Preoperative Inflammation Markers and De Ritis Ratio in Predicting Clinical Presentation and Prognosis of Patients with Testicular Germ Cell Tumors

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ABSTRACT

Objective: To evaluate the importance of neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to--lymphocyte ratio (PLR), neutrophil-to-monocyte ratio (NMR) and De Ritis ratio (DRR) in predicting clinical presentation and prognosis of patients with testicular germ cell tumors (TGCTs).

Study Design: Observational study.

Place and Duration of Study: Antalya Training and Research Hospital Antalya, Turkey, from January 2009 to March 2020.

Methodology: The characteristics and the results of biochemical and pathological examinations of patients who underwent radical orchiectomy were recorded. NLR, LMR, PLR, NMR, and DRR were calculated. The relationship among inflammation markers and DRR and clinical presentation and prognosis of TGCT was evaluated.

Results: Data of 99 patients were eligible for the study. Median age was 32 (27-39) years. Average size of the tumor was 5 (2.7 - 7) cm. Average duration of follow-up was 35.4 (8-62) months. Higher NLR and lower LMR were significantly correlated with higher rates of advanced-stage cancer, metastasis, and retroperitoneal lymph node invasion (RPLNI) ($p<0.05$). Based on the optimal cut-off values, there was a significantly higher rate of S stage, RPLNI, and metastatic disease in the high NLR group ($p<0.05$). Kaplan-Meier survival analysis found a statistically significantly lower mean survival rate in the high NLR group ($p<0.05$). There was no statistically significant difference between the DRR groups in the above-mentioned parameters ($p>0.05$).

Conclusion: Preoperative NLR can be used as an inexpensive and easily accessible marker to predict clinical presentation at diagnosis and mortality rates during follow-up of patients with TGCT. Preoperative LMR can also be associated with the clinical picture at the time of diagnosis of TGCT.

Key Words: *De ritis ratio, Lymphocyte-to-monocyte ratio, Neutrophil-to-lymphocyte ratio, Neutrophil-to-monocyte ratio, Platelet-to--lymphocyte ratio, Testicular germ cell tumor.*

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INTRODUCTION

Testicular cancer (TCa) is the most common solid tumor among men aged 15 to 44 years.[1] Testicular germ cell tumors (TGCTs) constitute the majority of all testicular tumors.[2] TGCTs are divided into two main types as seminomatous and non-seminomatous. The majority of patients with non-seminomatous germ cell testicular tumors (NSTGCTs) have elevated levels of either alpha-fetoprotein (AFP) or beta-human chorionic gonadotropin (β-hCG).[3] However, about half of the patients have a combined increase in AFP and β-hCG levels. Moreover, about a third of seminoma patients have elevated β-hCG levels. Lactate dehydrogenase (LDH) levels may increase in cases with metastasis. Radical orchiectomy is used for the surgical treatment of patients with TCa.

Inflammation is known to be of critical importance in cancer development.[4] Inflammation markers such as neutrophils, lymphocytes, monocytes and platelets, the levels of which can be evaluated by complete blood count, which is an inexpensive method, are frequently used in daily medical practice. In recent years, there is an increasing number of studies examining neutrophil-to-lymphocyte (NLR), neutrophil-to-monocyte (NMR), lymphocyte-to-monocyte (LMR), platelet-to-lymphocyte (PLR) ratios to examine the relationship between inflammation and cancer.

Aspartate transaminase (AST) and alanine transaminase (ALT) are liver enzymes and their levels are increased in the case of hepatocellular injury.[5] De Ritis ratio (DRR) was first defined in 1957 as the ratio of AST to ALT.[6] Although DRR increases in the

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case of viral hepatitis, the studies demonstrated its association with a wide variety of cancer types, including Tca.[7-11]

Table I: Patients' characteristics.

