The clinical value of complete blood count-based immun parameter in predicting testicular cancer pathology and prognosis

Testis kanseri patolojisini ve prognozunu öngörmede tam kan sayımına dayalı immün parametrenin klinik değeri

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Abstract

Aim: The management of testicular cancer (TC) requires more specific and applicable biomarkers. We aimed to determine the ability of complete blood count (CBC) based inflammatory markers to predict tumor pathology and prognosis in TC.

Methods: Patients who underwent inguinal orchiectomy for testicular germ cell tumors (TGCTs) at our hospital between January 2011 and December 2022 were included in the study. The medical records of patients with pathologically confirmed TC, including demographics, preoperative tumor markers, preoperative CBC, tumor characteristics, pathological outcomes, postoperative follow-up, and survival outcomes, were retrospectively collected. CBC-based inflammatory markers were compared between seminomatous and non-seminomatous TGCTs. To determine the independent prognostic significance of survival, the data were analyzed and fitted to the multivariate Cox proportional risk regression model.

Results: The median follow-up was 48 (1-140) months. In our chord, 69 patients had seminomatous TGCTs (Group 1), and 66 had non-seminomatous TGCTs (Group 2). The median ages of Groups 1 and 2 were 35 (22-74) years and 31 (21-72) years(p<0,05). The median platelet count (PC) was 238 (136-377) $10^3/mm^3$ in Group 1, and 260,5 (158-414) $10^3/mm^3$ in Group 2 (p<0.05). The median neutrophil count (p=0.75), monocyte count (MC) (p=0.762), lymphocyte count (LC) (p=0.726), neutrophil-to-lymphocyte ratio (p=0.128), platelet-to-lymphocyte ratio (p=0.201), and lymphocyte-to-monocyte ratio (p=0.782) there was no statistically significant difference between seminomatous and non-seminomatous TGCTs. A higher median systemic immune-inflammation index (SII) was statistically significantly associated with non-seminomatous TGCTs. Multivariate Cox regression analysis revealed that high PC and MC values and a low LC value were independently correlated with worse overall survival.

Conclusions: High PC and SII levels are associated with non-seminomatous TGCTs. However, SII is not associated with survival outcomes. Unlike the remaining parameters, high PC and MC and low LC were found to have independent prognostic effects on worse overall survival.

Keywords: Inflammation mediators; pathology; testicular cancer

Öz

Amaç: Testis kanserinin (TK) yönetimi daha spesifik ve uygulanabilir biyobelirteçler gerektirir. Tam kan sayımı (TKS) bazlı inflamatuar belirteçlerin TK'da tümör patolojisini ve prognozunu tahmin etme yeteneğini belirlemeyi amaçladık.

Yöntemler: Çalışmaya Ocak 2011 ile Aralık 2022 tarihleri arasında hastanemizde testis germ hücreli tümör (TGHT) nedeniyle inguinal orşiektomisi uygulanan hastalar dahil edildi. Patolojik olarak doğrulanmış TK'lı hastaların demografik özellikleri, ameliyat öncesi tümör belirteçleri, ameliyat öncesi TKS, tümör özellikleri, patolojik sonuçlar, ameliyat sonrası takip ve hayatta kalma sonuçları dahil olmak üzere tıbbi kayıtları geriye dönük olarak toplandı. TKS bazlı inflamatuar belirteçler seminomatöz ve seminomatöz olmayan TGHT'ler arasında karşılaştırıldı. Genel sağkalım ve hastalıksız sağkalımın ön gören bağımsız prognostoik faktörleri belirlemek için Cox regresyon analizleri kullanılmıştır.

