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The Prognostic Value of the Prechemotherapy Neutrophil - Lymphocyte Ratio in Gastric Cancer

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ABSTRACT

Background: gastric cancer is the 5th most common cancer worldwide, with about one million newly diagnosed cases annually. It causes one of the highest cancer burdens, as measured by disability-adjusted life years lost. It is the third-leading cause of cancer-related death worldwide, after lung and liver malignancies. It is increasingly recognized that variations within clinical outcomes in cancer patients are influenced by not only the oncological characteristics of the tumor, but also the host-response factors.

Aim of the work: this study aimed to investigate the prognostic value of prechemotherapy NLR in the gastric cancer patients and also to assess the association between high NLR and clinicopathological features; e.g. tumor stage, site, gross morphology …etc. **Patients and methods:** this retrospective study included patients, diagnosed with gastric or gastroesophageal cancer, who presented to Oncology Department in Ain Shams University Hospital from January 2013 till December 2016. 61 patients were included in this study. **Results:** we found a significant correlation between presence of ascites and high NLR. This relation wasn't discussed in any previous study as far as we know. There was a significant correlation between NLR and each of the following: - overall survival and event-free survival. This was consistent with the results of previous studies worldwide. Therefore, our study proved that the prechemotherapy NLR is a prognostic factor in gastric cancer.

Conclusion: the prechemotherapy NLR was significantly correlated with presence of ascites at diagnosis of gastric cancer. It is an independent prognostic factor in gastric cancer. It affects both event free survival and overall survival.

KEY WORDS:PRECHEMOTHERAPY, NEUTROPHIL - LYMPHOCYTE RATIO, GASTRIC CANCER.

INTRODUCTION

Gastric cancer is the 5th most common cancer worldwide, with about one million (952,000) new cases diagnosed annually **(1)**.

More than 70% of gastric cancers occur in the developing countries, particularly in Eastern Asia. The peak age for gastric cancer is 60-80 years **(2)**.According to the GLOBOCAN database, gastric adenocarcinoma (GC) is the third leading cause of cancer-related death worldwide, after lung and liver malignancies, resulting in around 723,000 deaths in 2012 **(2,3)**. Although there have been advances in diagnosis and management, most GC patients present with locally advanced or metastatic disease, with a 5-year survival rate of <10% **(4)**. In Egypt, gastric cancer is the 12th most common cancer in both sexes, representing 1.6 % of total cancers. It's the 12th leading cause of cancer death, representing 2.2 % of total cancer mortality. Median age of gastric cancer in Egypt is 56 years **(2)**. Environmental risk factors include *Helicobacter pylori* (*H. pylori*) infection, smoking, high salt intake and other dietary factors. Though most gastric cancers are considered sporadic, it was estimated that 5 % to 10 % have a familial component and 3 % to 5 % were associated with inherited cancer predisposition syndromes. The most common hereditary cancer predisposition syndromes are: hereditary diffused gastric cancer, Lynch syndrome, juvenile polyposis syndrome, Peutz-Jeghers syndrome and familial adenomatous polyposis **(5)**. Treatment strategies were determined by TNM staging system. However, many patients of the same TNM stage had different prognoses **(6)**. Gastric Cancer exhibits diverse prognoses according to various intrinsic characteristics. Therefore, the development of efficient treatment strategies for the various prognostic groups within GC is important. Thus, **Chan-Young *et al.*** (7) tried to understand the biological mechanisms of each subtype of GC, to effectively individualize each treatment strategy**.** Several prognostic factors in GC have been reported such as: performance status, tumor burden, tumor markers such as carbohydrate antigen 19-9 (CA-19-9), the high metabolic landscape of the tumor and weight loss during chemotherapy. They have been independently correlated with a poor prognosis **(8)**.

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oncological characteristics of the tumor, but also the host-response factors. The possibility of combining multiple clinically available host- and tumor related factors is of great interest; as it might serve as an excellent basis for clinical decision-making, treatment planning and establishing follow-up schedules [(1)].

