K Int J Health Sci. August 2023;Vol 6(1): 15-22

ORIGINAL ARTICLE

Association between hematological inflammatory markers and clinicopathological features in gastric cancer patients received adjuvant radiotherapy

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ABSTRACT

BACKGROUND*:Hematological inflammatory markers may be used as predictors for prognosis of gastric cancer. The aim of this study was to investigate the the association between pre-treatment hematological inflammatory markers and clinicopathological features in the gastric cancer patients.*

METHODS*: We retrospectively enrolled 118 patients diagnosed with gastric cancer who underwent surgery and received adjuvant chemoradiation at the Department of Radiation Oncology between July 2013 and June 2023. Clinicopathologic features such as age (≤50 and >50 years of age), sex, tumor location (cardia, corpus, antrum), T and N stage, histological type (adenocarcinoma, non-adencarcinoma), grade, lymphovascular invasion (LVI), and perineural invasion (PNI) were reviewed. Preoperative hematological inflammatory markers are neutrophil, lymphocyte, monocyte, platelet, mean platelet volume (MPV), plateletcrit, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR) were recorded.*

RESULTS*: Median age was 59 (23-85) years. Median age for men (n=89) and women (n=29) was 58 (29-85) and 61 (23-83) years, respectively. NLR, LMR, and PLR were found to be 2.8 (±1.51), 3.38 (±1.18), and 153.44 (±59.8), respectively. LMR was significantly higher in patients ≤50 years of age compared to those over 50 years (p= 0.02). While LMR was 3.26 (±1.16) in the patients ≤50 years of age, it was 3.86 (±1.15) in older ones. Neutrophil values and NLR were found moderately higher in men compared to women [5.2 (±2.05) vs. 4.3(±1.8) and 2.95 (±1.6) vs. 2.3 (±1.2), respectively] (p=0.04). There was a strong correlation between the T stage and platelet values (p= 0.006). Platelet value was found to be 167.5 (±61.3), 310.4 (±62.2), 270 (±56.1), and 275.2 (±71.2) in patients with T1, T2, T3,*

and T4, respectively. Other hematological inflammatory markers were not found to affect the clinicopathological features of the gastric cancer patients.

***CONCLUSIONS**: LMR, NLR and platelets are the hematological inflammatory markers which present relationship with clinicopathological features of the gastric cancer patients.*

***KEYWORDS:** Inflammatory markers, gastric cancer, clinicopathological features*

INTRODUCTION

Gastric cancer is the third-leading cause of cancer-related death because of diagnosis at advanced stage (1). Prognostic features affecting gastric cancer survival are tumor extension, histopathology, and metastatic lymph node status (2,3).

Since cancer mechanism is related closely to inflammation, systemic inflammatory markers have recently taken the interest of researchers with their associations with prognostic features and prognosis (3). Markers of systemic inflammation such as C-reactive protein, albumin, alkaline phosphatase, neutrophils, lymphocytes, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) were studied for their roles in inflammatory response and prediction of cancer prognosis (4-7).

In the study, we aimed to evaluate the association between hematological inflammatory markers and clinicopathological features of gastric cancer patients received adjuvant radiotherapy.

MATERIALS AND METHODS

We retrospectively enrolled 118 patients diagnosed with gastric cancer who underwent surgery and received adjuvant chemoradiation at the Department of Radiation Oncology between July 2013 and June 2023. Patients who had histologically confirmed gastric cancer, did not receive neoadjuvant treatment (chemo/radiotherapy) prior to surgery, with no other malignancy, and had complete medical records were included in the study. Patients who received neoadjuvant chemotherapy or radiotherapy, who had another malignancy (including hematological malignancies) and whose medical records were not completely available were excluded from the study. Study was approved by local ethical committee.

Tumor-node-metastasis (TNM) staging was done according to American Joint Committee on Cancer (AJCC) staging system. Clinicopathologic features such as age (≤50 and >50 years of age) (8), sex, tumor location (cardia, corpus, antrum), T and N stage, histological type (adenocarcinoma, non-adencarcinoma), grade, lympho vascular invasion (LVI), and perineural invasion (PNI) were reviewed. Preoperative hematological inflammatory markers: neutrophil, lymphocyte, monocyte, platelet, mean platelet volume (MPV), plateletcrit, NLR, LMR, and PLR were recorded.

All patients were treated with a dose of 45-50.4 Gy radiation with concurrent 5- flourourasil or capecitabine. Date of death or last follow-up time in surviving patients was recorded. Overall survival (OS) is defined as the time between the date of diagnosis and the date of death or last follow-up.