n=99	Median (IQR)
Age (years)	32 (27-39)
AFP (μg/L)	5.15 (2.26-217)
BHCG (U/L)	6.8 (1.1-64.6)
LDH (U/L)	249 (198-395)
ALT (U/L)	20 (15-30)
AST (U/L)	23 (19-28)
WBC (10^3/mm^3)	8400 (7300-10100)
Platelet (10^3/mm^3)	258000 (217000-318000)
Neutrophil (10^3/mm^3)	5300 (4300-6800)
Lymphocyte (10^3/mm^3)	2100 (1600-2600)
Monocyte (10^3/mm^3)	700 (500-900)
DRR	1.1 (0.86-1.36)
NLR	2.48 (1.81-3.87)
PLR	120.48 (100.9-167.5)
LMR	3 (2-4)
NMR	7.67 (6.4-9.20)
Tumor type n(%)	
Classical seminoma	45 (45.5)
Mixed germ cell tumor	41(41.4)
Embryonal carcinoma	9(9.1)
Yolk-sac tumor	2 (2)
Teratoma	1(1)
Choriocarcinoma	1 (1)
Tumor size (cm)	5 (2.7-7)
T stage n(%)	
T1	44 (44.4)
T2	45 (45.5)
T3	9(9.1)
T4	1 (1)
LVI (%)	48 (48.5)
S stage n(%)	
S0	61 (61.6)
S1	28 (28.3)
S2	5 (5.1)
S3	5 (5.1)
RPLNI n(%)	37 (37.4)
N stage n(%)	
N0	62 (62.6)
N1	9 (9.1)
N2	12(12.1)
N3	16 (16.2)
Metastasis n(%)	19 (19.2)
M stage n(%)	
M0	80 (80.8)
M1a	9 (9.1)
M1b	10 (10.1)
Stage grouping n(%)	
1A	27 (27.3)
1B	20 (20.2)
1S	9 (9.1)
2A	5 (5.1)
2B	12 (12.1)
2C	7 (7.1)
3A	7 (7.1)
3B	2(2)
3C	10 (10.1)
Progression n(%)	22(22.2)
Time to progression (months)	16 (6-46)
Mortality n(%)	12 (12.1)
Time to death (months)	9.5 (1.25-48)
Follow-up (months)	30 (8-62)

AFP: Alpha-fetoprotein. ALT: Alanine aminotransferase. AST: Alanine aminotransferase. BHCG: Beta-human chorionic gonadotropin, DRR: De Ritis ratio. LDH: Lactate dehydrogenase. LMR: Lymphocyte-to-monocyte ratio. LVI: Lymphovascular invasion. NLR: Neutrophil-to-lymphocyte ratio. NMR: Neutrophil-to-monocyte ratio. PLR: Platelet-to-lymphocyte ratio. RPLNI: Retroperitoneal lymph node invasion. WBC: White blood cell.

The main objective of this study was to investigate the importance of NLR, NMR, LMR, PLR and DRR in predicting the clinical presentation and prognosis at the time of diagnosis of TGCTs.

METHODOLOGY

The study was conducted after approval from the Ethics Committee of Antalya Training and Research Hospital Antalya, Turkey. Patients who underwent orchiectomy for testicular cancer at the hospital between January 2009 and March 2020 were retrospectively analysed. The patients with non-testicular germ cell tumors, incomplete data or follow-up, chronic use of immunosuppressive drugs or hematological disease, and liver-related diseases or liver metastases were excluded. Furthermore, the patients' age and preoperative laboratory results (AFP, β-hCG, ALT, AST, LDH, and blood cell counts, including white blood cells, neutrophils, lymphocytes, monocytes, and platelets), pathological examination results (size, type and histopathological features of the tumor), retroperitoneal lymph node invasion (RPLNI), distant metastasis status, progression and death, and follow-up time were recorded. Based on computed tomography and magnetic resonance imaging studies, lymph node involvement and distant metastasis status were evaluated. S stage was determined by measuring serum AFP, β-hCG and LDH levels in the second week after radical orchiectomy. TNM classification and Stage grouping were based on the 2016 Annual Report for the Union for International Cancer Control (UICC).[12] Preoperative NLR, NMR, LMR, PLR and DRR values were calculated and noted.

