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Research Article

The Effect of Vitamin D Deficiency on Platelet Indices in Various Anemia Groups

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Abstract

Objectives: Our study aimed to determine the effects of vitamin D deficiency in iron, folate (B9), and cobalamin (B12) deficient anemia patients and their platelet indices.

Methods: The study included 4000 patients who presented to the outpatient clinics of Ankara Etlik City Hospital between September 9, 2022, and May 1, 2023. Four groups were studied: patients with iron deficiency anemia, B9 deficiency anemia, B12 deficiency anemia, and a control group without anemia. These four groups were subdivided according to 25 (OH) vitamin D levels as patients with and without vitamin D deficiency. Each subgroup contained 500 patients. We compared mean platelet volume (MPV), platelet distribution width (PDW), platelet count (PLT), and platelet-large cell ratio (P-LCR) parameters between the groups according to the anemia and control groups' vitamin D levels. In addition, univariate linear regression analysis and multivariate linear regression analysis were performed to determine the factors affecting these parameters.

Results: We detected that the presence of vitamin D deficiency together with B12 deficiency anemia affected MPV values ($p<0.01$). We also detected that the presence of vitamin D deficiency together with iron deficiency anemia affected P-LCR ($p<0.01$).

Conclusion: Vitamin D deficiency increased the severity of platelet morphology deterioration in patients with B12 and iron deficiency anemia compared with patients with normal vitamin D levels. Patients with B12 and iron deficiency anemia should also be screened for vitamin D deficiency to prevent changes in platelet morphology. Therefore, complications associated with deterioration in platelet morphology and function in anemia patients might be prevented by vitamin D supplementation.

Keywords: Anemia, platelet, vitamin D, mean platelet volume, platelet distribution width, platelet- large cell ratio

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Platelets are small, disk-shaped blood cells that are crucial for maintaining hemostasis. Platelets are produced in the bone marrow by a process called thrombopoiesis. This process involves the differentiation and maturation of hematopoietic stem cells into megakaryocytes that produce and release platelets.[1] The hormone thrombopoietin (TPO), primarily produced in the liver and kidneys, regulates the production of platelets. TPO binds to its receptor on hematopoietic stem cells and stimulates their differentiation into megakaryocyte precursors.

Platelets become active once they encounter damaged blood vessels. Platelets play a primary role in blood clotting and release cytokines and growth factors that help promote tissue repair and regeneration.[2] Evidence can be proposed for large platelets aggregating faster, and increased platelet turnover is associated with increased

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platelet size and immature platelet fractions, which is associated with further complications.[3] Maintaining proper hemostasis requires the presence of normal platelet function and morphology. Mean platelet volume (MPV), platelet distribution width (PDW), and platelet-to-large cell ratio (P-LCR) are used as indicators of platelet morphology and function. MPV indicates the average size of platelets, PDW signifies platelet size heterogeneity, and P-LCR indicates the ratio of large platelets to normal-sized platelets.

It is of great concern that approximately one-third of the global population suffers from anemia, a medical condition marked by a hemoglobin level below the lower normal limit.[4] In older people, approximately one-third of patients have a nutritional deficiency that causes anemia, such as iron, folate, or a vitamin B12 deficiency. In another one-third of patients, there is evidence of renal failure or chronic inflammation.[5]

Hemoglobin requires iron to function properly. Inadequate iron in the body can lead to iron deficiency anemia (IDA), which causes the production of smaller and paler red blood cells. The reduction in hemoglobin significantly affects platelet appearance, decreasing the size and regularity of shape, and reducing the granule content.[6] Iron also plays a crucial role in thrombopoiesis by directly regulating the differentiation of megakaryocytic precursors, which can affect the function of platelets and hemostasis.

Folate (B9) and cobalamin (B12) are essential nutrients for erythropoiesis. B9 and B12 deficiencies impair DNA synthesis, leading to abnormal erythrocyte maturation and ineffective erythropoiesis. Folate and cobalamin deficiency can cause megaloblastic anemia, characterized by enlarged red blood cells and increased mean corpuscular volume. These changes in red cell morphology can also affect platelet size and activity, resulting in increased MPV and PDW along with altered platelet function.[7, 8]

Vitamin D is crucial for maintaining healthy bones, a robust immune system, and various physiological functions, such as erythropoiesis. Of note, vitamin D receptors (VDRs) can be found in both the megakaryocyte lineage and mature platelets.[9] Studies have linked a lack of vitamin D to adverse health effects, such as a higher predisposition to infections, autoimmune disorders, heart disease, and cancer.[10, 11] Studies also suggest that low vitamin D levels might lead to a higher chance of anemia and changes in the appearance of platelets.[12, 13] Low vitamin D levels can cause increased oxidative stress, changing the shape of platelets and activating them.