Statistical analysis

Data analysis was performed using statistical analysis with the Statistical Package for the Social Sciences for Windows (SPSS, version 22.0, Chicago, IL). Descriptive statistics were used to examine the following baseline characteristics of gastric cancers patients: age at diagnosis, sex, histology, T and N stage, tumor grade, LVI and PNI. Independent t-test was used for two variables, and the one-way analysis of variance (ANOVA) test was used for more than two variables to analyze the relationship between clinicopathological features and hematological inflammatory markers. Kaplan-Meier Log Rank test was used for comparison of survival times. The results

were accepted statistically significant when p-value was less than 0.05.

RESULTS

Median age was 59 (23-85) years. Median age for men (n=89) and women (n=29) was 58 (29-85) and 61 (23-83) years, respectively. T stage was T1 in 4 (3%), T2 in 8 (7%), T3 in 41 (35%), and T4 in 65 (55%) patients. The majority of the patient histopathology was adenocarcinoma (92%, n=108). PNI and LVI were reported in 96 (81.4%) and 109 (%92.4) patients, respectively. Nodal (N) stage was N0 in 26 (22%), N1 in 27 (23%), N2 in 18 (15%), and N3 in 47 (40%) patients, respectively. Tumor was located at antrum (50%), corpus (33%), and cardia (17%) in 59, 39, and 20 patients, respectively.

NLR, LMR, and PLR were found to be 2.8 (±1.51), 3.38 (±1.18), and 153.44 (±59.8), respectively. LMR was significantly higher in patients ≤50 years of age compared to those over 50 years (p= 0.02). While LMR was 3.26 (±1.16) in the patients ≤50 years of age, it was 3.86 (±1.15) in older ones (Table 1).

Neutrophil values and NLR were found moderately higher in men compared to women [5.2 (±2.05) vs. 4.3 (±1.8) and 2.95 (±1.6) vs. 2.3 (±1.2), respectively] (p=0.04). There was a strong correlation between the T stage and platelet values (p= 0.006). Platelet value was found to be 167.5 (±61.3), 310.4 (±62.2), 270 (±56.1), and 275.2 (±71.2) in patients with T1, T2, T3, and T4 tumors, respectively. Other hematological inflammatory markers were not found to affect the clinicopathological features of the gastric cancer patients.

Table 1. NLR, LMR and PLR values according to clinicopathological features of the patients

Variable	NLR Mean (±SD)	LMR Mean (±SD)	PLR Mean (±SD)
Age	*P=0.2*	*P=0.02*	*P=0.07*
≤50	2.44 (±0.8)	3.86 (±1.15)	134.03 (±47.7)
>50	2.88 (±1.6)	3.26 (±1.16)	158.40 (±61.8)
Sex	*P=0.04*	*P=0.06*	*P=0.2*
Female	2.3 (±1.2)	3.74 (±1.3)	142.2 (±51.4)
Male	2.95 (±1.6)	3.27 (±1.12)	157.1 (±62.1)
Histolopathology	*P=0.6*	*P=0.1*	*P=0.9*
Adeno	2.78 (±1.5)	3.33 (±1.15)	153.98 (±58)
Non-adeno	3 (±1.6)	3.96 (±1.43)	151.93 (±77)
Tumor stage	*P=0.2*	*P=0.6*	*P=0.5*
T1	2.5 (±0.95)	3.45 (±1.11)	*117.52 (*±24.3)
T2	2.13 (±0.58)	3.51 (±1.36)	*161.98 (*±51.8)
T3	3.18 (±1.99)	3.19 (±1.18)	*160.76 (*±67.6)
T4	2.65 (±1.21)	3.49 (±1.17)	*150 (±56.8)*
Grade	*P=0.6*	*P=0.5*	*P=0.9*
1	2.62 (±1.17)	3.33 (±1.32)	153.53 (±67.2)
2	2.38 (±0.39)	4.04 (±0.86)	152.34 (±29.4)
3	2.85 (±1.61)	3.35 (±1.17)	152.58 (±56.8)
LVI	*P=0.1*	*P=0.7*	*P=0.2*
Yes	2.85 (±1.56)	3.37 (±1.19)	155.33 (±60.7)
No	2.07 (±0.31)	3.53 (±1.09)	130.62 (±42.9)
PNI	*P=0.7*	*P=0.2*	*P=0.1*
Yes	2.78 (±1.6)	3.44 (±1.9)	149.8 (±59.1)
No	2.87 (±1.2)	3.14 (±1.2)	168.9 (±61.6)