Bulgular: Ortalama takip süresi 48 (1-140) aydı. Bizim çalışmamızda 69 hastada seminomatöz TGHT (Grup 1), 66 hastada ise seminomatöz olmayan TGHT (Grup 2) vardı. Grup 1 ve 2'nin ortanca yaşları sırasıyla 35 (22-74) ve 31 (21-72) yıldı(p<0,05). Ortanca trombosit sayısı (TS) Grup 1'de 238 (136-377) $10^3/mm^3$, Grup 2'de 260,5 (158-414) $10^3/mm^3$ idi (p<0,05). Ortanca nötrofil sayısı (p=0,75), monosit sayısı (MS) (p=0,762), lenfosit sayısı (LS) (p=0,726), nötrofil-lenfosit oranı (p=0,128), trombosit-lenfosit oranı (p=0,201) ve lenfosit/monosit oranı (p=0,782) seminomatöz ve seminomatöz olmayan TGHT'ler İstatistiksel olarak anlamlı fark yoktu Seminom olmayan TGHT grubunda Sistemik İnflamatuvar indeks(SII) istatiksel olarak anlamlı derecede daha yüksekti(p<0,05). Çok değişkenli Cox regresyon analizi, yüksek TS ve MS değerleri ile düşük LS değerinin bağımsız olarak daha kötü genel sağkalım ile ilişkili olduğunu ortaya çıkardı.

Sonuç: Yüksek TS ve SII seviyeleri seminom dışı TGHT'lerle ilişkilidir. Ancak SII hayatta kalma sonuçlarıyla ilişkili değildir. Geri kalan parametrelerin aksine, yüksek TS ve MS ile düşük LS'nin, daha kötü genel sağkalım üzerinde bağımsız prognostik etkilere sahip olduğu bulundu.

Anahtar Sözcükler: İnflamasyon mediyatörleri; patoloji; testis kanseri

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INTRODUCTION

Testicular cancer (TC) is a rare condition, representing 1% of adult neoplasms and 5% of urological neoplasms (1). However, among young adult men (aged 15-34 years), TC is the most common solid malignancy (2,3). More importantly, the incidence of TC has exhibited a notable increase over the past 40 years (4).

TC manifests itself in a very different manner, both clinically and pathologically. Testicular germ cell tumors (TGCTs), which comprise approximately 95% of all testicular tumors, are the most common type of TC (5). Histologically, they are classified into seminomatous and non-seminomatous TC. In TGCTs, non-seminoma is predominant in the third decade and seminoma in the fourth decade (6).

The treatment of TC is based on histopathological findings and tumor stage. Inguinal orchiectomy is an effective treatment for localized testicular tumors. However, regarding patient prognosis and oncological therapies, there are some differences between seminomatous and non-seminomatous TCs. Therefore, it is crucial to be aware of potential variations that may arise during the postoperative follow-up of the disease.

Several biomarkers, such as alpha-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase, are currently employed in clinical practice to predict and differentiate seminomatous and non-seminomatous TC. According to the International Germ Cell Consensus Classification, the clinical use of these biomarkers is mandatory for predicting both the diagnosis and prognosis (7). However, the specificity of these biomarkers is very low (8). Therefore, more specific and cost-effective biomarkers are required in the clinical management of TC.

While the immune system creates an immune response against pathogens, it also generates an immune response against tumor cells. The immune response against tumor cells causes a systemic inflammatory response, resulting in increased levels of inflammatory biomarkers in the peripheral circulation (9). There are some hypotheses that can affect the immune response against tumor cells. One of these hypotheses is immunological desensitization, through which some tumor cells may be able to evade the response of the immune system. The histological types of tumor cells are also effective parameters in determining the level of inflammatory response since they differ in terms of antigenic features. In addition, the level of immune response is valuable in the prediction of tumor biology (8,10).

The relationship between various complete blood count (CBC)-based inflammatory markers and cancer prognosis has recently been described (10,11,12). However, there is a need for the clear identification of CBC-based inflammatory markers in TC to assist clinicians in the treatment of the disease and improve disease management. In addition, the feasibility of implementing precision medicine can be facilitated by the widespread and reliable use of these biomarkers. To evaluate the immune response, the neutrophil-to-lymphocyte (NLR), plate-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), derived from CBC parameters, are utilized. In addition, the systemic immune-inflammation index (SII), which is calculated by multiplying the platelet count (PC) and NLR, was introduced in 2014 (13). These parameters are advantageous due to their cost-effective and easy-to-calculate nature.