The effects of iron, B9, and B12 deficiency anemias on erythrocytes are well known. However, their relationship with platelet morphology remains unresolved. In this study, we aimed to investigate the effect of vitamin D deficiency on platelet indices in iron, B9, and B12 deficiency anemia groups. This study could contribute to investigating vitamin D deficiency in the etiology and development of effective treatment strategies in anemia patients with abnormal platelet morphology to prevent complications.

Methods

The data of 4000 patients who presented to the outpatient clinics of Ankara Etlik City Hospital between September 9, 2022, and May 1, 2023, were retrospectively analyzed. Patients over age 18 years diagnosed with iron, B9, or B12 deficiency anemia were included. For anemia, hemoglobin levels < 12.0 g/dL in women and < 13.0 g/dL in men were established as cutoff values. Patients with a serum ferritin level of less than 34 pmol/L (15 µg/l) for iron deficiency, a serum B12 level of less than 150 pmol/L (203 pg/mL) for B12 deficiency, or a serum folate level of less than 10 nmol/L (4 ng/mL) for folate deficiency were considered for diagnosis. A 50 nmol/L (20 ng/ml) cutoff value was used for vitamin D deficiency. Patients with thrombocytopenia-related hematological disorders or infections (immune thrombocytopenic purpura, myelofibrosis, EBV, or HIV), malabsorption, hepatic or renal failure, anticoagulant usage, calcium metabolism disorders, hyperparathyroidism, platelet dysfunction (Glanzmann thrombasthenia or Bernard Soulier syndrome), and pregnancy were excluded. Patients without anemia and no diagnosed disease were selected as a control group.

The Sysmex XN-1000 (Kobe, Japan) device was used to analyze complete blood count parameters. Folate, cobalamin, ferritin, and 25 (OH) vitamin D were analyzed by electrochemiluminescence immunoassay and serum iron levels by colorimetric methods using a Cobas 8000 modular analyzer (Roche, Germany). Four groups were formed: patients with IDA, patients with B9 deficiency anemia, patients with B12 deficiency anemia, and a control group without anemia. These four groups were subdivided according to 25 (OH) vitamin D levels as patients with and without vitamin D deficiency. There were eight subgroups with 500 patients in each. Anemia groups were compared with control groups regarding MPV, PLT, PDW, and P-LCR parameters. Since this study was planned as patient screening with routine complete blood count parameters, the results of tests including peripheral blood smear and platelet aggregometry were excluded. We adhered to the Declaration of Helsinki and obtained Ethics Committee approval from the institution where we conducted our study.

The mean and standard deviation values were calculated for the data analysis of each group. Analysis of variance

(ANOVA) and Sidak-Tamhane T2 pairwise comparison tests were performed to analyze MPV, PDW, and P-LCR parameters according to anemia groups. Univariate and multivariate linear regression analyses were performed to determine the factors affecting these parameters. Significant parameters in univariate linear regression analysis were included in multivariate linear regression analysis. In the study, p-values less than 0.05 were considered significant. Analyses were performed with SPSS 25.0 software.

Results

Demographic characteristics of the patients are shown in Table 1. MPV did not differ between the groups we formed to assess iron and vitamin D deficiency (p=0.19) (Table 2). PDW had varying values between the groups we formed to evaluate iron and vitamin D. Groups with IDA and vitamin D deficiency had lower PDW values than the other groups (p<0.01). Also, groups with IDA had lower P-LCR values than the control groups (p<0.01). There was a significant difference between the iron deficiency anemia and vitamin D deficiency group and patients with IDA and without vitamin D deficiency. The iron deficiency with vitamin D deficiency group had significantly lower P-LCR values than the iron deficiency without vitamin D deficiency group (p<0.01). IDA groups had higher PLT counts than control groups (p<0.01).