A study had focused on tumor microenvironment, which was associated with the systemic inflammatory response and may play an important role in cancer tumorigenesis and progression [(8)]. This inflammatory response reflected a non-specific response to tumor hypoxia tissue injury and necrosis [(9)]. Systemic inflammatory response to tumors increases metastasis through the inhibition of apoptosis, augmentation of angiogenesis and DNA damage [(10)]. Many markers of systemic inflammation response to tumors have been investigated as prognostic and predictive biomarkers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [(11)]. Inflammatory cytokines and chemokines can be produced by both the tumor and associated host cells, such as leukocytes, and contribute to malignant progression**.**

Neutrophilia, as an inflammatory response, inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells and natural killer cells[(12)]. Neutrophils and other cells, such as macrophages, have been reported to secrete tumor growth promoting factors, including: - vascular endothelial growth factor, hepatocyte growth factor, IL-6, IL-8, matrix metalloproteinases and elastases. Thus, they likely contribute to a stimulating tumor microenvironment [(12)]. The importance of lymphocytes has been highlighted in several studies [(13-15)]. Increasing infiltration of tumors with lymphocytes has been associated with better response to cytotoxic treatment and prognosis in cancer patients [(14)]. The neutrophil to lymphocyte ratio (NLR), which is suggested as the balance between pro-tumor inflammatory status and anti-tumor immune status, has been shown to be associated with outcomes in patients with various types of malignancies [(14)] such as renal cell carcinoma, hepatocellular carcinoma and colorectal cancer [(15)].

A recent meta-analysis of nine studies concluded that an elevated NLR was associated with poorer rates of survival in GC patients. The nine selected studies included 3,709 patients with 36.5% classified as High NLR (HNLR). The cut-off value for HNLR was <3 in four studies, 3≤ to ≤4 and ≥5 in one study. Six studies assessed patients undergoing resection of the primary GC and three studies reported patients undergoing palliative chemotherapy for GC. NLR was calculated based on pre-treatment laboratory data using white blood cell (WBC) differentiated counts in all of the studies. Three of these cohorts enrolled <200 patients and six cohorts enrolled > 200 patients. [(16)].

Despite heterogeneity (I^2 65%, P = 0.004), the pooled HR of 2.16 (95% CI: 1.86 to 2.51, P <0.001) showed that patients with elevated NLR were expected to have shorter OS after treatment [(7)]. A study with cancer patients showed that chemotherapy can normalize elevated NLR early after the introduction of treatment; and that patients with normalized NLR may have improved outcome [(16)]. Also, prediction of the immune response in the tumor microenvironment is very important for selection of patients who will most likely benefit from cancer immunotherapy [(17)]. This study aimed to investigate the prognostic value of prechemotherapy NLR in Gastric cancer patients and also to assess the association between high NLR and clinicopathological features; e.g. tumor stage, site, gross morphology …etc.

Patients and methods

This retrospective study was included patients, diagnosed with gastric or gastroesophageal cancer, who presented to Oncology Department in Ain Shams University Hospital from January 2013 till December 2016.

61 patients were included in this study.

The inclusion criteria of these patients were: tissue biopsy confirming the diagnosis of gastric or GEJ cancer, availability of prechemotherpy CBC with differential count of leucocytes, no past history of another malignancy, or history of a simultaneous second malignancy, no history of hematologic disease, no history of prior exposure to chemotherapy and no history of active inflammatory process when the CBC was withdrawn.

First, we collected the following demographic data about the patients, at the time of diagnosis: age, sex, performance status by ECOG, history of smoking, history of diabetes mellitus and family history of malignancy.

Next, we collected and analyzed the following data about clinicopathological features of the tumor, at the time of diagnosis: tumor site, Bormann gross morphology of the tumor, tumor stage, presence of ascites, sites of metastasis,

number of metastatic sites, tumor grade, tumor type according to Lauren's classification, presence of lymphovascular invasion and perineural invasion.