There is limited data in the literature on the role of SII and other CBC-based parameters in predicting the histopathology and prognosis of TC. Therefore, this study aimed to investigate the ability of CBC-based inflammatory markers to predict tumor pathology and prognosis in individuals with TC.

MATERIAL AND METHODS

Patients aged 18 years and older who underwent inguinal orchiectomy for TGCTs at our hospital between January 2011 and December 2022 were included in the study. This study was approved by Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa (date: 13.06.2023, decision no: 712209). The diagnosis of TGCTs was confirmed pathologically, and both seminomatous and non-seminomatous TGCTs were included. The medical records of the patients, including demographics, preoperative tumor markers, preoperative CBC parameters, tumor characteristics, pathological outcomes, postoperative follow-up, and survival outcomes, were collected retrospectively. Patients with metastases at the time of diagnosis were excluded. Other exclusion criteria were missing data,

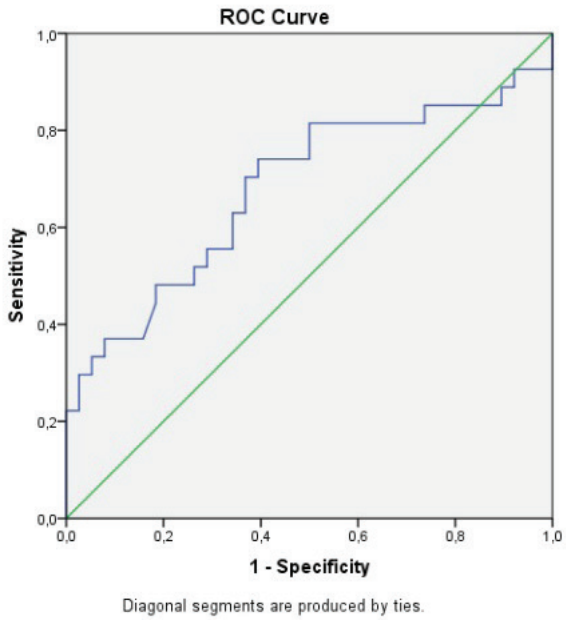

Figure 1. Receiver operating characteristic (ROC) curve analysis of systemic immune-inflammation index (SII) and platelet count for the differentiation of seminomatous and non-seminomatous testicular germ cell tumors.

the presence of any other malignancy, acute infections, and immune deficiency disease.

To minimize the effect of surgical inflammation, the peripheral blood samples of the patients were collected before inguinal orchiectomy. CBC-based inflammatory markers, including NLR, PLR, LMR, and SII, were calculated. SII was calculated using the following formula: PC x NLR (14,15).

A single pathologist (IG) analyzed all pathological specimens according to the guidelines of the American Joint Committee on Cancer (16). Systemic staging was performed using thorax and abdomen contrast-enhanced computed tomography (CT) images. Before surgery, informed consent was obtained from all patients. Following the recommendations of the European Association of Urology guidelines, tumor marker measurements, and chest/abdominal CT scans were performed on all patients. Follow-up data were collected, and survival and oncological outcomes were analyzed during patient visits.

Statistical Analyses

Statistical Package for the Social Sciences package program version 23.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test and the Mann-Whitney U-test were used to evaluate the data for categorical and continuous variables, respectively. The statistically significant parameters in univariate analysis were further evaluated using multivariable analysis. To determine the independent prognostic significance of survival, the data were analyzed and fitted to the multivariate Cox proportional risk regression model. Statistical significance was accepted as a p-value of <0.05

RESULTS

Inguinal orchiectomy was performed on 148 patients from January 2011 to December 2022. After excluding 13 patients who did not meet the inclusion criteria, 135 patients were enrolled in the study. In our cohort, 69 patients had seminomatous TGCTs (Group 1), and 66 had non-seminomatous TGCTs (Group 2). The median ages of Groups 1 and 2 were 35 (22-74) years and 31 (21-72) years, respectively(p<0,05). A total of 13 patients (9.6%) died during the median 48 (1-140) months of follow-up. The remaining demographic and clinicopathological data of the patients are presented in Table 1.