The analysis of the data was conducted using SPSS Statistics version 25.0 (IBM, Corp., Armonk, NY). The qualitative data were presented as frequency and percentage, while the quantitative data were presented as mean (IQR). The normality distribution was tested by the Shapiro–Wilk test. Mann-Whitney U-test and Kruskal-Wallis test were used for the comparison between categorical and quantitative variables. The Bonferroni/Dunn test was used for post hoc comparison of significant variables. The Chi-Square test was used for the comparison of qualitative data. Receiver operating characteristic (ROC) analysis was performed to determine the role of variables in predicting mortality. Variables were categorised according to the cut-off values determined by ROC analysis. Survival curves were generated by using the Kaplan-Meier analysis and compared with the log-rank test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The data of 141 patients who underwent radical orchiectomy for suspected testicular cancer were analysed. Patients with non-T-GCTs (n=18), incomplete data or follow-up (n=12), chronic use of immunosuppressive drugs or a hematological disease (n=9), and liver-related diseases or liver metastases (n=3) were excluded. Data of 99 patients were eligible for the study. Patients' median age was 32 (27-39) years, median tumor size was 5 (2.7-7) cm, and median follow-up time was 30 (8-62) months. The rates of RPLNI and distant metastases were 37.4% and 19.2%, respectively. Patients have been treated with chemotherapy or/and retroperitoneal lymph node dissection or/and radiotherapy according to their tumour stage. The characteristics of the patients are summarised in Table I.

Table II: Comparison of patients' DRR, NLR , PLR, LMR and NMR in terms of stage groupings, metastasis and retroperitoneal lymph node invasion.

	Stage grouping			
	Stage 1 (n=56) Median (IQR)	Stage 2(n=24) Median (IQR)	Stage 3(n=19) Median (IQR)	p
DRR	1.07(0.85-1.29)	1.10(0.80-1.35)	1.2(0.96-1.48)	0.357
NLR	2.2(1.66-3.07)[a]	2.5(2.07-3.88)[a,b]	3.37(2.47-6.86)[b]	0.002*
PLR	113.88(89.17-156.42)	133.17(105.89-177.20)	128.57(106.47-224.4)	0.085
LMR	3.07(2.39-4.48)[a]	2.82(2-4.15)[a,b]	2(1.4-3.16)[b]	0.024*
NMR	7.53(6.23-8.83)	8.27(6.45-10.59)	7.72(1.14-13.5)	0.359
	Metastasis			
	No (n=80) Median (IQR)	Yes (n=19) Median (IQR)	p	
DRR	1.08(0.84-1.31)	1.2(0.96-1.48)	0.173	
NLR	2.37 (1.73-3.43)	3.38(2.48-6.87)	0.002*	
PLR	119.12(97.74-160.56)	148.82(106.47-224.4)	0.097	
LMR	3(2.26-4.15)	2(1.40-3.17)	0.013*	
NMR	7.63(6.35-9.11)	8.29(7.14-13.5)	0.259	
	Retroperitoneal lymph node invasion			
	No (n=62) Median (IQR)	Yes (n=37) Median (IQR)	p	
DRR	1.06 (0.84-1.29)	1.14(0.88-1.45)	0.144	
NLR	2.22 (1.66-3.13)	2.83(2.27-4.93)	0.004*	
PLR	113.88 (89.02-158.62)	130.5(108.98-199.79)	0.028*	
LMR	3.07 (2.38-4.43)	2.33(1.59-3.62)	0.016*	
NMR	7.59(6.30-9.16)	8.14(6.51-10.39)	0.338	

*[a,b]Different lowercase letters in a row indicate statistically significant difference between groups; DRR: De Ritis ratio. LMR: Lymphocyte-to-monocyte ratio. NLR: Neutrophil-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio. PLR: Platelet-to-lymphocyte ratio. *Significant p-values.*

