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Evaluation of Neutrophil, Lymphocyte, Platelet, Mean Platelet Volume, Neutrophil-Lymphocyte Ratio, and Platelet-Lymphocyte Ratio in Prostate Cancer Patients Treated with Radiotherapy

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Abstract

Objective: Radiotherapy is one of the treatment methods for prostate cancer. Ionizing radiation can cause inflammation of tissues in and around the irradiated sites. But it is also suggested that low-dose radiation has anti-inflammatory effects. The present study was aimed at investigating the effects of radiotherapy on some inflammatory markers in prostate cancer patients who received radiotherapy.

Material and Methods: A total of 42 patients with prostate cancer and 30 healthy subjects were included in the present study. Venous blood samples of subjects were collected the day prior to radiotherapy (pre radiotherapy group), and on the last day last of radiotherapy (post radiotherapy group). Neutrophil, lymphocyte, platelet, mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) levels were measured and calculated. Also, the control group venous blood samples were used for comparison.

Results: Neutrophil values of the pre radiotherapy group were higher than the control group ($p<0.05$), and values of the post radiotherapy group were lower than the pre radiotherapy group ($p<0.001$). In addition, lymphocyte values of the post radiotherapy group were lower than the control and the pre radiotherapy groups ($p <0.001$ for both). Platelet values were decreased in the post radiotherapy group compared to the pre radiotherapy group ($p <0.01$). MPV values of the pre radiotherapy group were higher than the control and post radiotherapy groups ($p<0.05$, and $p<0.001$, respectively). NLR and PLR values were increased in the post radiotherapy group compared to the control and the pre radiotherapy groups ($p <0.001$ for all).

Conclusion: Our findings showed that neutrophil, and MPV were increased in the pre radiotherapy group compared to the control group. Neutrophil, lymphocyte, platelet, and MPV were decreased, NLR and PLR were increased in the post radiotherapy group compared to the pre radiotherapy group. However, further molecular studies are needed to clarify the mechanism related to this process.

Keywords: prostate cancer, radiotherapy, neutrophil, lymphocyte, platelet

Introduction

Prostate cancer is the most common cancer affecting males in developed countries (1). There are many studies in the literature about prostate cancer, but its underlying etiology still remains unclear. In some studies, it is reported that inflammation's role in multiple stages of prostate cancer development (1-3). Also, it has been suggested that neutrophils, T and B lymphocytes, and platelets play a prominent role in cancer inflammation and immunology (4, 5). Neutrophils, lymphocytes, and platelets, which are recognized as inflammation markers, can be easily obtained by a simple complete blood count test. Also, as different inflammation markers, the neutrophil/lymphocyte ratio (NLR), as well as the platelet/lymphocyte ratio (PLR) can be determined by dividing the sum of the neutrophil and platelet counts by the lymphocyte count (4). Neutrophils are immature phagocytes with a short half-life. They are the first cell to migrate in the early stage of inflammation regulated by macrophages and mast cells in the tissues. They have proteolytic enzymes and oxygen free radicals actively contributing to the damage produced during inflammatory processes (6, 7). In inflammation the different leucocyte types, macrophages, and lymphocytes are activated and recruited to the inflammatory site at a later stage (7). The platelets and mean platelet volume (MPV) are other inflammatory biomarkers, which are examined in our study.

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It is known that platelets are necessary for homeostasis and coagulation function. As a platelet function marker, MPV is an indicator of the average thrombocyte volume, recognized as a hallmark of platelet production rate, and stimulation. Larger platelets are more metabolically and enzymatically active than smaller platelets (4, 8).

When we reviewed studies associated with cancer and inflammation we saw that various inflammatory markers are studied in various cancer types. But in these studies, these markers were mostly examined on disease prognosis and survival (9-13). Prostate cancer patients frequently are treated with radiotherapy (14). It is also known that radiotherapy can initiate a pro-inflammatory immune response within the cancer microenvironment (15). Considering the possible effect of radiation on the inflammatory process, in the present study, we aimed to examine the association between values of neutrophils, lymphocytes, platelets, MPV, NLR, and PLR in prostate cancer patients before and after radiotherapy, and to compare these values with healthy subjects.

