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ORIGINAL ARTICLE

Preoperative Systemic Inflammation Response Index is Associated with Stage I Non-Seminoma Testicular Germ Cell Tumors: A Retrospective Pilot Study

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Abstract

Introduction: Testicular cancer accounts for 1% of all male neoplasms and 95% of cases are testicular germ cell tumors (TGCT). There are studies investigating the relationship between hematological inflammatory markers and testicular cancer. We aimed for the 1st time to investigate whether there is an association between Systemic Inflammation Response Index (SIRI) and clinical Stage 1 TGCT.

Methods: A total of 60 patients who underwent radical inguinal orchiectomy because of testicular mass between June 2019 and December 2020 were included. Age, preoperative serum alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), lactate dehydrogenase (LDH) levels and whole blood cell counts, tumor stage, and tumor size of the patients were recorded. Pre-operative neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), Systemic Immune Inflammation Index, and SIRI were compared to preoperative serum AFP, hCG, and LDH levels between seminoma (n=27) and non-seminoma (n=33) TGCT groups.

Results: No statistically significant difference was found between two groups in terms of tumor size, LDH level and tumor side, NLR, PLR, and Systemic Immune Inflammation Index ($p>0.05$). SIRI, serum AFP, and HCG levels were significantly higher in non-seminoma group ($p=0.006$, $p=0.001$, and $p=0.005$, respectively). In multivariate analysis, it was determined SIRI over 0.985 is associated with non-seminoma TGCT pathology (OR=5.662, 95% CI=1.284–24.966, $p=0.022$).

Discussion and Conclusion: In this pilot study, it was revealed that pre-operative SIRI is associated with non-seminoma TGCT. We believe it is important to explore the utility of SIRI in the differential diagnosis of TGCT in further studies.

Keywords: Cancer; inflammation; systemic inflammation response index; testicular germ cell tumor.

Testicular tumors accounts for 1% of all male neoplasms in the Western societies[1]. 95% of cases are testicular germ cell tumors (TGCT). TGCTs are divided into two: seminoma and non-seminoma[2]. Radical inguinal orchiectomy and pathological evaluation are recommended to confirm the diagnosis of cancer in case of suspicious testicular masses[1]. The differential diagnosis of the tumor type is extremely important as it will guide the post-operative follow-up and additional treatment plan[3]. Incorrect pathological diagnosis causes inadequate and improper disease management. Pre- and post-operative serum alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and

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lactate dehydrogenase (LDH) levels should be determined to support the diagnosis of TGCT and facilitate differential diagnosis[1]. However, the sensitivity of these serum markers is low and they have high false-positive rates. Furthermore, normal range of serum tumor markers do not rule out the diagnosis of TGCT[4]. Therefore, the search for an ideal biomarker for TGCT still continues[5,6].

Systemic inflammation has a role in cancer development[7]. Systemic inflammatory response can be monitored by various parameters calculated by blood cell count such as neutrophils, lymphocytes, monocytes, platelets, and their association with various urological malignancies have been investigated[8,9]. In 2016, Qi et al.[10] presented systemic inflammation response index (SIRI) based on peripheral monocyte, neutrophil and lymphocyte counts. This index reflects the state of systemic inflammation. In addition, SIRI is associated with many types of cancer[11-15]. In this pilot study, the aim was to investigate whether there is an association between SIRI and clinical Stage 1 TGCT.

