C-reactive Protein /Albumin Ratio Relationship in Testicular Cancer and Comparison with Non-Cancerous Patients: Another New and Meaningful Parameter

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ABSTRACT

The testicular tumor is a disease frequently seen in the young population and can metastasize rapidly. C-reactive Protein/Albumin Ratio (CAR), which is known to increase in case of malignancy, may also be associated with the testicular tumor. The study was designed by comparing pathological subtype, stage, and cancer-free group. A total of 107 patients aged 18-61 years who were diagnosed with testicular tumors between 2018 and 2022 were retrospectively screened. Patients's age, preoperative (pre-op) and postoperative(post-op) C-Reactive Protein (CRP), albumin, C-reactive Protein/Albumin Ratio (CAR), Neutrophil-lymphocyte Ratio (NLR), Platelet-lymphocyte Ratio (PLR) recorded. As the control group, 101 varicocelectomy patients aged 18-38 between 2017-2022 were examined. Data were analyzed according to pathological diagnosis, stage, and control group. Pre-op CAR values of Tm patients were 0.477 and post-op 0.407. (p= 0.069) While the CAR value of tumor patients was 0.477, it was found to be 0.081 in the control group. (p= 0.000) The cut-off value for CAR was 0.069. Of the 54 patients in the mixed germ cell tumor (MGCT) group, 22 were embryonal carcinomas (EC). 56 of 99 patients were T1, and pre-op and post-op CAR values were insignificant (p= 0.125, p= 0.919). CAR is an important parameter higher in testicular tumor patients than in the non-cancerous group. There was no significant difference between CAR values according to pathological subtype, tumor stage, and lymph node metastasis status.

Keywords: Biomaterials, Pathology, Testicular Cancer, Tumor Marker, Uro-oncology

INTRODUCTION

Testicular cancer is the most common solid malignancy in men aged 20-40.[1-3] It represents 1% of adult neoplasms and 5% of urological tumors.[4] The most extensive histological type; are germ cell tumors, consisting of seminomatous and non-seminomatous sub-histological types. Embryonal carcinoma, yolk sac, teratoma, and trophoblastic tumors are subtypes of the non-seminomatous group. The presence of more than one pathological type is defined as a mixed germ cell tumor (MGCT).[4,5] Risk factors include cryptorchidism, testicular dysgenesis, a family history of testicular tumor, hypospadias, and infertility.[6-8]

C-Reactive Protein (CRP) is an acute phase reactant primarily used to diagnose infectious and autoimmune diseases. It is increases in lung, pancreatic, hepatocellular, kidney, and bladder cancers.[9-11] Albumin is a negative acute phase reactant that decreases inflammatory or infectious conditions. Albumin deficiency is a potent prognostic indicator of inflammation. The C-reactive protein/Albumin Ratio (CAR) is a marker calculated by dividing CRP by albumin.

While inflammatory processes such as uveitis and pancreatitis yielded significant results, oncological pathologies such as gastrointestinal, hepatocellular, pancreatic, colorectal, and tumor also yielded significant results.[12-14]

It is still unclear if there is an important relationship between testicular tumors and CAR. Based on this thought, we wanted to examine the CAR values of patients who underwent urgent orchiectomy due to the testicular tumor before and after the operation and whether the results changed according to the pathological subtype and tumor stage. The patients who underwent primary infertility varicocelectomy at our clinic were used as a control group.

PATIENT AND METHODS

One hundred seven patients, aged 18 and 61, who applied to the Kartal City Hospital emergency polyclinic between 2018 and 2022, were diagnosed with testicular tumors with physical examination, scrotal ultrasound, and tumor markers and underwent orchiectomy and were retrospectively analyzed. Eight patients were excluded from the study because their pathology was benign. Thus, 99 patients were included in the study, and an informed consent form was filled. Age, pre-operative (pre-op), and post-operative (post-op) C-Reactive Protein (CRP), albumin, C-reactive protein/Albumin Ratio (CAR), Neutrophil-lymphocyte Ratio (NLR), Platelet-lymphocyte Ratio (PLR) scores of all patients were recorded. Post-op data were obtained from blood examination checked during the third month of control.

CAR was calculated by dividing the serum CRP level by the albumin level. Similarly, the serum neutrophil value was proportioned to the lymphocyte value for NLR calculation, and platelet value divided by lymphocyte value was obtained PLR.[13-16] For the control group, both the selection of non-cancerous patients and the option of patients in a similar age range were taken into account, and 101 patients aged 18-38 years who underwent varicocelectomy due to primary infertility in our clinic between 2017-2022.