NLR: Neutrophil to lymphocyte ratio, LMR: Lymphocyte to monocyte ratio,PLR: Platelet to lymphocyte ratio, LVI: Lymphovascular invasion, PNI: Perineural invasion

Median survival time for all of the patients was 49.14 (±14.1) months. Median OS in male and female patients was 65.8 (±16.6) months (95% CI: 33.3- 98.3) and 29.3 (±9.7) months (95% CI: 10.2-49.3), respectively (p= 0.035). Median OS for the patients ≤50 and >50 years was 75.5 (±33.9) months (95% CI: 9.05-141.9) and 45.3 (±11.1) months (95% CI: 23.5-67.1), respectively (p< 0.04). Patients with T3 and T4 tumors survived shorter than the others (p= 0.005). Median OS in T1-2 and T3-4 tumors was found to be 92.6 (±6.2) and 59.1 (±5.8) months, respectively (Figure 1).

OS in patients with nodal metastasis was significantly shorter (p= 0.03) (Figure 2).

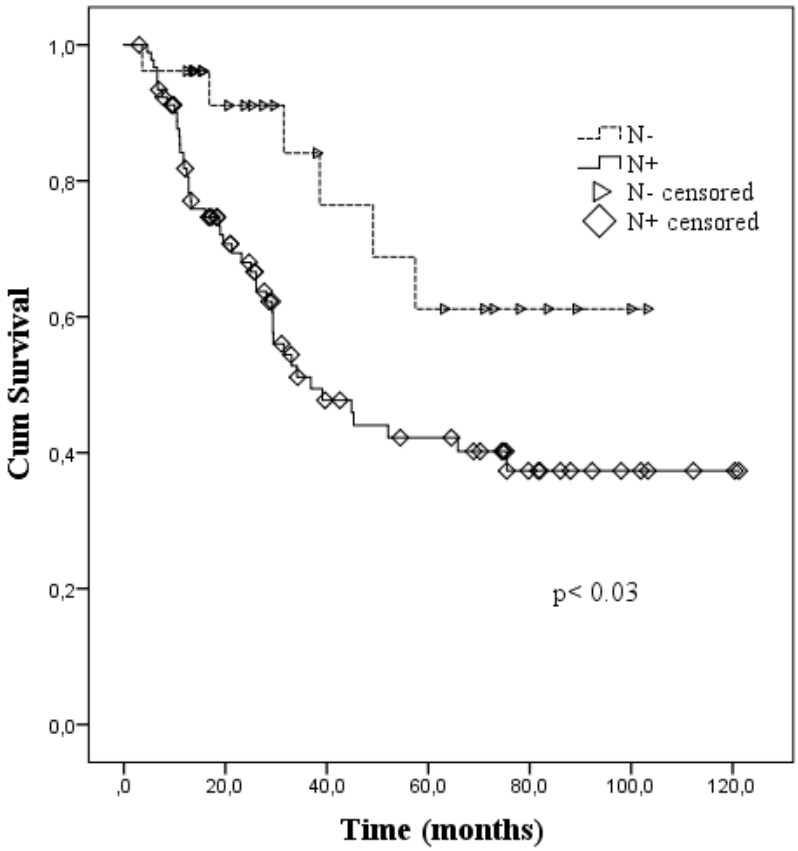

Figure 1. Overall survival according to nodal (N) status

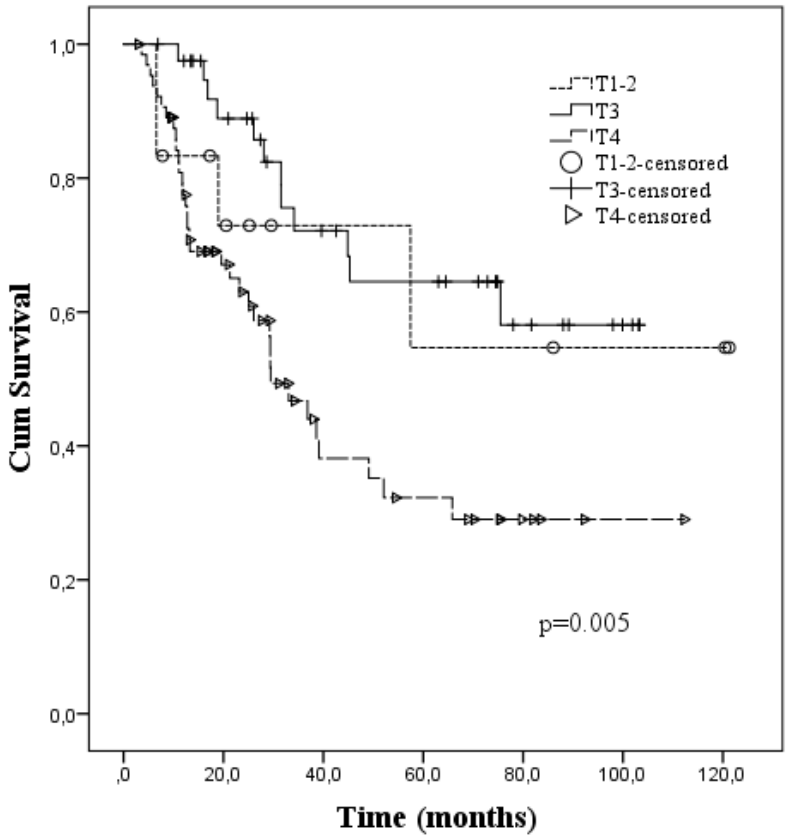

Figure 2. Overall survival according to tumor (T) stage

Grade was another significant feature affecting survival. Patients with grade 1 and 2 tumors survived longer compared to those with grade 3 tumors ($p< 0.02$). OS was not found to be affected by other clinicopathological features.

DISCUSSION

In this retrospective study, we found a relationship between pretreatment hematological inflammatory markers and prognostic features of gastric cancer patients who underwent surgery and received adjuvant radiotherapy.

Relationship between inflammation and cancer has been investigated by several researchers and a strong correlation has been conducted (4,5). Hematological inflammatory markers such as lymphocytes, monocytes, neutrophils, platelets, MPV, and plateletcrit have been shown to be associated with several malignancies (4-7, 9-11) .

Decrease in lymphocytes is an indicator of a weak immune response to malignancies and monocyte elevation is an indicator of high tumor burden in tumor

microenvironment (12), therefore, decreased LMR was reported to be associated with poor survival in several malignancies (13-15). In our study, LMR was significantly lower in older patients (>50 years) who had shorter survival compared to the young ones (≤50 years).