MPV did not differ between the groups we formed to assess vitamin B9 and vitamin D deficiency (p=0.92) (Table 3). PDW had differing values between the groups we formed to evaluate vitamin B9 and vitamin D. Groups with B9 deficiency anemia had higher PDW values than the control groups (p<0.01). There was no significant difference between the B9 deficiency anemia and vitamin D deficiency group and patients with B9 deficiency anemia and no vitamin D deficiency. P-LCR did not differ between the groups we formed to assess vitamin B9 and D deficiency (p=0.78). B9 deficiency anemia groups had lower PLT counts than control groups (p<0.01).

MPV had differing values between the groups we formed to assess vitamin B12 and vitamin D deficiency (Table 4). The B12 deficiency anemia and vitamin D deficiency group had higher MPV values than the other groups (p<0.01). PDW had different values between the groups we formed to evaluate vitamin B12 and vitamin D. Groups with B12 deficiency anemia had higher PDW values than the control groups (p<0.01). There was no significant difference be-

Table 1. Demographic characteristics of the patients

Groups	Sub-Groups (n=500 for each)	Age (years) ± SD	Gender (Male/Female)
Patients with Iron deficiency anemia	Vitamin D deficiency	47.05±16.58	162/338
	Vitamin D normal	43.21±10.00	196/304
Patients with B12 deficiency anemia	Vitamin D deficiency	47.29±13.09	178/322
	Vitamin D normal	43.12±10.45	156/344
Patients with B9 deficiency anemia	Vitamin D deficiency	45.31±14.58	188/312
	Vitamin D normal	48.73±13.26	181/319
Control group	Vitamin D deficiency	47.31±15.84	195/305
	Vitamin D normal	45.75±16.58	184/316

SD: Standard deviation.

Table 2. Comparison of the groups according to vitamin D and iron levels with the control groups

	Patients with Iron deficiency anemia		Control Groups			
Parameters	Vitamin D deficiency (1) Mean±SD	Vitamin D normal (2) Mean±SD	Vitamin D deficiency (3) Mean±SD	Vitamin D normal (4) Mean±SD	p	Post Hoc
MPV (fL)	10.64±0.92	10.49±1.00	10.57±1.15	10.32±1.17	0.18	-
PDW (fL)	11.00±2.19	12.02±1.76	12.77±3.08	12.47±2.40	<0.01	1<2,3,4
P-LCR (%)	24.02±8.51	27.95±8.12	29.50±10.90	29.60±8.80	<0.01	1<2<3,4
PLT (X10^3/µL)	330.60±134	323.11±116	291.69±139	281.78±96	<0.01	1,2>3,4

Anova test-post hoc- Sidak; *Significant below the level of 0.05; MPV: mean platelet volume; PDW: platelet distribution width; P-LCR: platelet larger cell ratio; SD: standard deviation.

Table 3. Comparison of the groups according to vitamin D and vitamin B9 levels with the control groups

	Patients with B9 deficiency anemia		Control Groups			
	Vitamin D deficiency (1)	Vitamin D normal (2)	Vitamin D deficiency (3)	Vitamin D normal (4)		
Parameters	Mean±SD	Mean±SD	Mean±SD	Mean±SD	p	Post Hoc
MPV (fL)	10.52±1.10	10.54±1.03	10.57±1.15	10.32±1.17	0.92	-
PDW (fL)	14.33±3.78	14.02±3.73	12.77±3.08	12.47±2.40	<0.01	1,2>3,4
P-LCR (%)	29.07±8.10	29.30±8.50	29.50±10.90	29.60±8.80	0.78	-
PLT (X10^3/µL)	237.97±117	234.71±105	291.69±139	281.78±96	<0.01	1,2<3,4

Anova test-post hoc- Sidak, *Significant below the level of 0.05; MPV: mean platelet volume; PDW: platelet distribution width; P-LCR: platelet larger cell ratio; SD: standard deviation.