Materials and Methods

After obtaining approval of Ankara City Hospital Ethics Committee (No: E1-20-1436), the data of 78 patients who underwent radical inguinal orchiectomy because of testicular mass between June 2019 and December 2020 were retrospectively analyzed. This study was conducted in accordance with the Declaration of Helsinki. Patients' age, preoperative serum AFP, hCG, LDH levels, and pre-operative complete blood cell counts including monocyte, neutrophil, lymphocyte and platelet values, tumor stage, and tumor size were recorded. The staging was performed according to the International Union Against Cancer 2016 TNM classification[1]. Patients with surgical pathology of TGCT according to TNM classification and clinical Stage 1 were included in the study. According to pathological examination, the patients were divided into two: seminoma and non-seminoma. Contrast-enhanced chest, abdomen, and pelvis computed tomographies were performed before discharge to exclude metastatic disease. A total of 18 patients with stromal tumors of the testis (2), testicular mass lesions considered to be the metastasis of another tumor (1), metastatic testicular cancer (2), infectious or inflammatory masses (2), active or chronic any infection (1), chronic inflammatory/rheumatic disease (1), hematological disease (1), patients receiving immunosuppressive agents (2), and patients with missing data (6) were excluded from the study. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were calculated. Systemic Immune Inflammation Index (SII) was calculated by: neutrophil x platelet/lymphocyte count[9]. SIRI was calculated by: neutrophil x monocyte/lymphocyte count[10]. Preoperative NLR, PLR, SII, and SIRI were compared to preoperative serum AFP, hCG, LDH levels, and seminoma and non-seminoma groups.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), v 22.0 (SPSS Inc. Chicago, USA) was used for the statistical analysis. For the descriptive statistics, while categorical variables were presented as numbers and percentages, continuous variables were presented as median (min-max). The suitability of continuous variables to normal distribution was evaluated using histogram and probability charts, and Kolmogorov–Smirnov analytical method. Student's t-test was used for the comparative analysis between groups, in case of the data of continuous variables showed normal distribution as a result of normality. If it does not show normal distribution, Mann–Whitney U test was used. The Chi-square test was used for comparing of categorical variables between independent groups. The relationship of SIRI between AFP and HCG was assessed by Spearman correlation analysis. The ability of SIRI to predict seminoma and non-seminoma was evaluated by Receiver Operating Characteristic (ROC) curve analysis and Area Under Curve. Youden index was used to calculate cutoff value. Multivariate logistic regression analysis (MVA) was used to reveal the association between clinical variables and non-seminoma TGCT. 95% Confidence interval and odds ratio (OR) were given as a result of MVA. P value under 0.05 was considered statistically significant.

Results

Sixty patients who met the inclusion criteria were included. Table 1 shows patients' pre-operative characteristics. The median age in seminoma (n=27) and non-seminoma (n=33) groups was 38 (20–85) and 30 (18–67) years, respectively, and the difference was statistically significant (p=0.02). There was no statistically significant difference between groups in terms of tumor size, LDH level, and tumor side (p>0.05). Serum hCG and AFP levels were significantly higher in the non-seminoma group (p=0.005 and p=0.001, respectively). While there was no statistically significant difference between groups regarding NLR, PLR, and SII, SIRI was significantly higher in the non-seminoma group (p=0.006). The cutoff value of SIRI according to Youden Index with ROC curve analysis in predicting seminoma and non-seminoma was reported to be 0.985 (sensitivity 71%, specificity 70.4%, p=0.001) (Fig. 1).

Table 1. Preoperative characteristics of the patients

	Seminoma (n=27)	Non-seminoma (n=33)	p
Age, years (min-max)	38 (20–85)	30 (18–67)	0.018
Tumor size, cm (min-max)	5 (1.5–15)	5 (1.5–16)	0.736
hCG, mUI/mL (min-max)	1 (0.1–92)	4 (0.1–94786)	0.005
AFP, ng/mL (min-max)	2.31 (1–201)	21.6 (0.9–31310)	0.001
LDH, U/L	239 (137–2435)	242.5 (159–3424)	0.382
SIRI	0.87 (0.32–2.44)	1.21 (0.39–5.42)	0.001
NLR	1.94 (1.04–5.95)	2.49 (0.55–5.5)	0.067
PLR	132.02 (45.65–265.66)	123.05 (39.31–244.62)	0.726
SII	500.03 (109.11–1857.38)	674.53 (123.27–2660.52)	0.11
Tumor side, n (%)			0.466
Left	13 (48.1)	19 (57.6)	
Right	14 (51.9)	14 (42.4)	

hCG: Human chorionic gonadotropin; AFP: Alpha-fetoprotein; LDH: Lactate dehydrogenase; SIRI: Systemic inflammation response index; SII: Systemic immune-inflammation index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; pT: Pathological tumor stageValues in bold statistically significantly different. *p<0.05.