Material and Methods

Case Selection

A total of 42 male patients (mean age 65.19, range 55-76 years) diagnosed with histologically confirmed adenocarcinoma of the prostate and treated with radiotherapy at the Istanbul Training and Research Hospital, Department of Radiation Oncology between April 2019 and March 2020 were included in the study. A total of 30 healthy male volunteers of similar age (mean age 60.82, range 45-71 years), who did not receive any medication constituted the control group. Medical history, including inflammatory diseases, infectious diseases, autoimmune diseases, diabetes, hypertension, distant metastases, or other malignant diseases were designated as exclusion criteria for patients with prostate cancer. Known history of chronic, inflammatory, or malignant diseases were the exclusion criteria for the healthy control subjects. Patients with prostate cancer were treated with VMAT (Varian Trilogy Rapid Arc Radiotherapy Device; Varian Medical Systems, Inc., Palo Alto, CA, USA) (Total dose range 66-78 Gy) with a 1.8 Gy to 2.0 Gy per fraction. The present study was approved by the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Ethics Committee, and was performed in accordance with The Declaration of Helsinki. All patients gave written informed consent.

Sample collection and analysis

The day prior to radiotherapy (pre radiotherapy group) and the day radiotherapy was completed (post radiotherapy group) venous blood samples were collected into tubes containing EDTA from patients with prostate cancer. The same volume of blood was collected into tubes from the healthy control subjects. Blood samples were analyzed using Cell-DYN C1600 (Abbott Pharmacuetical Co., Ltd., Lake Bluff, IL, USA) blood count device using blood collected as aforementioned.

Statistical analysis

Data are presented as mean ± the standard deviation (SD). Statistical analysis was performed using the Wilcoxon, Paired t - test and Mann - Whitney U test. Correlation analysis using Spearman's rank was used to study the association between markers. $p<0.05$ was considered to indicate a statistically significant difference. All calculations were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Patient data

Demographic data of patient and control groups are presented in Table 1. Neutrophil, lymphocyte, platelet, MPV, NLR, and PLR values are presented in Table 2 as the mean ± SD.

Neutrophil, lymphocyte, platelet, MPV, NLR, and PLR results of all studied groups

Neutrophil values of the pre radiotherapy group were higher than the control group ($p<0.05$). The values of the post radiotherapy group were lower than the pre radiotherapy group ($p<0.001$). There was no significant change in the comparison of the post radiotherapy group with the control group ($p>0.05$) (Table 2).

Lymphocyte values were decreased in the post radiotherapy group compared to the control group ($p <0.001$). The values of the post radiotherapy group were also lower than the pre radiotherapy group ($p<0.001$). There was no significant change in the comparison of the pre radiotherapy group with the control group ($p>0.05$) (Table 2).

Platelet values were decreased in the post radiotherapy group compared to the pre radiotherapy group ($p <0.01$). There were no significant differences between other groups (Table 2).

MPV values of the pre radiotherapy group were higher than the control group ($p<0.05$). MPV values were decreased in the post radiotherapy group compared to the pre radiotherapy group ($p <0.001$). There was no significant change with comparison of other groups ($p>0.05$) (Table 2).

NLR values were increased in the post radiotherapy group compared to the control group ($p <0.001$). The values of the post radiotherapy group were higher than the pre radiotherapy group ($p<0.001$). There was no significant change in the comparison of the pre radiotherapy group with the control group ($p>0.05$) (Table 2).

Similarly, PLR values were increased in the post radiotherapy group compared to the control group ($p <0.001$). The values of the post radiotherapy group were higher than the pre radiotherapy group ($p<0.001$). There was no significant change in the comparison of the pre radiotherapy group with the control group ($p>0.05$) (Table 2).

Correlation results of all studied markers in the pre radiotherapy group

In the pre radiotherapy group, PLR values were positively correlated with NLR and platelet values (r=0.516, and r=0.786, respectively). But, PLR values were negatively correlated with MPV and lymphocyte values (r=-0.675, and r=-0.331, respectively). Also, there were positive correlations between NRL and neutrophil (r=0.649), and negative correlations between NLR and lymphocyte (r=-0.587), and between platelet and MPV (r=-0.449) (Table 3), (Figure 1 A-B).