NLR: we calculated the median prechemotharpy neutrophil-to-lymphocyte ratio (NLR). We classified the patients accordingly into two groups; high-NLR group and low-NLR group. Next, we compared the median OS in the high-NLR group and the low-NLR group; to assess if NLR was a prognostic factor regarding OS.We compared the median EFS in the high-NLR group and the low-NLR group; to assess if NLR was a prognostic factor regarding EFS.

We assessed the correlation between NLR and each of the previously-mentioned patient's and tumor characteristics.

We assessed the correlation between NLR and response to chemotherapy.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

Statistical Analysis

The collected data were revised, coded and tabulated using the statistical pattern for social science (IBM® SPSS® statistics version 22 for windows, 2016). We used Chi-square test to assess correlation. We use Kaplan-Meier curves to show the relation between NLR and both EFS (Event-free survival) and OS (overall survival).

RESULTS

Table 1: patient's demographic characteristics

		Frequency	Percent
Age	≤55	32	52.5%
	>55	29	47.5%
Gender	Male	31	50.8%
	Female	30	49.2%
Smoking	No	14	23.0%
	Yes	47	77.0%
Co-morbidities (DM)	No	48	78.7%
	Yes	13	21.3%
Performance Status (ECOG)	1	38	62.3%
	2	19	31.1%
	3	4	6.6%

Table 2: ascites at diagnosis

Ascites at diagnosis	Frequency	Percent
No	49	80.3%
Yes	12	19.7%

Table 3: tumor stage

Stage	Frequency	Percent
I	1	1.6%
II	3	4.9%
III	17	27.9%
IV	31	50.8%
Unknown	9	14.8%

Table 4: prechemotherapy neutrophil to lymphocyte ratio

NLR	Frequency	Percent
≤2.4	31	50.8
>2.4	30	49.2
Total	61	100.0

Table 5: correlation between ascites and NLR

			Ascites at diagnosis		Total	p value
			No	Yes		
NLR	≤2.4	Count	28	3	31	0.046
		% within Ascites at diagnosis	57.1%	25.0%	50.8%	
	>2.4	Count	21	9	30	
		% within Ascites at diagnosis	42.9%	75.0%	49.2%	
Total		Count	49	12	61	
		% within Ascites at diagnosis	100.0%	100.0%	100.0%	

Table 6: correlation between event free survival (EFS) and NLR

NLR	N	Median			P value
		Estimate	95% Confidence Interval		
			Lower Bound	Upper Bound	
≤2.4	19	8.000	2.896	13.104	
>2.4	21	5.000	3.610	6.390	0.001
Overall		6.000	5.045	6.955	

Table 7: correlation between overall survival (OS) and NLR

NLR	N	Median			P value
		Estimate	95% Confidence Interval		
			Lower Bound	Upper Bound	
≤2.4	22	9.000	5.338	12.662	
>2.4	29	6.000	4.250	7.750	0.013
Overall		8.000	5.689	10.311	

DISCUSSION

This study included 61 patients with gastric adenocarcinoma who either received the first cycle of chemotherapy in our hospital or presented with prechemotherapy CBC. The median EFS was 6 months. In **Wang *et al*** [18] study on Chinese patients it was 5 months**.**

The median OS was 8 months. According to **Zeeneldin *et al.*** [2] the median OS was 6 months. In **Wang *et al.*** [4] results the median OS was 13 months. In **Deng *et al.*** [19] study on Chinese patients, the median OS was 24 months**.** **Jung *et al*.** [20] stated that the median OS was 27.2 months (20)**.** This might be explained by the diversity of population and different stages included in our study. The median prechemotherapy NLR in our study was 2.4 and it was used as the cut-off value; where patients with NLR ≤2.4 were classified into the low NLR group and patients with NLR >2.4 were classified into the high NLR group. This is comparable to the cut-off value of 2.36 used in study of **Deng *et al.*** **(19)** and the cut-off value of 2.5 used in **Jin *et al.*** [21] study. Other studies used slightly lower or higher cut-off values. **Kim *et al.*** [22]**.** used 2 as a cut-off value . In contrast**, Lee *et al.*** [24] used a cut-off value of 3 and **Shimada *et al.*** [32]. used a cut-off value of 4**.**

There was no significant correlation between smoking and NLR. In **Musri *et al***. there was a significant correlation between smoking and high NLR (p=0.046) [25].