Higher NLR were significantly correlated with higher rates of advanced-stage cancer, metastasis, and RPLNI (p = 0.002, p = 0.002 and p = 0.004, respectively, Table II). Similarly, lower LMR were significantly correlated with higher rates of advanced-stage cancer, metastasis, and RPLNI (p = 0.024, p = 0.013 and p = 0.016, respectively, Table II). Based on the optimal cut-off values, NLR and DRR were each divided into two groups, as high and low (Table III). LDH levels and tumor size were significantly higher in the high NLR group (p = 0.003 and p = 0.015, respectively). Furthermore, there was a significantly higher rate of S stage, RPLNI, and metastatic disease in the high NLR group (p = 0.023, p = 0.015 and p = 0.005, respectively). However, there was no statistically significant difference between the high and low DRR groups (p >0.05, Table III).

Kaplan-Meier analysis demonstrated significantly lower mean survival time in the high NLR group (77.41 months) compared to the low NLR group (96.18 months, p = 0.008, Figure 1-A). There was no significant difference in mean survival time between the high DRR (86.17 months) and low DRR (96.23 months) groups (p = 0.064, Figure 1B). Overall survival time was found as 91.53 months.

DISCUSSION

In the present study, it was concluded that NLR of >3.219 can be a diagnostic tool in predicting RPLNI at the time of diagnosis, presence of metastasis and positivity of serum markers after orchiectomy (S stage) in patients with TGCT. It has also been found that NLR of >3.219 may be associated with a high risk of long-term mortality.

Moreover, lower LMRs were significantly associated with higher rates of advanced-stage cancer, metastasis and RPLNI at the time of diagnosis. Based on the optimal cut-off value of 0.942, DRR has not been proven to be a useful tool in predicting the clinical presentation and prognosis of TGCT. No optimal cut-off value could be established for NMR, LMR and PLR, which showed the absence of a significant relationship between these ratios and the clinical presentation and prognosis of TCGT. Lymphocytes are known to inhibit the proliferation and migration of tumor cells.[13] Therefore, they have an important role in tumor immunity with antitumor effects. Studies on the prognostic value of NLR in TCa showed significantly higher NLR in patients with TCa compared to the control group.[14-17] Arda *et al.* detected significantly higher NLR in the cancer group compared to the healthy non-operated varicocele group. However, NLR was not found to be significant in predicting tumor size, RPLNI and cancer-specific survival rate.[14] Another study reported significantly higher NLRs in the cancer group.[15] Furthermore, in a study with a higher number of participants reported significantly higher NLRs in the cancer group compared to the control group.[16] Similar results were obtained in a study comparing patients with localised TCa and varicocele.[17] This study included only patients with TGCT. Therefore, no comparison was made with the control group. However, this study concluded that NLR has promise as an alternative marker to β-hCG, AFP and LDH in predicting the clinical presentation of TGCT at the time of diagnosis.

Studies investigating the importance of NLR in predicting the prognosis of TGCT have obtained conflicting results.[18-20] Ilktac *et al.* reported a significant decrease in NLR after orchiectomy in patients with localised TGCT.[18]

Table III: ROC analysis and comparison of patients' characteristics according to the cut-off values of NLR and DRR.