Correlation results of all studied markers in the post radiotherapy group

In the post radiotherapy group, PLR values were positively correlated with NLR and platelet values (r=0.586, and r=0.380, respectively). But, PLR values were negatively correlated with lymphocyte values (r=-0.704). Also, there were negative correlations between NLR and lymphocyte (r=-0.647), and a positive correlation between NLR and neutrophil (r=0.491). Moreover, platelet values negatively correlated with MPV (r=-0.343) (Table 4), (Figure 2 A-B).

Table 1. Demographic data of prostate cancer and control groups.

	Control (n:30)	Prostate Cancer (n:42)	p- value
Age (Year)	60.82±6.70[a]	65.19±7.84[a]	0.114
Histology			___
Adenocarcinoma, n (%)	NA	42 (100%)	
Total Radiation Dose (Gy)	NA	66 -78.0	___
Radiation Dose per fraction (Gy)	NA	1.8–2.0	___
Tumor Stage			
T2b, n (%)		15 (35.7%)	___
T2c, n (%)	NA	17 (40.4%)	
T3b, n (%)		10 (23.8%)	

[a]Mean ± standard deviation; NA, not applicable.

Table 2. Comparison of the inflammatory markers of prostate cancer and control groups

	Control	Pre Radiotherapy	Post Radiotherapy
Neutrophil (x10^3/ml)	3.61±1.01	4.19±1.12[a*]	3.55±1.16[c***]
Lymphocyte (x10^3/ml)	1.86±0.49	1.94±0.52	0.92±0.33[b***,c***]
Platelet (x10^3/ml)	218.20±36.10	232.000±45.98	212.90±46.10[c**]
MPV (fl)	8.37±1.20	8.93±0.96[a*]	8.44±1.01[c***]
NLR	2.14±0.96	2.26±0.71	4.24±1.74[b***,c***]
PLR	145.30±42.09	121.70±38.81	256.60±47.88[b***,c***]

All values are presented as the mean ± standard deviation; MPV, mean platelet volumes; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; [a]Control vs. Pre Radiotherapy, [b]Control vs. Post Radiotherapy, [c]Pre Radiotherapy vs. Post Radiotherapy, *p<0.05, *p<0.01, ***p<0.001.

Table 3. Correlation of the inflammatory markers of prostate cancer pre radiotherapy

	Neutrophil	Lymphocyte	Platelet	MPV	NLR
Lymphocyte	p=0.233 r=0.187				
Platelet	p=0.451 r=0.119	p=0.385 r=-0.137			
MPV	p=0.751 r=-0.051	p=0.886 r=-0.022	**p=0.002** **r=-0.449**		
NLR	**p<0.001** **r=0.649**	**p<0.001** **r=-0.587**	p=0.184 r=0.209	p=0.848 r=-0.031	
PLR	p=0.825 r=-0.035	**p<0.001** **r=-0.675**	**p<0.001** **r=0.786**	**p=0.043** **r=-0.331**	**p<0.001** **r=0.516**

MPV, mean platelet volumes; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; p, significance; r, correlation coefficient; significant values were presented in bold.

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Table 4. Correlation of the inflammatory markers of prostate cancer post radiotherapy

	Neutrophil	Lymphocyte	Platelet	MPV	NLR
Lymphocyte	p=0.104 r=0.254				
Platelet	p=0.567 r=0.091	p=0.146 r=0.228			
MPV	p=0.296 r=0.164	p=0.683 r=-0.064	**p=0.029** **r=-0.343**		
NLR	**p<0.001** **r=0.491**	**p<0.001** **r=-0.647**	p=0.657 r=-0.070	p=0.368 r=0.142	
PLR	p=0.295 r=-0.165	**p<0.001** **r=-0.704**	**p=0.013** **r=0.380**	p=0.281 r=-0.170	**p<0.001** **r=0.586**

MPV, mean platelet volumes; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; p, significance; r, correlation coefficient; significant values were presented in bold.