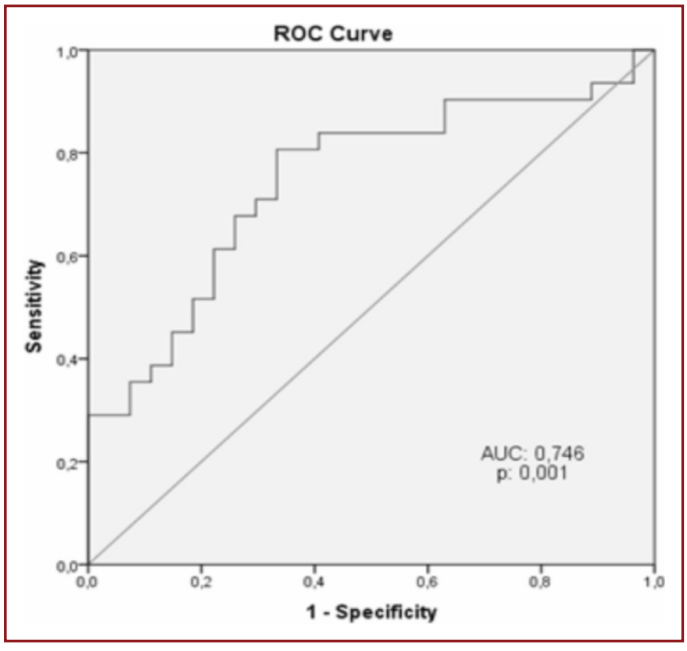

Figure 1. ROC curve analysis (sensitivity 0.71 and specificity 0.704).

The comparison of the pathological stages between groups was shown in Table 2. There was no statistically significant difference between groups regarding pathological stage (p=0.49).

Table 3 shows the correlation of SIRI between serum AFP and hCG levels. A positive correlation was found between SIRI and serum AFP level (r=0.402, p=0.002). There was no statistically significant correlation between SIRI and hCG level.

Table 4 shows the association between clinical variables (age, tumor size, hCG, AFP, and SIRI) between groups in MVA. In MVA, it was found that SIRI over 0.985 was associated with non-seminoma testicular tumor pathology (OR=5.662, 95% CI=1.284–24.966, p=0.022).

Table 2. Comparison of pT between groups

	Seminoma	Non-seminoma	p
pT			0.49
1	17 (51.5)	16 (59.3)	
2	12 (36.4)	10 (37)	
3	4 (12.1)	1 (3.7)	

pT: Pathological tumor stage.

Table 3. The correlation of SIRI between AFP and HCG

	SIRI	
	r	p
AFP	0.402	0.002
hCG	0.186	0.166

SIRI: Systemic inflammation response index; hCG: Human chorionic gonadotropin; AFP: Alpha-fetoprotein; r: Correlation coefficient values in bold statistically significantly different. *p<0.05.

Table 4. Multivariate logistic regression analysis of age, tumor size, HCG, AFP, and SIRI >0.985

	OR	95% CI	p
Age	1.03	(0.972–1.092)	0.313
Tumor size	1.182	(0.942–1.484)	0.149
hCG	0.994	(0.977–1.012)	0.527
AFP	0.99	(0.976–1.004)	0.145
SIRI	5.662	(1.284–24.966)	0.022

hCG: Human chorionic gonadotropin; AFP: Alpha-fetoprotein; SIRI: Systemic Inflammation Response Index; OR: Odds ratio; CI: Confidence Interval Values in bold statistically significantly different. *P<0.05.

Discussion

The seventh feature of cancer, which has inflammatory cells and mediators such as cytokines and chemokines, which constitute the main component of the tumor microenvironment, is cancer-related inflammation[16]. Systemic inflammation response is one of the important factors of cancer progression[17]. It was reported that immune inflammatory cells such as neutrophils, lymphocytes, and platelets may contribute to cancer cell proliferation, invasion, and also migration[17]. Therefore, the indexes calculated using hematological parameters have been investigated to evaluate cancer diagnosis and prognosis[11]. In the present pilot study, we aimed to investigate the association between SIRI and Stage 1 TGCT, and it was demonstrated for the 1st time, SIRI is associated with Stage 1 non-seminoma testicular tumors.