CBC-based inflammatory markers were evaluated in Group 1 and Group 2. The median PC was 238 (136-377) $10^3/mm^3$ in Group 1 and 260,5 (158-414)$10^3/mm^3$ in Group 2 ($p < 0.05$). The median neutrophil count (NC) ($p = 0.75$), monocyte count (MC) ($p = 0.762$), lymphocyte count (LC) ($p = 0.726$), NLR ($p = 0.128$), PLR ($p = 0.201$), and LMR ($p = 0.782$) 'There was no statistically significantly differ between the seminomatous and non-seminomatous TGCT groups. A higher median SII was statistically significantly associated with non-seminomatous (Table 2**).**

Receiver operating characteristic curve analysis was performed to determine the ability of SII and PC to differentiate between seminomatous and non-seminomatous TGCTs. Accordingly, the sensitivity and specificity were determined to be 77% and 45%, respectively, for SII and 77% and 40%, respectively, for PC (shown in Figure 1).

The multivariate Cox regression analysis conducted by adjusting the remaining clinical and pathological variables revealed that PC ($p = 0.009$), LC ($p = 0.014$), and MC ($p = 0.007$) were independently correlated with poor overall survival but not correlated with me-

Table 1. Demographic and clinicopathologic features of patients

	Seminoma (*n* = 69)	Non-seminoma (*n* = 66)	p value
Age, years, median (min–max)	35 (22–74)	31 (21–72)	<0,05
Side, overall (%)			0,945
Right	37 (53,6)	35 (53)	
Left	32 (46,4)	31 (47)	
Stage*, overall (%)			0,167
I (A,B,S)	45 (65,2)	52 (78,8)	
II (A,B,C)	18 (26,0)	12 (18,2)	
III (A,B,C)	6 (8,8)	2 (3)	
Preop LDH (U/L), median (min–max)	260 (0-11148)	226 (0-3335)	0,295
Preop AFP (U/mL), median (min–max)	3,95 (0-39781)	3,8 (0-12692)	0,918
Preop HCG (mIU/mL), median (min–max)	2,49 (0-19504)	2,3 (0-12726)	0,92
Tumor size, cm, median (min–max)	4,2 (0,6-15,09	3,85 (0,4-9,60)	0,127
Follow up, month, median (min–max)	51 (1-111)	46,5 (1-140)	0,418

Data were expressed as median (range) or number (percentage) whenever appropriate. The statistical significance limit of all evaluations was accepted as p <0.05. LDH: Lactate dehydrogenase, AFP: Alpha-fetoprotein, HCG: Human chorionic, Min: Minimum, Max: Maximum, n: Number, %: percentage.

*Prognostic groups for testicular cancer (UICC, 2016, 8th edn.).

tastasis-free survival. Table 3 shows the results of the multivariate analysis of the parameters determined to be statistically significant in the univariate analysis.

DISCUSSION AND CONCLUSION

This study revealed that PC and SII could be used to distinguish between seminomatous and non-seminomatous TGCTs. Unlike the remaining parameters, PC, LC, and MC were found to have an independent prognostic effect on overall survival. The presence and effects of a cancer-related systemic immune inflammatory response have been investigated in many types of urological cancers; however, research on TC is limited.

The immune system plays a dual role in the tumor microenvironment, involving both oncogenesis and anti-oncogenesis. The association between cancer and inflammation has also been well documented (9,17,18). The immune system influences the development and progression of cancer cells. Recent research has revealed how tumor microenvironmental inflammation influences the growth and survival of tumor cells. The cells of the immune system are actively involved in each of these processes. Thus, it is possible to acquire more knowledge about tumor biology through immune system-related cell measurements.