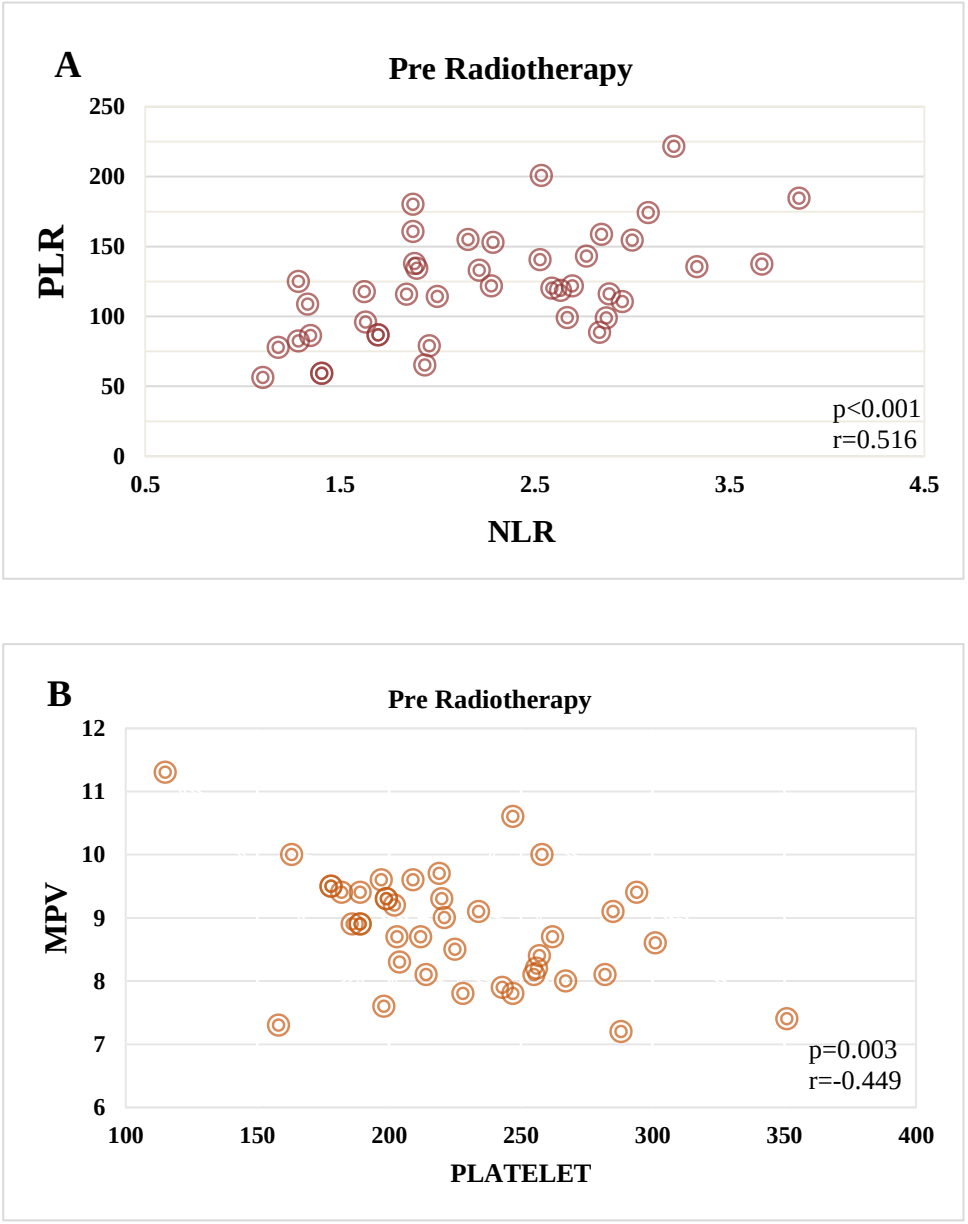

Figure 1 Correlations between NLR and PLR (**A**), platelet and MPV (**B**) in the pre radiotherapy group. NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MPV, mean platelet volumes; p, significance; r, correlation coefficient.