SIRI was first used to predict pancreatic cancer survival in patients who received gemcitabine-based chemotherapy[10]. SIRI was also shown to have a higher prognostic value for pancreatic cancer, and a correlation was reported between the SIRI and pancreatic cancer stage[10]. Furthermore, high SIRI was shown to be associated with poor prognosis in human cancers and can be used as a predictor in follow-up of cancer treatment[18]. Chen et al.[11] suggested that SIRI is a better prognostic predictor than other hematologic inflammatory markers in patients with locally/locally advanced clear cell renal cancer. Another study showed that SIRI can be used as a prognostic indicator of poor outcomes in patients with gastric cancer[13]. Furthermore, a study reported that SIRI is an independent prognostic factor after radical resection in patients suffering squamous cell carcinoma in esophagus[12].

The relationship of hematological inflammatory markers with testicular cancer has been previously investigated. Yuksel et al.[19] reported that white blood cell count and NLR can be used as a simple diagnostic test in localized testicular cancer. In another study, it was demonstrated that pre-operative NLR and lymphocyte/monocyte ratio could be used as a cheap marker to predict mortality rates in the diagnosis and follow-up of TGCTs[20]. Another inflammatory marker used for various types of cancer is SII, developed by Hu et al.[9] Chovanec et al.[21] reported an association between high SII and poor outcomes in patients with TGCTs. Fanhauser et al.[22] demonstrated that SII is an independent predictive factor for overall survival in metastatic TGCT patients treated with cisplatin-based chemotherapy. Contrary to the studies mentioned above, in our study, we found no significant difference between seminoma and non-seminoma groups regarding NLR or SII. It should be noted that, in our study, survival, mortality rates, etc., have not been investigated and therefore it can be considered that there is a discrepancy between previous studies.

Marshall and Dayan concluded that some tumors share a common infiltration with lymphocytes and plasma cells. It was suggested by the authors that these cells are the organism's response to tumor presence[23]. Moreover, circulating neutrophils produce cytokines such as tumor necrosis factor, interleukin-1 (IL-1), and IL-6[24]. Since neutrophils facilitate tumor proliferation by weakening the immunity and lymphocytes have a role in host cell mediated immunity, these cellular parts can represent the host's inflammatory response[25,26].

The pathological examination of orchiectomy materials may cause challenges in the differential diagnosis of TGCT. For instance, the differentiation of seminoma from embryonal carcinoma can be challenging in the presence of cellular atypia[3]. On the other hand, the tubular variant of the seminoma may resemble gland-forming embryonal carcinoma[27]. Furthermore, seminoma can mimic the yolk sac tumor by forming tubular and microcystic growth pattern[27]. Noteworthy, serum tumor markers used to support the diagnosis of TGCT subtypes may not be functional in differential diagnosis in some cases due to their low sensitivity and normal levels do not exclude the tumor presence. In such cases, SIRI may have a potential to be used in the differential diagnosis of seminoma and non-seminoma tumors. We believe that the studies in the future should focus on this topic.

Our study has limitations to be acknowledged. The retrospective nature, the small number of the patients, and the single-center study design are the main limitations of the present study. Furthermore, we evaluated SIRI only preoperatively, and we did not examine its prognostic significance. As this is a pilot study, our results need to be supported by further studies to draw wide conclusions.

Conclusion

In this pilot study, we revealed that preoperative SIRI is associated with Stage 1 non-seminoma TGCT. As a future perspective, we believe it is important to explore the utility of SIRI in the differential diagnosis of TGCT in further studies. Therefore, prospective studies with large series should be conducted to reveal the relationship between SIRI and TGCT.