Recently, researchers have investigated the utility of SII, which is easily calculated using peripheral LC, NC, and PC, as a prognostic predictor in urological cancers (9). SII reflects the relationship between the immune response and host inflammation (19). In a retrospective study, Imamoglu et al. reported the role of SII and other CBC-based inflammatory markers in predicting TC stage (20). They detected a significant association between high-stage TC and high SII. In a meta-analysis including a total of 833 patients with TC from six cohorts, high SII levels were reported to be associated with lower overall survival and progression-free survival (21). Another meta-analysis covering 22 articles showed the predictive role of SII for poorer overall survival in many urological and non-urological cancers (22). Additionally, not only overall survival but also progression-free survival and cancer-specific survival have been found to be related to high pretreatment SII levels (23). SII can be affected by various clinical conditions. Therefore, the findings of our study were unable to prove the predictive value of SII in the context of TC. However, we determined that a high SII value might be a marker for non-seminomatous TC.

Platelets have a protective effect on tumor cells against the anti-tumor immune response (24), leading to the protection of the adhesion and invasion func-

Table 2. Markers of inflammation ratios by stages

	Seminoma (n = 69)				Non-seminoma (n = 66)				
	Whole group	Stage I	Stage II-III	p value*	Whole group	Stage I	Stage II-III	p value*	p value**
Neutrophil count, (10^3/mm^3), median (min–max)	5,3 (1,4-16)	5,2 (1,4-16)	4,3 (1,8-8,4)	0,677	5,7 (0,6-16,3)	5,75 (0,6-16,3)	5,5 (3,6-10,4)	0,925	0,075
Platelet count, (10^3/mm^3), median (min–max)	238 (136-377)	251 (136-377)	224,5 (159-340,5)	0,301	260,5 (158-414)	265,5 (158-414)	245,5 (187-374)	0,409	<0,05
Monocyte count, (10^3/mm^3), median (min–max)	0,6 (0,1-1,6)	0,6 (0,3-1,6)	0,55(0,1-1,1)	0,468	0,6 (0,1-2,4)	0,6 (0,1-2,4)	0,5 (0,2-0,8)	0,14	0,762
Lymphocyte count, (10^3/mm^3), median (min–max)	1,8 (0,5-6,4)	2 (0,5-6,4)	1,65 (1-3,4)	0,48	1,8 (0,5-3,6)	1,8 (0,6-3,6)	1,45 (0,5-3,25)	0,076	0,726
NLR, median (IQR 25–75%)	2,6 (1,7-3,5)	2,6 (0,4-13,3)	2,6 (1,13-5,43)	1	2,9 (2,3-4,5)	2,8 (0,26-16,3)	3,5 (1,45-18,0)	0,239	0,128
PLR, median (IQR 25–75%)	137,1 (101,6-166,7)	137,1 (45,4-374)	136,8 (60-213)	0,97	140,9 (105-198,6)	131,8 (68,7-481,5)	181 (63-374)	0,239	0,201
LMR, median (IQR 25–75%)	3,07 (1,3-4,3)	3,1 (1-23)	3 (1,6-10)	0,668	3,3 (2,2-4,2)	3,4 (0,85-17)	3,2 (1,5-5,24)	0,857	0,782
SII, median (IQR 25–75%)	651,9 (373,8-1024,2)	695,3 (118,4-2654)	567 (202,5-1183,4)	0,641	796,1 (524,5-1250,7)	769 (41,2-5150,8)	984,7 (339,3-3366)	0,415	<0,05

Data were expressed as median (range) or number (percentage) whenever appropriate. The statistical significance limit of all evaluations was accepted as p <0.05.

NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, LMR: Lymphocyte monocyte ratio, SII: Systemic inflamation index, IQR: Interquartile range. Min: Minimum, Max: Maximum, n: Number, %: percentage.

*Analysis according to stages within the groups.