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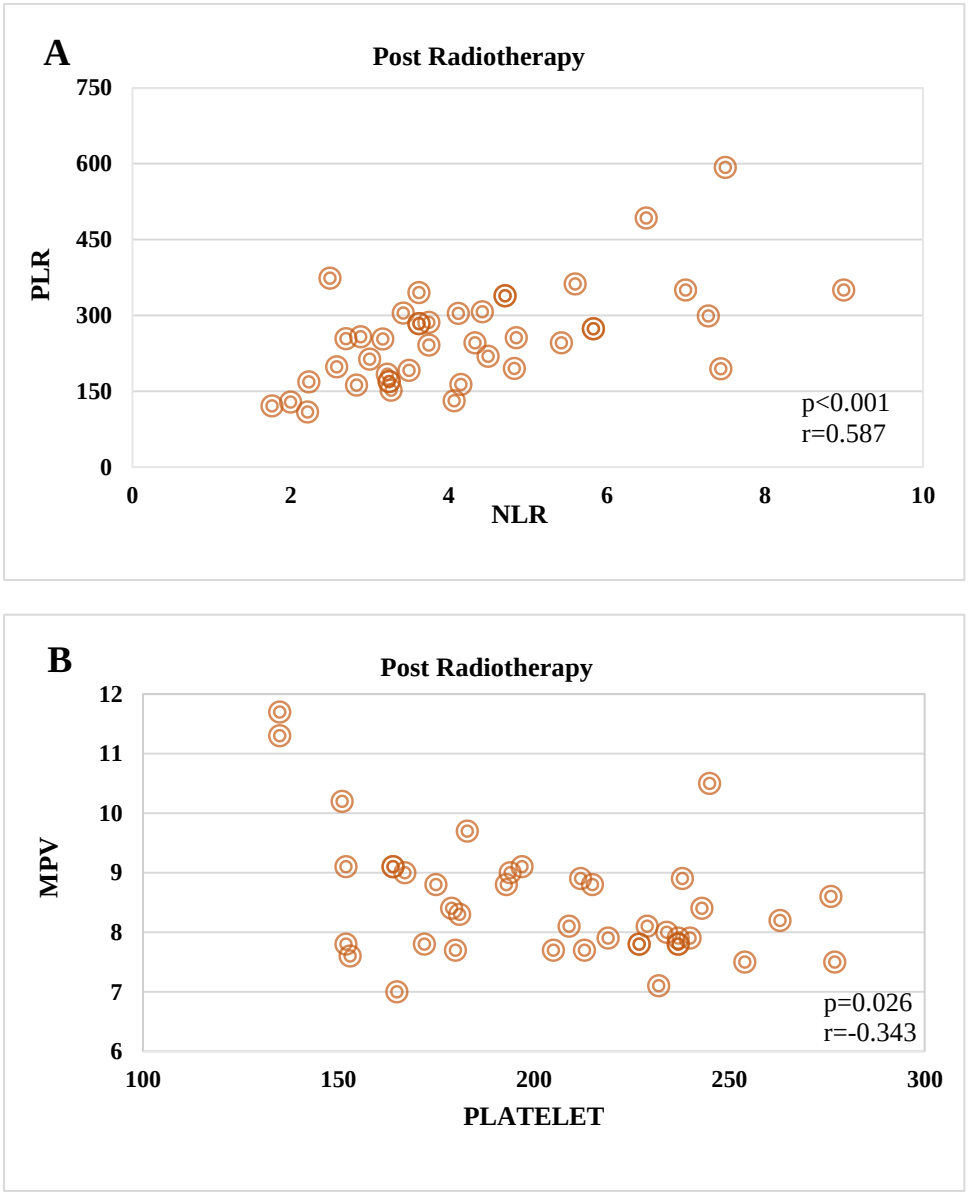

Figure 2. Correlations between NLR and PLR (A), platelet and MPV (B) in the post radiotherapy group. NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MPV, mean platelet volumes; p, significance; r, correlation coefficient.

Discussion

The inflammatory process plays a role in cancer development. The effect of radiotherapy on the inflammatory process may be an important role in both the pathogenesis and prognosis of the disease (1-3). The present study was performed to examine the role of radiotherapy on inflammatory markers such as neutrophils, lymphocytes, platelets, MPV, NLR, and PLR in prostate cancer patients.

