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ORIGINAL RESEARCH

Pre-treatment Peripheral Neutrophil-Lymphocyte Ratio as a Prognostic Marker in Gastric Cancer

Monika Magdy[1] · Tarek Hussein[1] · Ahmed Ezzat[1] · Ahmed Gaballah[1]

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Abstract

Background Gastric cancer is the fifth cancer worldwide. Inflammatory response increases metastasis through apoptosis inhibition and angiogenesis augmentation. The neutrophil-lymphocyte ratio (NLR), which is a balance between pro-cancer inflammatory and anti-cancer immune responses, was proved as prognostic marker. Peripheral NLR is a good reflection of tumor microenvironment.

Methods We retrospectively collected data of gastric and gastro-esophageal cancer patients treated from January 2015 till December 2016. Sixty-one patients were included. Pre-treatment NLR was calculated. We extracted the different clinic-epidemiological and pathological data. Event-free and overall survivals were plotted using Kaplan-Meier curves.

Results The median age was 55. Male to female ratio was 1:1. Forty-seven patients were smokers. Most of the patients (93.4%) had good performance status (ECOG 0-2). Forty-six patients had gastric and 15 had gastro-esophageal cancer. 50.8% had diffuse gastric type. Grade III represented 49.2% and grade II 46%. Twelve patients had ascites at diagnosis. Stage at presentation was 1.6%, 4.9%, 27.9%, 50.8%, and 14.8% for stage I, II, III, IV, and unknown respectively. The median NLR was 2.4. The NLR showed no significant correlation with different clinic-epidemiologic and pathological variables except presence of ascites; $p = 0.046$. Median event-free survival (EFS) and overall survival (OS) were 6 and 8 months respectively. High NLR was significantly associated with worse survival; EFS, 5 months vs 8 months (95% CI, $p = 0.001$). OS, 6 months vs 9 months (95% CI, $p = 0.013$).

Conclusion Gastric cancer is an aggressive and fatal disease. NLR can be used as a prognostic marker.

Keywords Neutrophil-lymphocyte ratio · NLR · Gastric cancer · Egypt

Introduction

Gastric cancer (GC) is the fifth most common malignancy worldwide; with almost one million cases diagnosed annually [1]. It is an aggressive cancer; its 5-year survival rate is about 20% in most of the world. In Egypt, GC ranks 12th, representing 1.6% of all cancer types, and is responsible for 2.2% of cancer-related deaths [2].

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 [1].

Systemic and tissue response to tumor is an important prognostic factor in carcinogenesis. Grivennikov et al. [3] stated that tissue inflammation is involved in all stages of tumorigenesis. It induces initiation of tumors through mutations, genomic instability, and epigenetic modifications. It also stimulates tissue repair process, with proliferation of pre-malignant cells and activation of angiogenesis. Additionally, it suppresses anti-tumor immune response and enhances metastasis.

✉ Ahmed Gaballah
drgaballah@gmail.com; Ahmed_gaballah@med.asu.edu.eg

Monika Magdy
monika_rcg@yahoo.com

Tarek Hussein
drgaballah@hotmail.com

Ahmed Ezzat
Ahmedezzat200011@gmail.com

[1] Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Abbasia, Cairo, Egypt

Table 1 Patients' characteristics

Variable		Frequency	Percentage
Age	≤ 55	32	52.5
	> 55	29	47.5
Gender	Male	31	50.8
	Female	30	49.2
Smoking	Yes	47	77
	No	14	23
Performance status (ECOG)	0–1	38	62.3
	2	19	31.1
	3	4	6.6

Table 3 Site of metastasis

Site of metastasis	Frequency	Percentage
Non-regional LNs	13	42
Pleural effusion	10	32.2
Peritoneal metastasis	9	29
Liver	8	25.8
Lung	5	16.1
Bone	3	9.7
Adnexa	3	9.7
Others	1	3.2

On the contrary, anti-tumor immune response correlates with better prognosis and better survival. Amedei et al. [4] stated that in GC, intra-tumoral infiltration by cytotoxic T cells and memory T cells is associated with better survival.

The peripheral lymphocyte count reflects the anti-tumor immune response within the tumor microenvironment, while the neutrophil count reflects the pro-tumor inflammatory response. Cho et al. [5] questioned the role of pre-chemotherapy neutrophil-to-lymphocyte ratio (NLR) as a prognostic factor in GC. He concluded that patients with low NLR had higher chemotherapy disease control rate (90% versus 80.4%) and also longer progression free survival (PFS) and overall survival (OS) (186 days versus 146 days, and 414 days versus 280 days, respectively).