Age, pre-op albumin, CRP, CAR, NLR, and PLR values of the patients who underwent retroperitoneal lymph node dissection (RPLND) in the oncological process were also recorded and compared with the patients who did not undergo RPLND.

Ethical approval was obtain from Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethical Comitee (Date: 26.08.2022 / IRB no: 2022/514/232/2).

Statistical Analysis

All data were uploaded to SPSS IBM 25 program. The cases were split into two groups: testicular tumor and control group. Also, seminoma and mixed germ cell tumors as pathological groups were examined. Mixed germ cell tumor patients were analyzed within themselves based on the percentage of tumors of the dominant pathological type. In addition, all testicular tumor patients were compared by calculating pre-op and post-op CAR, NLR, and PLR values according to TNM staging. Paired Samples t Test, Wilcoxen Signed Rank Test, Student t Test, Mann-Whitney U test, and ANOVA tests were used for statistical analysis.

RESULTS

The mean age of 99 testicular tumor patients was 32 years, with a mean pre-op CRP of 19.6 and albumins of 45.3. While the CAR value of the tumor group was 0.477, the pre-op CAR value of the con-

Table 1. Values of testicular tumor and control group patients

	Testicular Tumor patients (n= 99)	Control group patients (n= 101)	p
Age (year)	32.1 ± 9.9	27.2 ± 6.7	0.000*
Pre-op CRP (mg/dL)	19.6 ± 40.3	3.59 ± 2.06	0.000*
Pre-op Albumin (g/dL)	45.3 ± 4.11	47.5 ± 2.77	0.000*
CAR	0.477 ± 0.982	0.081 ± 0.072	0.000*
NLR	6.27 ± 23.1	1.81 ± 0.68	0.054*
PLR	136.7 ± 55.5	100.9 ± 29.5	0.000*

* Student t-test

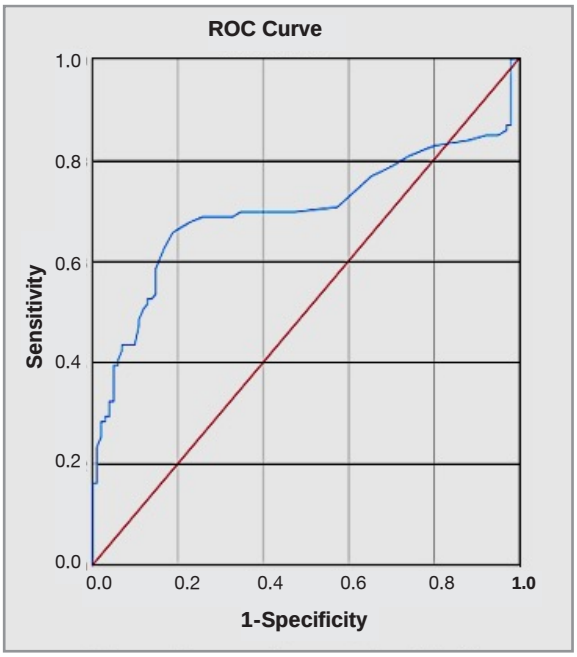

Figure 1. Receiver operating characteristic (ROC) curve of C-reactive protein/albumin ratio (CAR)

trol group was 0.081 (p= 0.000). There was also a statistically significant difference between the two groups regarding age, pre-op CRP, albümin, and PLR values (Table 1).

ROC curve analysis was performed to foresight testicular tumor, showing that age, CRP, albumin, CAR, NLR, and PLR values were significant. A cutoff value of 0.069 was obtained for CAR. Moreover, the highest AUC (Area Under the Curve) (95%) value was found in NLR with 0.781 (Figure 1).

When all tumor patients were pathologically investigated, 49 pure seminomas, 38 mixed germ cell tumors (MGCT), seven embryonal carcinomas (EC), four teratomas, and 1 Leydig cell tumor (LHT) came across. Due to the low number of pure EC, teratoma, and LHT patients, these patients were included in the MGCT group, and statistics were made. In the event of statistics are made by comparing the data of the seminoma group and non-seminoma (NS) +MGCT patients, we found that the pre-op and post-op CAR values of the seminoma group were 0.43, and 0.21, and the other group was 0.51, and 0.62 respectively, and we did not bring to light a statistically significant difference (p= 0.311; p= 0.763) (Table 2)

Another critical analysis was the comparison of all tumor patients by TNM staging. While 56 of the 99 patients were T1, 28 were testicular intra-epithelial neoplasia (TIN), 11 were T2, and 4 were T3. As a result of the analysis, no significant difference was established in pre-op and post-op CRP, albumin, CAR, NLR, and PLR values. (Table 3)

MGCT patients were compared within themselves, and based on the high percentage of tumors, four groups were formed: seminoma, teratoma, embryonal carcinoma (EC), and yolk sac (YS). Of 38 MGCT patients, 22 had predominant EC, eight teratomas, four seminomas, and 4 YS. There were no patients with Leydig cell tumor (LHT) predominant MGCT. While the pre-op CRP and CAR values of the dominant seminoma group pointed out a significant difference, the post-op CRP and CAR values of the teratoma group were significant difference (p= 0.004; p= 0.000) (Table 3).

