

## Research Article

# Can Neutrophil-To-Lymphocyte Ratio or Platelet-To-Lymphocyte Ratio Predict Chemotherapy Response in Testicular Cancer?

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### Abstract

**Objectives:** The relationships of NLR (neutrophil lymphocyte ratio) and PLR (platelet lymphocyte ratio) with treatment response and prognosis of many types of cancer have been previously investigated. However, there is no study in the literature about the relationship of NLR and PLR with treatment response in testicular germ cell tumors (GCTs). We aimed to investigate the relationship between pre-treatment NLR and PLR values with treatment response and prognosis in patients with testicular GCT.

**Methods:** The data of 40 patients with testicular cancer (TCa) who were followed at our center between 2017-2020 and received 3-4 cycles of BEP protocol were retrospectively screened and included who met the criteria for inclusion in the study.

**Results:** Complete response (CR) to chemotherapy was obtained in 57.5% of the patients, and partial response (PR) was obtained in 35% of the patients. In comparison to the CR group, the mean NLR values were significantly higher in the non-CR group ( $p=0.02$ ). Mean PLR values were also significantly higher in the non-CR group ( $p=0.026$ ). Statistically significant positive correlations were found between tumor stage and NLR & PLR values ( $r=0.505$ ,  $p=0.001$  for NLR;  $r=0.397$ ,  $p=0.011$  for PLR). A statistically significant positive correlation was found between tumor stage and neutrophil level ( $r=0.365$ ,  $p=0.020$ ), while a statistically significant negative correlation was found between tumor stage and lymphocyte level ( $r=-0.314$ ,  $p=0.048$ ).

**Conclusion:** In the present study we found a correlation between high NLR and PLR values and low CR rates. This relationship can be supported by further studies.

**Keywords:** Chemotherapy response, NLR, PLR, testicular cancer

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Testicular germ cell tumors (GCTs) are the most common solid tumor in men aged 20–34, and its incidence has increased in recent years.<sup>[1]</sup> Testicular germ cell tumors are chemosensitive tumors. GCT is among the solid tumors with the best treatment response, with a five-year survival rate in excess of 95%. Standard treatment in patients with GCT is radical inguinal orchiectomy with/without adjuvant platinum-based chemotherapy.<sup>[2]</sup>

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are parameters derived from complete blood count which is an easily performed, widely available and inexpensive test. These indices are utilized in clinical practice due to their ability to reflect systemic inflammatory response. NLR and PLR are also used as forms of inflammatory- and immunological-based scoring methods for prognostic purposes in many cancers.<sup>[3-7]</sup> High NLR and

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PLR values have been shown to be associated with tumor aggressiveness and poor prognosis.<sup>[8-10]</sup> Systemic inflammatory response has been found to be significantly associated with tumor progression and tumor response in many malignancies, such as gastroesophageal, ovarian, lung and breast cancers.<sup>[11-16]</sup> It has been reported that high NLR and PLR values in the pre-immunotherapy period can be used as potent prognostic markers associated with poor survival in many tumor types.<sup>[17-23]</sup>

The relationships of NLR and PLR with treatment response and prognosis of many types of cancer have been previously investigated. However, there is no study in the literature about the relationship of NLR and PLR with treatment response in GCTs. The present study aimed to investigate the relationship between pre-treatment NLR and PLR values with treatment response and prognosis in patients with testicular GCT.

## Methods

Forty patients with GCT who were followed in our clinic between 2017–2020 and received 3 or 4 cycles of BEP chemotherapy protocol (bleomycin 30 mg/day 1, 8, 15/21, cisplatin 20 mg/m<sup>2</sup>/day 1-5/21, etoposide 100 mg/m<sup>2</sup>/day 1-5/21) were included in the present retrospective study. Patients with seminomatous and nonseminomatous GCT who were older than 18 years of age and whose body mass index (BMI) values were within the normal range were included in the study. Patients with chronic disease or secondary malignancies were excluded. Along with the demographic data of all patients, their height, body surface areas and complete blood count parameters were recorded. NLR and PLR were calculated with the formula: Neutrophil count (/ $\mu$ L)/Lymphocyte count (/ $\mu$ L) and Platelet count (109/L)/Lymphocyte count (/ $\mu$ L).

## Statistical Analysis

All statistical analyses were performed using SPSS version 25 (IBM, Armonk, USA). A p value of 0.05 or lower was considered statistically significant. Descriptive statistics were given as percentage and median (range or interquartile range) values. The relationships between NLR & PLR and other clinicopathological parameters was studied by non-parametric tests. Spearman correlation and regression analyses were performed to determine relationships between the variables.