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References

1. Laguna MP, Albers P, Algaba F, Bokemeyer C, Boormans JL, Fischer S, et al. "EAU Guidelines on testicular cancer 2020 European Association of Urology Guidelines", EAU Annual Congress Amsterdam 2020. Arnhem The Netherlands: European Association of Urology Guidelines Office 2020.
2. Ji C, Wang Y, Wang Y, Luan J, Yao L, Wang Y, et al. Immune-related genes play an important role in the prognosis of patients with testicular germ cell tumor. Ann Transl Med 2020;8:866.
3. Bernard B, Sweeney CJ. Diagnosis and treatment of testicular cancer: A clinician's perspective. Surg Pathol Clin 2015;8:717–23.
4. Barlow LJ, Badalato GM, McKiernan JM. Serum tumor markers in the evaluation of male germ cell tumors. Nat Rev Urol 2010;7:610–7.
5. Lakpour N, Saliminejad K, Ghods R, Reza Sadeghi M, Pilatz A, Khosravi F, et al. Potential biomarkers for testicular germ cell tumour: Risk assessment, diagnostic, prognostic and monitoring of recurrence. Andrologia 2021;53:e13998.
6. Song Y, Qi X, Kang J, Wang X, Ou N, Zhu J, et al. Identification of new biomarkers in immune microenvironment of testicular germ cell tumour. Andrologia 2021;53:e13986.
7. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.
8. Ohno Y. Role of systemic inflammatory response markers in urological malignancy. Int J Urol 2019;26:31–47.
9. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212–22.
10. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H, et al. A novel Systemic Inflammation Response Index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer 2016;122:2158–67.
11. Chen Z, Wang K, Lu H, Xue D, Fan M, Zhuang Q, et al. Systemic inflammation response index predicts prognosis in patients with clear cell renal cell carcinoma: A propensity score-matched analysis. Cancer Manag Res 2019;11:909–19.
12. Geng Y, Zhu D, Wu C, Wu J, Wang Q, Li R, et al. A novel Systemic Inflammation Response Index (SIRI) for predicting postoperative survival of patients with esophageal squamous cell carcinoma. Int Immunopharmacol 2018;65:503–10.
13. Li S, Lan X, Gao H, Li Z, Chen L, Wang W, et al. Systemic Inflammation Response Index (SIRI), cancer stem cells and survival of localised gastric adenocarcinoma after curative resection. J Cancer Res Clin Oncol 2017;143:2455–68.
14. Topkan E, Kucuk A, Ozdemir Y, Mertsoylu H, Besen AA, Sezen D, et al. Systemic inflammation response index predicts survival outcomes in glioblastoma multiforme patients treated with standard stupp protocol. J Immunol Res 2020;2020:8628540.
15. Valero C, Pardo L, Sansa A, Garcia Lorenzo J, López M, Quer M, et al. Prognostic capacity of Systemic Inflammation Response Index (SIRI) in patients with head and neck squamous cell carcinoma. Head Neck 2020;42:336–43.
16. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. Carcinogenesis 2009;30:1073–81.
17. Fan L, Wang R, Chi C, Cai W, Zhang Y, Qian H, et al. Systemic immune-inflammation index predicts the combined clinical outcome after sequential therapy with abiraterone and docetaxel for metastatic castration-resistant prostate cancer patients. Prostate 2018;78:250–6.
18. Wei L, Xie H, Yan P. Prognostic value of the systemic inflammation response index in human malignancy: A meta-analysis. Medicine Baltimore. 2020;99:e23486.
19. Yuksel OH, Verit A, Sahin A, Urkmez A, Uruc F. White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: A simple secondary serum tumor marker. Int Braz J Urol 2016;42:53–9.
20. Olcucu MT, Karamik K, Yilmaz K, Okuducu Y, Cakir S, Ates M. Preoperative inflammation markers and De Ritis Ratio in predicting clinical presentation and prognosis of patients with testicular germ cell tumors. J Coll Physicians Surg Pak 2020;30:1041–6.
21. Chovanec M, Cierna Z, Miskovska V, Machalekova K, Kalavska K, Rejlekova K, et al. Systemic immune-inflammation index in germ-cell tumours. Br J Cancer 2018;118:831–8.
22. Fankhauser CD, Sander S, Roth L, Gross O, Eberli D, Sulser T, et al. Systemic inflammatory markers have independent prognostic value in patients with metastatic testicular germ cell tumours undergoing first-line chemotherapy. Br J Cancer 2018;118:825–30.
23. Marshall AH, Dayan AD. An immune reaction in man against seminomas, dysgerminomas, pinealomas, and the mediastinal tumours of similar histological appearance? Lancet 1964;2:1102–4.
24. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, et al. Pretreatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009;58:15–23.
25. Kim M, Moon KC, Choi WS, Jeong CW, Kwak C, Kim HH, et al. Prognostic value of systemic inflammatory responses in patients with upper urinary tract urothelial carcinoma. World J Urol 2015;33:1439–57.
26. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: Prognostic role and therapeutic strategies. Mol Cancer 2017;16:137.
27. Ye H, Ulbright TM. Difficult differential diagnoses in testicular pathology. Arch Pathol Lab Med 2012;136:435–46.