This result was confirmed by other trials conducted by Jin et al. [6], Mohri et al. [7], and Namikawa et al. [8]. In a meta-analysis of 19 articles, Sun et al. [9] concluded that high NLR was associated with lower PFS and DFS.

Choi et al. [10] evaluated the prognostic value of markers of systemic inflammation and its correlation with immune cells in the tumor microenvironment. He concluded that peripheral blood analysis can reflect the tumor microenvironment.

In this, non-randomized, observational, non-interventional trial, we aimed at evaluating the value of the pre-treatment

Table 2 Tumor characteristics

Variables		Frequency	Percentage
Site of primary tumor	Gastro-esophageal (GEJ)	15	24.6
	Body of the stomach	24	39.3
	Pylorus	22	36.1
Gross morphology by endoscopy	Polypoid (type I)	4	6.6
	Fungating (type II)	28	45.9
	Ulcer (type III)	8	13.1
	Infiltrative type (type IV)	21	34.4
Lauren's classification	Diffuse	31	50.8
	Intestinal	28	46
	Unknown	2	3.2
Lympho-vascular invasion (LVI)	Present	6	9.8
	Not present	19	31.2
	Unknown	36	59
Perineural invasion (PNI)	Present	7	11.5
	Not present	18	29.5
	Unknown	36	59
Ascites at diagnosis	Present	12	19.7
	No	49	80.3
TNM staging at presentation	I	1	1.6
	II	3	4.9
	III	17	27.9
	IV	31	50.8
	Unknown	9	14.8

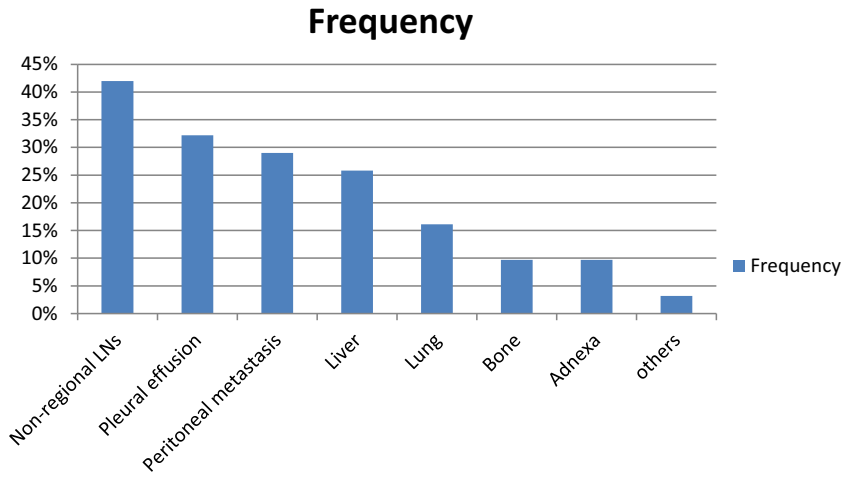

Fig. 1 Site of metastasis frequency

peripheral blood NLR as a prognostic factor in GC patients, treated at Ain Shams University, Clinical Oncology Department, between January 2015 and December 2016.

Patients and Methods

During the selected period, all cases with pathologically diagnosed gastric or gastro-esophageal cancer were included, irrespective of their stage at presentation. Patients who received any active cancer treatment prior to recruitment were excluded.

A baseline pre-treatment complete blood count (CBC) was obtained, in addition to all the routine investigations requested by standard practice, according to patients' presentation and staging.

All demographic, tumor-, and patient-related data were collected. The patients were then treated based on the standard protocols at our department.

We planned to calculate the NLR, as the ratio of the absolute neutrophil count to the absolute lymphocyte count. At the end of the trial, we planned to calculate the median NLR value, and to sub-group the patients into low and high NLR groups (below or above the median value, respectively).

Table 4 Correlations between NLR and different tumor and patients' characteristics

Variables			NLR		*p* value
			≤ 2.4	> 2.4	
Age	≤ 55	No. of patients	16	16	0.548
	> 55		15	14	
Sex	Male	No. of patients	15	16	0.448
	Female		16	14	
Smoking	Yes	No. of patients	23	24	0.408
	No		8	6	
Site of 1ry tumor	GEJ	No. of patients	8	7	0.556
	Body		12	12	
	Pylorus		11	11	
Gross morphology by endoscopy	Type I	No. of patients	3	1	0.108
	Type II		15	13	
	Type III		5	3	
	Type IV		8	13	
Lauren's classification	Diffuse	No. of patients	14	17	0.255
	Intestinal		16	12	
LVI	Yes	No. of patients	3	3	0.548
	No		11	8	
PNI	Yes	No. of patients	4	3	0.649
	No		10	8	
Presence of metastasis at presentation	Yes	No. of patients	17	14	0.549
	No		12	9	

Table 5 Correlation of NLR and presence of ascites

			NLR		*p* value
			≤ 2.4	> 2.4	
Presence of ascites	Yes	No. of patients	3	9	0.046
	No		28	21	

The primary end-point of the study was to assess the prognostic significance of pre-treatment NLR on event-free survival (EFS) and overall survival (OS).