Roc analysis							
Mortality	**Cut-off value**	**AUC (95%CI)**		**Sensitivity (%)**		**Specificity (%)**	
DRR	≥0.942	0.668(0.513- 0.822)		91.7		39.1	
NLR	≥3.219	0.705(0.541-0.868)		66.7		73.6	
LMR	≤3.536	0.366(0.177- 0.556)		33.3		66.7	
PLR	≥178.33	0.589(0.405-0.772)		41.7		82.8	
NMR	≥10.993	0.616(0.417-0.816)		41.7		87.4	
Progression							
DRR	≥0.942	0.556(0.423-0.688)		77.3		39.0	
NLR	≥3.219	0.625(0.489-0.760)		50		74.0	
LMR	≤3.536	0.460(0.306-0.613)		36.4		67.5	
PLR	≥178.33	0.604(0.462-0.746)		40.9		85.7	
NMR	≥10.993	0.635(0.491-0.780)		36.4		89.6	
Comparison of patients' characteristics according to the cut-off values of NLR and DRR.							
		NLR			**DRR**		
		Low (n=68)	**High (n=31)**	**p-value**	**Low (n=35)**	**High (n=64)**	**p-value**
Age (years)	Median IQR	32 27-38.5	33 25-39	0.818	33 29-39	32 26-38.75	0.639
AFP (µg/L)	Median	3.98	8.35	0.152	5.15	5.27	0.930
	IQR	2.20-137.2	2.37-583.33		2.37-77.8	2.08-253	
BHCG (U/L)	Median	4.25	12.6	0.369	2.5	8.4	0.376
	IQR	1.13-55.75	1-133		1-64.6	1.35-67	
LDH (U/L)	Median	223	337	0.003*	227	262.5	0.892
	IQR	194.25-302.5	214-605		207-316	191-438	
Tumor size (cm)	Median	4	6.3	0.015*	4	5	0.512
	IQR	2.5-6	4-8		2.5-7	2.78-7.5	
Tumor type	Seminoma	33 (73.3)	12 (26.7)	0.363	16 (35.6)	29 (64.4)	0.969
	Non-Sem.	35 (64.8)	19 (35.2)		19 (35.2)	35 (64.8)	
LVI	No (%)	35 (68.6)	16 (31.4)	0.990	18 (35.3)	33 (64.7	0.990
	Yes (%)	33(68.8)	15 (31.2)		17(35.4)	31 (64.6)	
S stage	S0 (%)	47 (77)	14 (23)	0.023*	23 (37.7)	38 (62.3)	0.535
	S1+2+3 (%)	21 (55.3)	17(44.7)		12 (31.6)	26 (68.4)	
RPLNI	No (%)	48 (77.4)	14 (22.6)	0.015*	24 (38.7)	38 (61.3)	0.366
	Yes (%)	20 (54.1)	17 (45.9)		11 (29.7)	26 (70.3)	
Metastasis	No (%)	60 (75)	20 (25)	0.005*	31 (38.8)	49 (61.2)	0.147
	Yes (%)	8 (42.1)	11 (57.9)		4 (21.1)	15 (78.9)	

*AUC: Aea under the curve. AFP: Alpha-fetoprotein. BHCG: Beta-human chorionic gonadotropin. CI: Confidence interval. DRR: De Ritis ratio. LDH: Lactate dehydrogenase. LMR: Lymphocyte-to-monocyte ratio. LVI: Lymphovascular invasion. NLR: Neutrophil-to-lymphocyte ratio. NMR: Neutrophil-to-monocyte ratio. PLR: Platelet-to-lymphocyte ratio. RPLNI: Retroperitoneal lymph node invasion. *Significant p-values.*

They also reported that NLR was significantly higher in non-localised tumors than localised tumors and that NLR showed a decrease in the postoperative period in patients with and without an elevation in tumor markers. They also suggested that NLR can be used as a biomarker for the postoperative follow-up of patients with TGCT. Another study on NLR and the prognosis of TGCT found higher rates of residual disease, advanced-stage disease, and shorter survival in patients with higher NLR.[19] In contrast to these studies, Bolat *et al*. could show no statistically significant difference between NLR and study parameters.[20] Our study showed that NLR can be used to predict RPLNI at the time of diagnosis of TCGT and a potential increase in serum markers after radical orchiectomy. Moreover, it is found that patients with higher NLR had lower cancer-specific survival rates. Prospective studies and meta-analyses are needed to obtain clearer results on this subject.

There is an increasing number of studies on the use of LMR as a biomarker in cancer prognosis.[21] In a meta-analysis investigating the value of LMR in non-hematological malignancies, Nishijima *et al.* showed that lower LMR may be associated with poor oncological outcomes.[22]

Similarly, a meta-analysis on the prognostic value of LMR in urological cancers showed a relationship between LMR and survival rate.[23] However, this study did not include patients with TCa. Our study showed that lower LMR was significantly associated with higher rates of advanced-stage cancer, metastasis and RPLNI at the time of diagnosis. However, it is showed that there is no relationship between LMR and progression and mortality, which may be attributed to the relatively low number of patients in this study.

