NLR. Overall survival of patients with NLR ≥ 3 was also shorter than those with NLR<3(P=0.022, log-rank).*

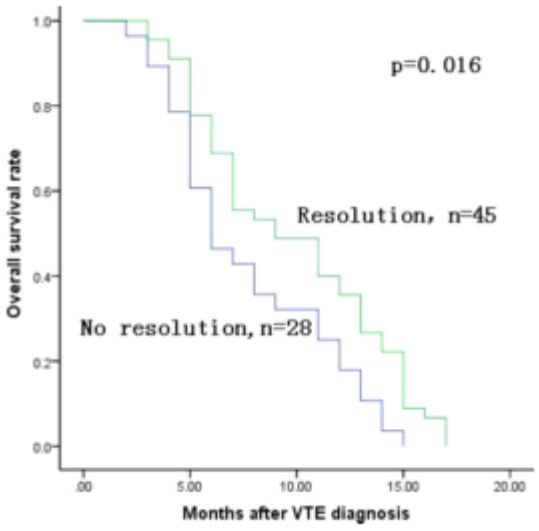

Figure 2. *Kaplan-Meier survival curves of gastric cancer patients newly diagnosed with VTE. The patients were divided into resolution group and no resolution group. Patients who achieved VTE resolution had better OS than that of patients who failed to achieve VTE resolution (P=0.016, log-rank).*

Table 3. *Cox proportional hazards model for overall survival*

Variables	H.R	95% CI	p
NLR at VTE diagnosis			
<3.0	1	-	0.032
≥ 3.0	1.56	1.32-1.87	

UICC stage			
I,II	1		0.043
III,IV	2.11	1.29-3.44	
Response to anticoagulation			
Resolution	1		0.162
No resolution	1.65	0.86-3.32	

In addition, multivariate analysis of Cox regression showed high levels 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 poor independent prognostic factors for OS (Table 3).

Discussions

Recently, there also several studies suggested that NLR has diagnostic value for VTE or cancer. Bakirci et al. [24] found that the NLR value of patients with VTE was significantly higher than healthy controls, indicating that NLR has a diagnostic value for VTE. Arima K et al. [25] found that NLR over 5 independently predicted the occurrence of PDAC in pancreatic neoplastic diseases, regardless of other tumor markers CEA and CA19-9. A meta-analysis showed that NLR could be used to predict OS and PFS in lung cancer patients and could be an important biomarker of lung cancer prognosis [26]. On the basis of above study, our study further confirmed that NLR can predict the survival of gastric cancer-associated VTE.

In this study, a higher NLR value was found to be associated with tumor progression in gastric cancer. Patients with high NLR exhibited more frequent UICC stage III and IV disease, T3 and T4 tumor depths than patients with low NLR. This indicated that high NLR value was associated with later stage and greater tumor size, which are poor prognostic factors for cancer patients. In addition, statistical significance was still existed after adjusting for tumor stage and response to anticoagulation in the multivariate analysis. Cancer growth can cause a continuous systemic inflammatory response, and the host's inflammatory response to cancer cells is also associated with tumor progression [27]. NLR, which has been shown to be an indicator of systemic inflammation, may be associated with prognosis in cancer patients [28]. More and more evidence suggests that NLR is associated with the prognosis of gastric cancer [29] and many different types of cancer [30-32].

These results suggest a close relationship between NLR and cancer progression. In addition, an increase in neutrophil counts can suppress the host’s immune response and stimulate and promote tumor progression [33,34]. At the same time, the host’s immune response to the tumor depends on the lymphocytes, which can reflect the host’s defensive activity against tumor progression [35,36]. Since the increase in neutrophil counts and the decrease in lymphocyte counts in peripheral blood have been shown to be associated with tumor progression, NLRs based on neutrophil and lymphocyte counts may reflect tumor progression [37].

In this study, we retrospectively investigated the clinical significance of NLR and other factors for VTE in patients with gastric cancer. The results show that high levels of NLR are associated with lower VTE resolution. In addition, low serum albumin was significantly associated with adverse events in anticoagulant therapy in this study. NLR and serum albumin are two acute phase reactant markers that can reflect inflammation and poor general conditions, which are sometimes associated with increased risk of VTE [38,39].

We show that NLR is associated with the survival of VTE after adjusting the confounding factors. At the same time, our study further confirmed that high NLR predicted poor prognosis in patients with gastric cancer [40,41]. Numerous studies have shown that biomarkers associated with inflammation or thrombosis, such as albumin, CRP, and FDP, are also risk factors associated with survival [42]. Inflammatory markers are associated with the severity of the disease and the therapeutic effect. Meng et al. reported that platelet-to-lymphocyte ratio is strongly associated with disease severity and virological response in patients with HCV-associated liver disease. Based on these findings, we propose that inflammatory markers, including NLR, may predict the survival of VTE in cancer patients. However, further studies are needed to determine how inflammation and clotting conditions affect the survival of cancer patients.

However, this study had some limitations. First, the sample size of this study is relatively small, which may lead to sampling errors. Second, this study was retrospectively evaluated, and there may be some selection bias. Therefore, a prospective study is needed to validate our results because few studies have examined the relationship between NLR and thrombosis in cancer patients.

In summary, we demonstrated that NLR at the time of VTE diagnosis can be a useful biomarker for predicting the response and prognosis of patients with gastric cancer after anticoagulant therapy. However, further large prospective studies are necessary to validate our findings.

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