EFS was calculated from the date of any active treatment initiation till the date of either the first progression or death. OS was calculated from the same date of diagnosis till the date of death due to any cause.

Our secondary end-point was to test the correlation of NLR with different tumor- or patient-related factors.

Results

Patients' Characteristics

At the end of inclusion, 61 patients were enrolled in the trial. The median age was 55 years. The male to female ratio was 1:1 (31 and 30 respectively). Most of the patient had good performance status ECOG 1 (62.3%) and only four patients (6.6%) were ECOG 3. Smoking was reported in 77% of patients and 21.3% of patients were diabetics (Table 1).

Tumor's Characteristics

The primary tumor location was the body of the stomach in 39.3%, pylorus in 36.1%, and GEJ in 24.6%. Most of the tumors appeared grossly as a fungating mass (type II) (45.9%). The other types, infiltrating (type IV), ulcer (type III), and polypoid (type I) represented 34.4%, 13.1%, and 6.6%, respectively. According to Lauren's classification, 50.8% were diffuse type, 46% were intestinal type, and 3.2% were unknown. Lymphovascular infiltration (LVI) was positive in 9.8%, while perineural invasion (PNI) was found in 11.5%. Half of the patients (50.8%) were stage IV at presentation. Ascites was present at presentation in 12 patients (19.7%) (Table 2).

Regarding patients with stage IV disease at presentation, 54.8% had single site of metastasis and 45.2% had multiple sites of metastasis. Site of metastasis are listed in Table 3.

The most common site of metastasis was non-regional lymph nodes, 42% of metastatic patients. Other sites of metastasis are presented in Fig. 1.

Neutrophil-Lymphocyte Ratio

The median NLR was calculated to be 2.4. Thirty-one patients had NLR ≤ 2.4 (low NLR) and 30 patients had NLR > 2.4 (high NLR).

We correlated the NLR with different patient- and tumor-related variables and there was no statistical significant difference of the NLR among different subgroups, as illustrated in Table 4. However, presence of ascites was an exception, where high NLR was associated with higher incidence of ascites compared to low NLR (30% versus 9.6%, respectively; *p* value 0.046) (Table 5).

Survival Correlations

After a median follow-up period of 8 months (range 4–20 months), the median event-free survival (EFS) of the whole population was 6 months and the median overall survival (OS) was 8 months.

In a univariate analysis using Kaplan-Meier curves, high NLR was associated with lower EFS, 5 months versus 8 months (95% CI, $p = 0.001$) (Fig. 2). Also, high NLR was associated with statistically significant worse survival of 6 months versus 9 months (95% CI, $p = 0.013$) (Fig. 3).

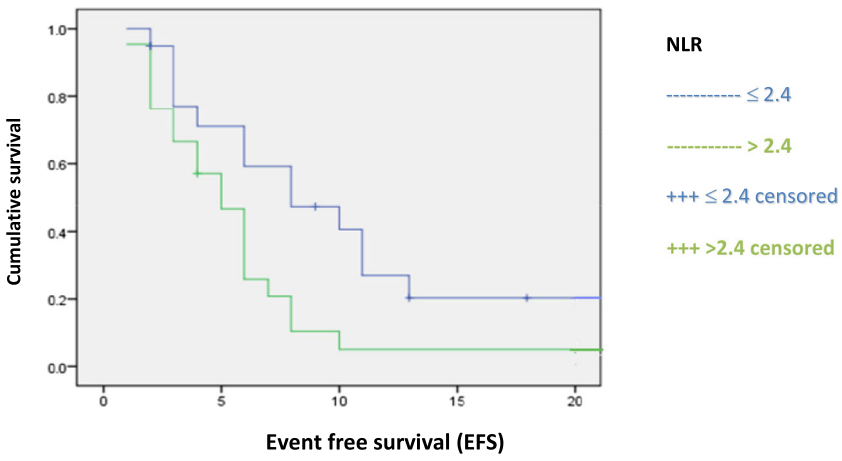

Fig. 2 Correlation between NLR and EFS (95% CI, SE 5.045–6.955, $p = 0.001$)