Neutrophils contribute substantially to cancer progression both by direct effects on the cancer cells, and indirect effects on the cancer microenvironment. While in many cases neutrophils have been shown to promote cancer progression, there are also protective effects, particularly when antibody immunotherapy is performed (16).

Lymphocytes are the cells that prevent cancer cell proliferation. It is reported that increased infiltration of cancers with lymphocytes has been associated with better prognosis in cancer patients. The elevated circulating lymphocyte counts have been associated with prolonged survival. Also, normalization of initial lymphocytopenia has been associated with an improved clinical outcome (3).

In the last years, it has been verified that activated platelets are involved in cancer development, and metastasis. Interaction between platelets and cancer cells is not dependent on the platelet quantity but on the volume and size as larger platelets have more granules and receptors (17).

Also, NLR and PLR have been frequently used as markers for the determination of prognosis and survival in many cancer types (3, 9, 10, 13). NLR represents the state of balance between neutrophils and lymphocytes. The elevated NLR values may reflect both an elevated neutrophil-dependent inflammatory reaction and a lower lymphocyte-mediated antitumor immune response (3). The values of PLR have a similar effect with NLR in predicting the prognosis of cancer patients. The mechanism of poor prognosis caused by elevated PLR may be related to cancer metastasis or lymphocyte reduction associated with increased platelet count in cancer patients (18).

In literature, there are studies examining these inflammatory markers in different types of cancers. For example, Kiliçalp et al. reported that the MPV level was significantly higher in pre-operative gastric cancer patients compared to healthy subjects (10). Kemal et al. noted that NLR and PLR values were significantly higher in lung cancer patients compared to healthy subjects (4). But Yaylaci et al. informed that no significant differences between papillary thyroid cancer and benign goiter groups were apparent in the NLR, MPV, platelet, neutrophil, and lymphocyte levels ($p>0.05$) (19).

Our results showed that neutrophil, lymphocyte, platelet, MPV, and NLR values in the pre radiotherapy group were higher than the control group. However, only neutrophils and MPV levels were increased statistically significantly in the pre radiotherapy group as compared to the control group ($p<0.05$ for both). The results of our study may indicate the role of neutrophils in cancer progression and communication of increased volume of platelet with cancer cells.

When we reviewed studies associated with inflammation in cancer patients treated with radiotherapy, it was seen that the lymphocyte and NLP values in non-small cell lung cancer patients were increased in the post radiotherapy group compared to the pre radiotherapy group (20). Son et al. demonstrated that a low NLR in pre radiotherapy was significantly associated with better progression-free survival, and overall survival in patients with locally advanced hepatocellular carcinoma (21).

dos Santos et al. reported that a significant decrease in the total leukocytes, neutrophils, lymphocytes, monocytes, and platelets counts were seen from the first week of treatment with conventional external beam radiation therapy (22). Wu et al. informed that a decreased circulating lymphocyte count during neoadjuvant therapy for locally advanced rectal cancer was associated with better cancer regression. It was noted that lymphocytes may be involved in the immune response provoked by radiotherapy and chemotherapy (23).

The results of our study indicated that neutrophil, lymphocyte, platelet, and MPV were decreased, but NLR and PLR were increased in the post radiotherapy group compared to the pre radiotherapy. Increased NLR and PLR values in our findings support the effect of radiotherapy on the inflammatory process.

Conclusion

Our findings showed that neutrophils and MPV values were increased in the pre radiotherapy group compared to the control group. Moreover, neutrophils, lymphocytes, platelets, and MPV values were decreased, and NLR and PLR values were increased in the post radiotherapy group compared to the pre radiotherapy group. These data may indicate effects of radiotherapy on inflammatory markers. However, further molecular studies are needed to clarify the significance and underlying mechanisms of these markers in prostate cancer radiotherapy.

Ethical approval: The study was approved by the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Ethics Committee.

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Author's contributions: NB, ÖM; Study design and patient examinations, Biochemical analyzes, **NB;** Revisions

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