After the follow-ups, it was determined that 31 of 99 patients had retroperitoneal lymph node dissection (RPLND). No significant difference was observed between the patients who underwent and did not undergo RPLND (Table 4).

Table 2. Comparison of seminoma vs nonseminomatous and mixed germ cell tumors tm results.

	Age	Albumin 1	Albumin 2	CRP 1	CRP 2	CAR 1	CAR 2	NLR 1	NLR 2	PLR 1	PLR2
Seminoma n= 49	35.1±10	45.79±4.48	46.06±3.55	17.04±32.4	9.25±13.8	0.43±0.88	0.21±0.33	8.88±31.7	2.95±1.71	126.7±40.1	135.1±54.6
NS+MGCT n= 50	28.7±8.7	44.89±3.66	43.79±5.15	22.4±47.7	24.2±55.5	0.51±1.09	0.62±1.49	3.39±2.79	3.09±2.43	147.7±67.4	150.4±83.3
p	0.001*	0.278*	0.013*	0.353**	0.621**	0.311**	0.763**	0.287**	0.524**	0.239**	0.737**

* Student t test; ** Mann Whitney U Test; NS: Nonseminomatous; MGCT: Mixed germ cell tumors

Table 3. Relationship of C-reactive protein/albumin ratio by TNM and classification of Mixed Germ Cell Tumor patients by Dominant Tumor Type

TNM	n= 99	Age	CRP 1	CRP 2	Albumin 1	Albumin 2	CAR 1	CAR 2	NLR 1	NLR 2	PLR 1	PLR 2
TIN	28	30.2	8.93	13.07	46.9	46.1	0.212	0.286	2.67	2.50	130.3	128.3
T1	56	32.6	21.94	17.26	45.2	45.0	0.524	0.451	8.72	3.12	129.3	139.9
T2	11	35.3	38.52	19.25	42.1	42.3	1.01	0.486	4.20	3.69	184.0	188.2
T3	4	30.3	9.61	19.03	45.5	44.0	0.206	0.419	2.96	3.41	154.6	148.7
Mean	32.1	19.6	16.3	45.3	44.9	0.477	0.407	6.27	2.50	136.7	142.3	
p*	0.484	0.186	0.963	0.012	0.129	0.125	0.919	0.695	0.374	0.019	0.110	
Tumor Type												
Seminoma	4	30.7	66.8	11.7	44.2	43.7	1.653	0.280	2.92	3.24	140.5	194.9
Teratoma	8	30.13	37.4	56.8	45.6	43.0	0.819	1.419	3.85	3.06	158.3	173.3
Embryonal carcinom	22	27.18	14.65	8.14	44.6	43.3	0.337	0.378	3.77	3.05	152.1	146.7
Yolk sac	4	35	9.03	3.12	46.2	46.0	0.196	0.066	2.78	2.44	101.9	107.1
Mean	30	31.97	19.9	44.9	43.6	0.562	0.456	3.59	3.01	146.9	153.2	
p*	0.176	0.006	0.000	0.565	0.277	0.004	0.000	0.829	0.663	0.702	0.768	

*Anova

DISCUSSION

It is acknowledged that the high rate of CRP in the oncological diagnosis process is related to many malignancies. Huang et al. reported that high CRP is associated with survival after surgery in prostate cancer, bladder cancer, upper urothelial system carcinoma, and penile cancer; however, its relationship with testicular tumor survival has not been clearly presented.[17] Saito et al. reported that C-reactive protein is relevant to the risk of late complications and the development of non-germ cell cancer in testicular cancer.[18]

In a recent study by Wu M et al. in 2022 on the relationship between C-reactive protein/Albumin Ratio (CAR) and urological cancers, the relationship between renal cell carcinoma, bladder cancer, and prostate cancer was examined, and it was emphasized that high CAR before treatment is a prognostic factor associated with survival.[19] Again, when the relationship between CAR and bladder cancer is examined, it is known that a cutoff value is determined for disease-specific survival.[20] Gao et al., while the CAR cutoff value for papillary renal cell carcinoma patients in 2019 was 0.094, this value was determined as 0.060 and 0.115 in the study by Chen et al.[21,22] On the other hand, we found the CAR cutoff value for the testicular tumor to be 0.069, and we especially state that we point out a significant difference between the CAR value of the tumor group and the control group.