Table 4. Comparison of the groups according to vitamin D and vitamin B12 levels with the control groups

	Patients with B12 deficiency anemia		Control Groups			
	Vitamin D deficiency (1)	Vitamin D normal (2)	Vitamin D deficiency (3)	Vitamin D normal (4)		
Parameters	Mean±SD	Mean±SD	Mean±SD	Mean±SD	p	Post Hoc
MPV (fL)	10.83±1.68	10.43±0.94	10.57±1.15	10.32±1.17	<0.01	1>2,3,4
PDW (fL)	14.04±3.10	13.61±3.00	12.77±3.08	12.47±2.40	<0.01	1,2>3,4
P-LCR (%)	28.99±8.22	29.64±7.87	29.50±10.90	29.60±8.80	0.65	-
PLT (X10^3/µL)	257.05±156	238.25±129	291.69±139	281.78±96	<0.01	1,2<3,4

Anova test-post hoc- Sidak, *Significant below the level of 0.05; MPV: mean platelet volume; PDW: platelet distribution width; P-LCR: platelet larger cell ratio; SD: standard deviation.

tween the group with B12 deficiency anemia and vitamin D deficiency and patients with B12 deficiency anemia and no vitamin D deficiency. P-LCR did not differ between the groups that assessed vitamin B12 and vitamin D deficiency (p=0.65). B12 deficiency anemia groups had lower PLT counts than control groups (p<0.01).

To determine the factors affecting the MPV, PDW, P-LCR and PLT parameters, the parameters were considered as continuous variables. Firstly, univariate linear regression analysis was performed to determine factors affecting each parameter. The factors that we obtained statistically significant results in univariate regression analysis were included in the multivariate linear regression analysis model. Regarding MPV, we found that reduced vitamin B12 (β=-0.002, P<0.001) and vitamin D levels (β=-0.005, P<0.001) led to higher MPV values. For PDW, increased ferritin (β=0.019, P<0.001), decreased vitamin B12 (β=-0.004, P<0.001), and vitamin B9 (β=-0.087, P<0.001) led to high PDW values. When P-LCR was evaluated, decreased ferritin (β=0.043, P<0.001) and vitamin D (β=0.027, P<0.001) led to low P-LCR values. Finally, decreased levels of vitamin B9 (β=2.712, P<0.001) and B12 (β=0.158, P<0.001) and increased ferritin (β=-0.853, P<0.001) and vitamin D (β=-0.248, P<0.001) led to lower PLT (Table 5).

Discussion

Platelets are essential for hemostasis. Furthermore, the normal number and morphology of platelets are essential for maintaining hemostasis. Platelet abnormalities that affect the size, shape, and granulation can also cause abnormalities in platelet morphology.[14] MPV, PDW, P-LCR, and PLT are the platelet indices that specify the morphology and function of platelets. In this study, we compared anemia and control groups based on platelet indices, with the additional vitamin D deficiency. As such, we could determine how vitamin D deficiency, which can occur in patients with anemia, could affect the platelet indices.

In our study, when we compared the iron deficiency groups with the control groups, we found that the iron deficiency groups had marked increased PLT. However, when we evaluated the iron deficiency groups according to vitamin D deficiency, there was no significant difference in platelet count. Reactive thrombocytosis is expected in IDA, which we also detected in our study. The cause of re-

Table 5. Potential influencing factors of MPV, PDW, P-LCR and PLT

	Univariate Linear Regression β (95% CI)	p	Multivariate Linear Regression β (95% CI)	p
MPV				
Gender	0.027 (-0.14 – 0.069)	0.190		
Age	0.002 (0.000 – 0.004)	0.034	0.002 (0.000 – 0.004)	0.110
Ferritin	-0.001 (-0.002 – 0.000)	0.053		
B12	-0.001 (-0.001 – 0.000)	<0.001	-0.002 (-0.003 – 0.001)	<0.001
B9	0.005 (0.002 – 0.008)	0.003	0.003 (0.000 – 0.004)	0.069
D vit	-0.005 (-0.006 – -0.004)	<0.001	-0.005 (-0.006 – -0.004)	<0.001
PDW				
Gender	0.154 (0.005 – 0.304)	0.043	0.143 (0.001 – 0.284)	0.052
Age	0.005 (-0.003 – 0.013)	0.191		
Ferritin	0.028 (0.025 – 0.031)	<0.001	0.019 (0.016 – 0.023)	<0.001
B12	-0.003 (-0.003 – 0.002)	<0.001	-0.004 (-0.005 – -0.003)	<0.001
B9	-0.083 (-0.094 – 0.071)	<0.001	-0.087 (-0.099 – -0.075)	<0.001
D vit	0.000 (-0.003 – 0.004)	0.876		
P-LCR				
Gender	0.137 (-0.464 – 0.737)	0.655		
Age	-0.015 (-0.046 – 0.016)	0.359		
Ferritin	0.045 (0.031 – 0.059)	<0.001	0.043 (0.028 – 0.057)	<0.001
B12	-0.001 (-0.004 – 0.002)	0.562		
B9	-0.068 (-0.115 – 0.022)	0.004	-0.036 (-0.083 – 0.012)	0.143
D vit	0.026 (0.012 – 0.041)	<0.001	0.027 (0.013 – 0.041)	<0.001
PLT				
Gender	0.760 (-5.768 – 7.288)	0.819		
Age	-0.080 (-0.417 – 0.258)	0.643		
Ferritin	-1.134 (-1.282 – -0.985)	<0.001	-0.853 (-1.007 – -0.698)	<0.001
B12	0.119 (0.084 – 0.154)	<0.001	0.158 (0.122 – 0.195)	<0.001
B9	2.606 (2.106 – 3.105)	<0.001	2.712 (2.171 – 3.253)	<0.001
D vit	-0.229 (-0.385 – -0.074)	0.004	-0.248 (-0.398 – -0.099)	<0.001