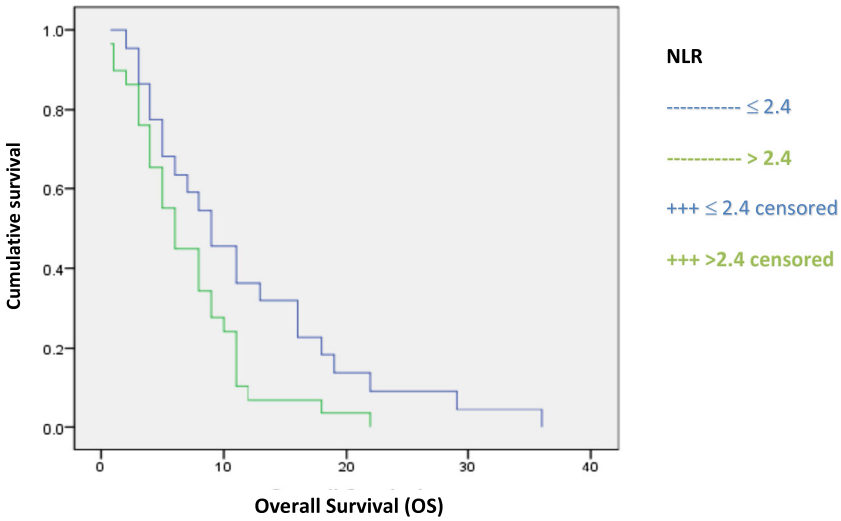

Fig. 3 Correlation between NLR and OS (95% CI, SE 5.689–10.311, $p = 0.013$)

This data was consistent in multivariate analysis considering the OS but not PFS with p value for OS ($p = 0.048$) and 0.095 for EFS (Table 6).

Discussion

Gastric cancer is an aggressive disease. In our trial, 50% of the patients presented with metastatic disease. Comparatively, stage IV patients presented 37.4% of the REGATE trial Bang et al. [11], with wide range differences worldwide—87.4% in Turkey and 27.9% in Asia/Pacific.

The commonest site of metastasis was non-regional LNs (42%), followed by pleural effusion (32.2%), and peritoneum (29%). This is similar to the data obtained from Jung et al. [12], where distant LNs represented about 74.3% of metastatic cases, followed by peritoneum (35.8%). However, our results are different from the data obtained from Tanta registry, where peritoneum was the commonest site (62.1%), followed by liver then distant LNs.

The median NLR in our trial was 2.4, which is almost the same ration obtained from other trials [6, 13]. Other trials concluded different results ranged between 2 and 4 [14–16].

Table 6 Multivariate overall survival (OS) analysis in correlation with neutrophil-lymphocyte ratio

Source	Dependent variable	Type III sum of squares	Mean square	p value
Corrected model	Overall survival	292.635(a)	73.159	.180
	Event-free survival after first line	91.210(b)	22.803	.429
Intercept	Overall survival	369.764	369.764	.007
	Event-free survival after first line	150.203	150.203	.017
Age	Overall survival	108.201	108.201	.124
	Event-free survival after first line	13.914	13.914	.443
Stage	Overall survival	75.855	75.855	.195
	Event-free survival after first line	38.112	38.112	.209
Laurens classification	Overall survival	32.091	32.091	.395
	Event-free survival after first line	.888	.888	.846
PNL	Overall survival	185.971	185.971	.048
	Event-free survival after first line	68.963	68.963	0.095
Error	Overall survival	1070.332	42.813	
	Event-free survival after first line	573.090	22.924	
Total	Overall survival	5015.000		
	Progression-free survival after first line	2011.000		
Corrected total	Overall survival	1362.967		
	Progression-free survival after first line	664.300		

There was no significant correlation between NLR and different patient- or tumor-related factors. These data go with several prognostic trials [12, 16–19].

The only factor which was associated significantly with high NLR was the presence of ascites, and according to our knowledge, this finding is reported for the first time. Furthermore, the patients who developed ascites during chemotherapy belong to the high NLR group.

High NLR was significantly associated with shorter EFS. This was similar to the conclusion of Wang et al. [20], Cho et al. [5], and Musri et al. [19].

Also, the high NLR group had lower OS compared to the low NLR group and this was similar to the data from Wang et al. [20] and Yamanaka et al. [21].

Study Limitation

This study had some limitations represented in the small sample size, as well as not performing the baseline CBC in a central laboratory.

Conclusion

The peripheral NLR can be used as a prognostic factor in GC patients, irrespective of the different tumor- and patient-related factors. High NLR is a bad prognostic marker and is associated with worse EFS and OS.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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