Glasgow Prognostic Score (GPS), based on CRP and albumin values, is a factor that shows both inflammatory components and nutritional status in cancer patients. Group-1 if albumin ≥ 3.5 g/dL and CRP < 1.0 mg/dL, Group-2 if albumin < 3.5 g/dL or CRP ≥ 1.0 mg/dL, if albumin < 3.5 g/dL and CRP ≥ 1.0 mg/dL It is classified as Group-3. It has been shown that GPS has a prognostic role in cancer-specific survival and overall survival in upper urinary tract tumors.[23] Because both CRP

Table 4. Comparison of those with and without retroperitoneal lymph node dissection

	n	Age	Albumin 1	Albumin 2	CRP 1	CRP 2	CAR 1	CAR 2	NLR 1	NLR 2	PLR 1	PLR2
RPLND +	31	32.22	44.7	44.0	20.5	28.9	0.493	0.727	3.39	3.33	145.0	149.3
RPLND -	68	32.09	45.6	45.4	19.1	10.6	0.469	0.261	7.59	2.88	132.9	139.2
p		0.938*	0.339*	0.145*	0.090**	0.027**	0.111**	0.05**	0.919**	0.579**	0.541**	0.928**

* Student t test; ** Mann Whitney U Test; RPLND= Retroperitoneal lymph node dissection

and albumin values of testicular tumor and control group patients in our study were compatible with group 2, GPS was not used in the study.

The primary purpose of our study was to determine a certain cutoff value for CAR in the testicular tumor. However, we felt the need to use NLR and PLR scores in our study, which were previously found to be significant for many cancer types. Looking at the literature, it is evident that studies emphasize that NLR and PLR values yield significant results for diagnosing, staging, and metastasis of testicular tumors.[24-26] We observed a significant difference between the testicular tumor and control groups in PLR value. We did not obtain significant results for NLR and PLR according to either pathological subtypes or TNM staging.

The most elementary result of our study was that there was a significant difference between the testicular tumor group and the control group for CAR. However, when we classified the patients according to TNM, it was staggering for us that there was no significant difference. Another interesting result was that the CAR values of 4 seminoma-predominant and eight teratoma-predominant MGCT patients, which we mentioned in Table 4, were significant. But, we cannot say that there are sufficient patients for these pathological types. We foresee that different statistical results can be obtained with the increase in the number of patients. In addition, the predominance of embryonal carcinoma in 22 of 38 MGCT patients was why we compared MGCT patients. If the predominant type of MGCT patients were mostly seminoma, pure seminoma would not be compared with the MGCT group.

Retroperitoneal lymph node dissection (RPLND) was performed in 31 of the 99 patients in our study. Since we found the RPLND situation associated with a poor prognosis, we felt the need to compare it with other testicular tumor patients, despite the relatively small number of patients. However, as a result of the data we obtained, there was no significant difference between the pre-op CAR, NLR, and PLR values between those who underwent RPLND and those who did not. The critical detail that limits us at this stage is the incompatibility of the RPLND surgical process between patients. While only 4 of the 31 patients in this group underwent RPLND within three months of post-op, it was observed that this period extended to two years in some patients. Since this time could not be standardized, the post-op values of the patients who underwent RPLND could not be compared. We acknowledge that this detail is a deficiency of our study.

The limitations of our study; the fact that it was retrospective, single-centered, the number of cases was low, a relatively short period, such as the third month, was preferred to obtain the post-op data, and comorbid patients were also included in the research. At this point, we thought that if the follow-up process was prolonged, CRP, albumin, and hemogram values examined in patients during the oncological process would be higher, affecting the results.

Another deficiency of the study is that it is not known whether the had cancer-related death, especially during the follow-up period. Therefore, we acknowledge that we cannot propose a specific prognostic value for CAR. In addition, we state that the inability to analyze the postoperative CAR, NLR, and PLR data of patients with varicocelectomy is a deficiency. We foresee it is expected that hemogram, CRP, and albumin are not examined in the follow-up of varicocelectomy patients. However, in order to obtain more comprehensive data, we should also state that we have in mind to evaluate hemogram, CRP, and albumin for the control group for future studies.

Conclusion

Testicular tumor patients have a higher CRP/albumin ratio (CAR) value compared to the non-cancerous population. However, we should specifically point out that CAR does not yield significant results according to staging and pathological type. It is not yet possible to establish a standard CAR value and predict survival. Different results can be obtained with multicenter and long-term studies in which more patients are included.

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