There was no significant difference in NLR between different tumor sites. Also, **Jung *et al.*** [20], **Hsu *et al.*** [26] and **Choi *et al.*** [17] there was no correlation between NLR and tumor site.

There was no significant difference in NLR between different gross morphology types. Again, in **Jung *et al*.** [20] study there was no association between gross morphology and NLR **.**

There was no significant difference in NLR between diffused and intestinal GC types. Similarly, there was no association between Lauren's classification subtypes and NLR in **Jung**

et al. study [20]. In **Choi *et al.*** [17] study there was also no correlation between NLR and tumor histological type whether according to WHO classification or Lauren's classification **.**

There was no significant difference in NLR between different grades of differentiation. This was also noticed by **Jung *et al*** [20], **Deng *et al.*** [19]**, Hsu *et al.*** [26] **and Musri *et al.*** [25].

There was no significant difference in NLR between metastatic and non-metastatic patients. Hence, there was no significant correlation between NLR and presence of metastasis at diagnosis.

In **Sahin *et al.*** [27] there was no statistically significant difference in NLR between non-metastatic and metastatic groups (p=0.555). However, there was a statistically significant difference in median NLR values in stage II, III, and IV, compared to stage I. Additionally, when comparing stage III and IV to stage II, the median NLR levels were significantly higher (p<0.05) **.** Also, in **Deng *et al*.** study [19]. those patients with tumor stage III-IV had a higher NLR than those with tumor stage I-II**.** According to **Hsu *et al*.** [26]. there was a significant correlation between metastasis and high NLR**.**

There was a significant correlation between NLR and presence of ascites at diagnosis (p value= 0.046). Additionally, all patients who had newly developed ascites after chemotherapy belonged to the high NLR group. To our knowledge, no previous study evaluated the correlation between prechemotherapy NLR and presence of ascites at diagnosis in gastric cancer.

There was a significant correlation between the NLR and EFS; where the median EFS in the low NLR group and the high NLR group were 8 months and 5 months, respectively (p value = 0.001). Similarly, in ***Wang et al*.** the median EFS in low NLR group and the high NLR group were 6 months and 3 months, respectively (P<0.001) [4].

There was a significant correlation between the NLR and OS; where the median OS in low NLR group and the high NLR group were 9 months and 6 months, respectively (p value= 0.013). **Wang *et al.*** [4] mentioned that the median OS in the low NLR group and the high NLR group were 18 months and 10 months, respectively (P<0.001) **.**

Studies which were limited to metastatic patients only also confirmed the prognostic value of prechemotherapy NLR. According to **Yamanaka *et al*.** [28] the median OS was 12.3 months *vs.* 8 months in the low NLR group and high NLR group, respectively **.** According to **Cho *et al*.** [29] low NLR group patients had longer progression-free survival (PFS) than the high NLR group patients (6.2 months vs.4.8 months; P = 0.001) and longer overall survival (OS) than the high NLR group patients (13.8 months vs.9.3 months; P < 0.001) **. Musri *et al*.** [17]. showed that the median PFS was 7.9 months in patients with low NLR and 6.2 months in patients with high NLR (p=0.011). The median OS was 11.6 months in patients with low NLR and 8.3 months in patients with high NLR (p<0.001) **.**

There are some limitations to this study. It was a retrospective study. Some of the patients enrolled in the study died shortly after diagnosis and before proper staging was done. Some of the patients, who received chemotherapy, had been lost before evaluation of the effect of chemotherapy. The prechemotherapy CBC was not withdrawn in a unified lab for all patients.

CONCLUSION

The prechemotherapy NLR was significantly correlated with presence of ascites at diagnosis of gastric cancer. It was an independent prognostic factor in gastric cancer. It affects both event free survival and overall survival.

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