ALT and AST are markers that are frequently used in routine medical practice and reflect liver functions. Although DRR has previously been used to diagnose viral hepatitis, studies showed its association with different cancers.[7-11] While ALT is an enzyme found in the cytoplasm of hepatocytes, AST is found in both the cytoplasm and mitochondria of hepatocytes. Moreover, AST is expressed in different organs. Increased turn-over in tumor cells causes a higher increase in AST levels compared to ALT levels due to cell damage.[24] This has highlighted DRR as a potential biomarker. Two studies on the relationship between DRR and TCa reported that DRR can predict poor prognosis.[9,10] However, the present study did not demonstrate a comparable relationship. Large scale further prospective studies will help clarify this issue.

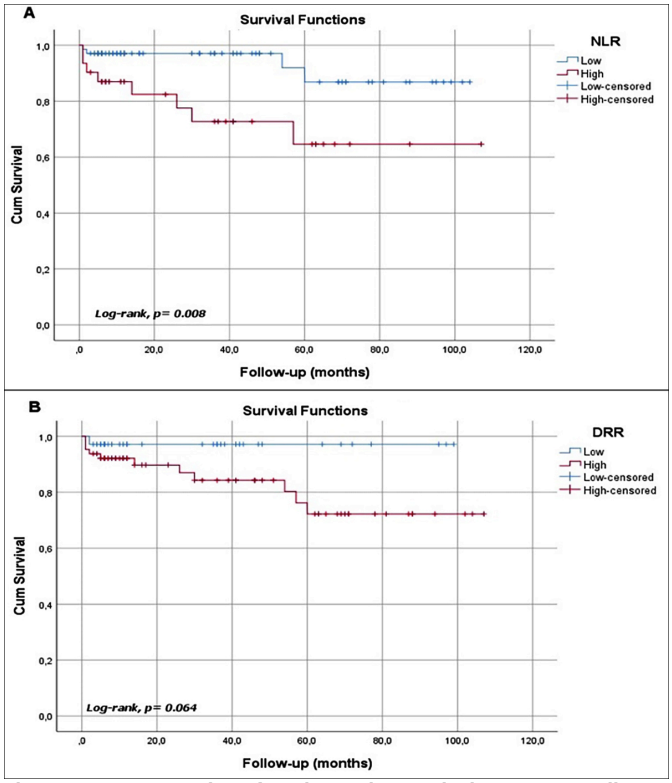

Figure 1: Demonstration of Kaplan-Meier survival curves according to the cut-off values of NLR and DRR. (A) High NLRs were significantly associated with decreased survival. (B) No association was found between DRR and survival.
DRR: De Ritis ratio. NLR: Neutrophil-to-lymphocyte ratio.

This study has some limitations, primarily it is a retrospective study design. Moreover, the low number of patients is another limitation of the study. Finally, special conditions such as smoking and metabolic syndrome that may affect the levels of inflammation markers have not been recorded.

CONCLUSION

Preoperative NLR can be used as an inexpensive and easily accessible marker to predict the stage of cancer, metastasis status and RPLNI at diagnosis and mortality rates during follow-up of patients with TGCT. There may also be a relationship between preoperative LMR and the stage of TGCT, metastasis status, and RPLNI at the diagnostic stage. Prospective multi-center studies with higher numbers of patients are needed to obtain more reliable results.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

ETHICAL APPROVAL:

Ethics Committee approval was received for this study from the Ethics Committee of Antalya Training and Research Hospital (approval date and No. 8/14 - 04.06.2020).

AUTHORS' CONTRIBUTION:

MTO: Conception, materials, data collection and analysis, writing, critical study.
KK: Conception, materials, writing.
KY: Materials, critical review.
YO, MA: Critical review.
SC: Data collection.

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