**Analysis according to groups.

Table 3. Multivariable cox regression analysis for overall survival

	Overall Survival		
	HR	CI (95%)	p value
Platelet Count	1,031	1,008 - 1,056	0.009
Lymphocyte Count	0,005	0,00 - 0,350	0.014
Monocyte Count	27,682	2,527 - 303,287	0.007
PLR	0,976	0,948 - 1,004	0.089
LMR	1,242	0,881 - 1,752	0.216
SII	1	0,999 - 1,001	0.559

The statistical significance limit of all evaluations was accepted as p <0.05. Abbrevations: HR, Hazard ratio; CI, Confidence interval; PLR, platelet to lymphocyte ratio; LMR, Lymphocyte to monocyte ratio; SII, sytstemic inflamation index

tion of circulating tumor cells. Studies based on in vitro models have also reported growth factor secretion from platelets (25). In clinical practice, Imamoglu et al. showed the valuable role of PLR in the differentiation of stage 1 and advanced non-seminomatous TC cases [20]. In another study, PLR was found to be significantly higher in patients with pT3 TC than in pT1 and pT2 cases (26). However, there was no statistically significant difference between the patients with pT1 and pT2 TC. In our study, PC was associated with poor overall survival in TGCTs. This may be related to the oncogenic effect of platelets in the cancer microenvironment. Additionally, a high PC value may be a marker for the prediction of prognosis in non-seminomatous TC.

Neutrophils and lymphocytes are key elements of the inflammatory response in many types of cancer. Lymphocytes are directly related to the host's immune response to cancer (27). In cancer pathways, they also activate cell death and inhibit tumor cell proliferation

and migration. Thus, the suppression of lymphocyte function by activated neutrophils causes lower antitumor activity (27). Based on these findings, it has been considered that LMR can contribute to the clinical approach. Neutrophils can stimulate endothelium and parenchymal cells, which helps circulating tumor cells disseminate (28). In the cancer microenvironment, neutrophils secrete inflammatory mediators and angiogenic proteins, leading to cancer growth and the dissemination of cancer cells. In particular, tumor-associated neutrophils are crucial to the biology of cancer. It has been demonstrated that neutrophils support the development of tumors and inhibit the antitumor immune response. Additionally, neutrophils and macrophages secrete growth factors, such as epidermal growth factor, vascular endothelial growth factor, and interleukin-6, which affect the tumor microenvironment (29). From a clinical perspective, there are valuable studies in the literature investigating neutrophils and lymphocytes in patients with TC. Herraiz-Raya et al. reported that a neutrophil count of >8,000 mL was related to high progression and mortality rates (30). Another study also demonstrated the significance of NLR changes during anticancer therapy as a predictor of treatment efficacy (14). Additionally, it was emphasized that NLR could differentiate stage 1 TC from advanced TC stages only in individuals with seminomatous testicular tumors (16). However, there are some studies demonstrating the limited capacity of these labile parameters for clinical use (5). These studies suggest that NC is a parameter affected by many factors; therefore, it cannot have a predictive role in cancer prognosis. In our study, unlike LMR, NC, and NLR, LC was found to be associated with poor overall survival in TGCTs.

There is very limited research investigating the predictive value of MC in TC. One study demonstrated the association between a high MC value and unfavorable prognosis in testicular diffuse large B-cell lymphoma (31). However, there is a lack of data concerning MC in TGCTs. Our study provided evidence of a worse prognosis in patients presenting with high MC values.

Our study had certain limitations. First, it had a retrospective, non-randomized, and single-center design. Second, our cohort did not include individuals with non-germ cell tumors of the testis. Third, although our sample included TGCTs, there are different clinicopathologic features of these cases that may have affected the values of CBC-based inflammatory parameters. Lastly, the timing of blood sampling and any other clinicodemographic factors may have influenced the findings of the study.

This study revealed that high PC and SII levels were independently associated with non-seminomatous TGCTs. However, SII was not associated with survival outcomes. Unlike the remaining parameters, high PC and LC values and a low MC value were found to have independent prognostic effects on worse overall survival

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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