## Results

The demographic and pathological characteristics of the patients are presented in Table 1. The median age of the patients was 29.5 (IQR 24.25–35.75) years. While 31 of the pa-

**Table 1.** Patients characteristics

	Seminom (n=9)	Non-seminom (n=31)	Total (n=40)
Age	31 (18-44)	29 (18-67)	29.5 (18-67)
Stage, n (%)			
1	1 (11.1)	12 (38.7)	13 (32.5)
2	5 (55.6)	8 (25.8)	13 (32.5)
3	3 (33.3)	11 (35.5)	14 (35)
S0	7 (77.7)	11 (35.5)	18 (45)
S1	2 (22.3)	17 (54.8)	19 (47.5)
S2	0	1 (3.2)	1 (2.5)
S3	0	2 (6.5)	2 (5)
Metastatic site, n (%)			
Lymph node	6 (66.6)	17 (54.8)	23 (57.5)
Retroperitoneal	4 (44.4)	14 (45.2)	18 (45)
Mediastinal	2 (22.2)	7 (22.5)	9 (22.5)
Lung	2 (22.2)	6 (19.3)	8 (20)
liver	1 (11.1)	0	1 (2.5)
Risk group, n (%)			
Good	7 (77.7)	23 (74.2)	30 (75)
Intermediate	2 (22.3)	2 (6.5)	4 (10)
Poor	-	6 (19.3)	6 (15)

tients had nonseminomatous GCT (77.5%), 9 had seminomatous GCT (22.5%). Thirteen patients had stage 1 (32.5%) and 2 (32.5%) tumors, and 14 patients had stage 3 (35%) tumors. Twenty-three patients had lymph node metastases (57.5%), 9 patients had mediastinal metastases (22.5%) and 8 patients had pulmonary metastases (20%). The vast majority of patients had S0 (45%) and S1 (47.5%) disease. In addition, 75% (n=30) of the patients were in the good (n=30), 10% (n=4) were in the intermediate and 15% (n=6) were in the poor prognostic risk group (Table 1).

In the present study, the median follow-up duration is 10 (IQR 4–20) months. While 62.5% of the patients received 3 cycles of BEP, 30% of them received 4 cycles of BEP. Complete response (CR) to chemotherapy was obtained in 57.5% of the patients, and partial response (PR) was obtained in 35% of the patients. Of the three deaths in total, two were accepted as chemotherapy-induced deaths. The remaining patient had severe tumor burden and his death was considered disease-induced death. No statistically significant difference was found between the good prognostic risk group and the combined (intermediate and poor prognostic risk) group in terms of CR and non-CR (p=0.196). Compared to the CR group, the non-CR group had significantly higher neutrophil levels (4353±1341 vs. 5470±2076, respectively, p=0.046), while lymphocyte levels were found to be significantly lower (2153±863 vs. 1614±504, respectively, p=0.027). In comparison to the CR group,

the NLR values were significantly higher in the non-CR group ( $2.27 \pm 1.44$  vs.  $3.48 \pm 1.69$ , respectively,  $p=0.02$ ) (Fig. 1). PLR values were also significantly higher in the non-CR group ( $145.31 \pm 69.80$  vs.  $193.90 \pm 59.10$ , respectively,  $p=0.026$ ) (Table 2, Fig. 2). Statistically significant positive correlations were found between tumor stage and NLR & PLR values ( $r=0.505$ ,  $p=0.001$  for NLR;  $r=0.397$ ,  $p=0.011$  for PLR). A statistically significant positive correlation was found between tumor stage and neutrophil level ( $r=0.365$ ,  $p=0.020$ ), while a statistically significant negative correlation was found between tumor stage and lymphocyte level ( $r=-0.314$ ,  $p=0.048$ ).

## Discussion

The present study investigates the effects of pre-treatment PLR and NLR with regard to the response to treatment in patients with GCT. We observed that patients with low pre-treatment PLR and NLR values had better response to treatment.

Systemic inflammation plays an important role in all stages of tumorigenesis. Inflammation can induce tumorigenesis through genetic mutations, genomic instability and epigenetic modifications. Inflammation also activates tissue