High NLR was reported to be associated with poor prognosis in cancer (16) and this association was well established in gastric cancers (17, 18). Neutrophils have pro-tumoral behavior resulting in angiogenesis, DNA injury, inhibition of T-cells' antitumoral activity, and induction of metastasis in contrast to the lymphocytes which establish anti-tumoral effect (19, 20). Both the increase in neutrophils and the decrease in lymphocytes result in tumoral genesis and growth (21). There was a moderate elevation in neutrophils and NLR in male patients compared to females. While the number of men in the study population is approximately three-fold of the women, this result may not be significant. The difference might be established in further studies with equal number of males to females.

Increased PLR has been reported to be a prognostic factor for poor OS and disease-free survival and associated with poor clinicopathological features in gastric cancer patients by a meta-analysis (22). Platelet formation is induced during malign transformation by the production of thrombopoietin hormone which is stimulated with a proinflammatory cytokine (interleukin 6). Thrombopoietin induces division of megakaryocytes in the bone marrow which results in platelet formation (11, 23). Tumor growth is known to stimulate and increase the platelet formation with secretion of certain factors which can lead to thrombocythemia. Both elevation in platelets and overexpression of coagulation factors by tumor cells are unfavorable prognostic markers in several malignancies (24-26). In our study, there was an increase in the platelets in patients with advanced tumor stages. But PLR was not significantly increased.

MPV, the average size of platelets, indicates the platelet production rate and stimulation, and is also an inflammatory marker and has been shown to be prognostic in locally advanced gastric cancer (9). Plateletcrit is the combination of MPV and platelets and it gives more information about platelet mass (27, 28) Plateletcrit has been reported to be a prognostic marker in lung cancer patients (10). In our study, neither MPV nor plateletcrit was found to be associated with the clinicopathological features of the gastric cancer patients.

CONCLUSION

LMR, NLR and platelets are the hematological inflammatory markers that reveal relationship with the clinicopathological features of gastric cancer patients. However, further studies with larger study population are needed to support these findings.

Acknowledgment

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

HA: Collected the data. AK: Analyzed the data statistically. HA and AK: Wrote the main manuscript text. AK: Prepared the tables and figures. HA and AK: Contributed to the design and management of the study. All authors reviewed and revised the manuscript. All authors approved of the manuscript text.

Conflicts of Interest

The authors declare no conflicts of interest.

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