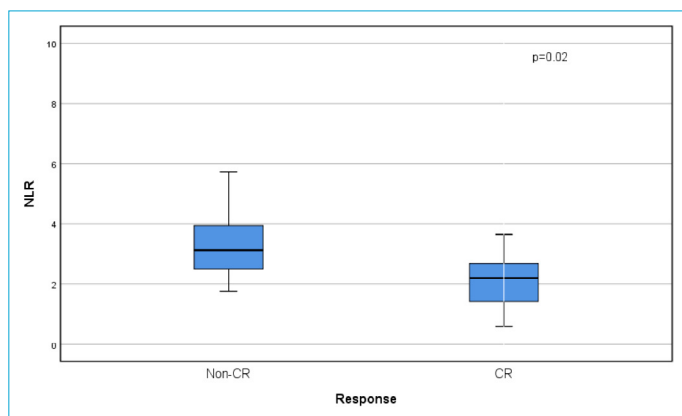
repair which induces proliferation of premalignant cells, stimulates angiogenesis, causes immunosuppression, and facilitates metastasis by creating microenvironments in which malignant cells can thrive.<sup>[24]</sup> Neutrophils and lymphocytes are crucial inflammatory mediators in many types of cancer. It has been reported that the increase in neutrophil count supports tumor growth and suppresses anti-tumor immune response.<sup>[25]</sup> Activated neutrophils suppress lymphocyte function, leading to immunosuppression and the release of enzymes with low anti-tumor activity.<sup>[26,27]</sup> It has been reported that platelets increase the invasion capacity of circulating tumor cells, trigger epithelial-mesenchymal transition, and thus, facilitate metastasis.<sup>[28,29]</sup> In the light of all this information, it can be thought that NLR and PLR scoring can be used to predict inflammatory condition.

High levels of inflammatory markers such as NLR and PLR have been used as factors reflecting high prognostic risk and low chemotherapy responses in various solid tumor types, including breast, gastroesophageal and colorectal cancer.<sup>[30-34]</sup> Similarly, high NLR, PLR and neutrophil levels and low lymphocyte levels were found to be high prognostic risk factors in the present study. While progression-free survival (PFS) and overall survival (OS) were used as endpoints in similar studies, the present study was based on radiological responses to chemotherapy. In line with the present study, higher rates of CR were observed in breast cancer patients with low NLR and PLR values.<sup>[16]</sup> In agreement with our results, previous studies observed that increased NLR and PLR values resulted in weaker response to chemotherapy in patients with advanced gastric cancer.<sup>[34]</sup>

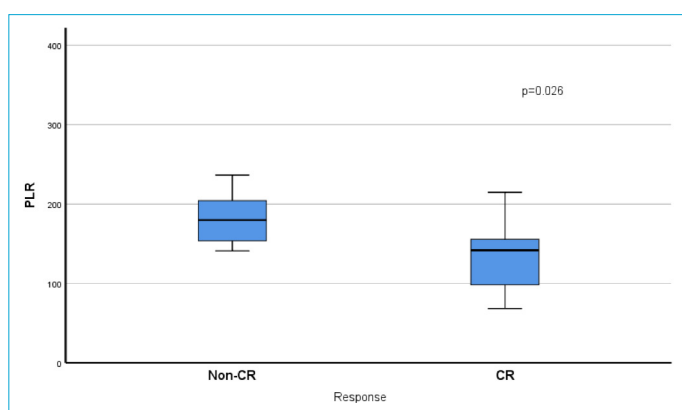
Patients with normal BMI values were included in the present study in order to prevent obesity from being a confounder.<sup>[35]</sup> This added positive value to the present study. It should be noted that a previous similar study, determined no statistically significant positive correlations between seminomatous testicular GCT stage and NLR, PLR and neutrophil levels.<sup>[36]</sup> However, in the present study, a positive correlation was found between tumor stage and these inflammatory markers in seminomatous and non seminomatous GCT.

The present study is valuable in that it is the first study in the literature evaluating NLR and PLR in the context of treatment response in patients with GCT. The limitations of the study were that our study group was relatively small and heterogeneous, in addition to the fact that the majority of patients had early stage tumors. Another limitation of the study was that the study period was not long enough to identify PFS and OS data.

Inflammatory biomarkers have been used to predict endpoints such as PFS and OS after chemotherapy or immuno-



**Figure 1.** Association between NLR ratio and Response.



**Figure 2.** Association between PLR ratio and Response.

therapy and response to treatment in many types of cancer. Studies on the use of inflammatory biomarkers in GCT were relatively few. The present study found a correlation between high NLR and PLR values and low CR rates. This relationship can be supported by further studies.

#### Disclosures

**Ethics Committee Approval:** This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board (Number: 2021/115).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – S.K., I.K., O.A., O.B.Ç.K.; Design – S.K., I.K., O.A., O.B.Ç.K.; Supervision – S.K., I.K., O.A., O.B.Ç.K.; Materials – S.K., I.K.; Data collection &/or processing – S.K., I.K.; Analysis and/or interpretation – S.K., I.K., O.A., O.B.Ç.K.; Literature search – S.K., I.K.; Writing – S.K.; Critical review – O.A., O.B., Ç.K.

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