MPV: mean platelet volume; PDW: platelet distribution width; P-LCR: platelet larger cell ratio; β: Beta Coefficient; CI: Confidence Interval.

active thrombocytosis in IDA is not fully understood, but increased TPO is considered in the etiology. However, in a mouse study by Evstatiev et al., thrombocytosis developing due to iron deficiency was found to be TPO-independent.[15] For PDW and P-LCR parameters, when the groups with IDA and control groups were compared, we found that the group with vitamin D and IDA differed significantly from the other groups. Consequently, we found that IDA had a higher platelet count, unchanged average size, lower size variability, and a lower proportion of large cells than the control group. Remarkably, we also found that vitamin D deficiency contributed to reduced size variation and a lower proportion of large cells. In light of these findings, the data implies that the effect of iron deficiency anemia and vitamin D deficiency on platelet indices is synergistic. Meanwhile, our regression analysis confirms this synergistic effect on P-LCR while our group comparisons show this effect on PDW. The close relationship between vitamin D and iron metabolism can explain this synergistic effect. Vitamin D affects iron metabolism, and iron affects vitamin D metabolism. Hepcidin is a hormone that regulates the body's iron metabolism. It is produced mainly by the liver and secreted into the bloodstream where it binds to ferroportin that transports iron out of cells and into the bloodstream. When hepcidin binds to ferroportin, it triggers the internalization and degradation of ferroportin, reducing the amount of iron released into the bloodstream.[16] Vitamin D plays a crucial role in iron metabolism by regulating hepcidin expression. Moreover, studies show that vitamin D levels are inversely related to hepcidin levels and, as a result, are directly related to iron levels.[17, 18] When assessing the effects of iron on vitamin D metabolism, enzymes that convert vitamin D to its active form and fibroblast growth factor 23 (FGF23) are of interest. Hydroxylase group en-

zymes are required to convert vitamin D into its active form, and use iron as a cofactor. FGF23 is a hormone that plays a crucial role in regulating phosphate and vitamin D levels in the body. It is primarily produced by osteocytes residing in mature bone tissue. FGF23 acts on the kidney and parathyroid gland to reduce the amount of phosphate in the blood by decreasing phosphate absorption in the intestines and increasing phosphate excretion in the urine. FGF23 also reduces the production of active vitamin D, which helps to lower phosphate levels by reducing its absorption in the gut.[19] It has been found that iron deficiency causes an increase in FGF23 levels and therefore, causes a decrease in vitamin D levels.[20] The close relationship between vitamin D and iron deficiencies might have caused a synergic effect on PDW and P-LCR parameters. A retrospective study by Kuku et al. evaluating 615 IDA patients found an inverse relationship between platelet count and MPV and PDW parameters.[21]

We found higher PDW values and lower platelet counts in groups with B9 deficiency anemia compared with the control groups. However, when comparing groups with B9 deficiency according to vitamin D, we found that vitamin D deficiency did not make a difference in patients with B9 deficiency anemia. Based on these data, B9 deficiency affects PDW and platelet count, but does not synergize with vitamin D deficiency in affecting these parameters. This condition can be explained by the fact that, unlike iron, there is no strong link between B9 and vitamin D metabolism. We found higher MPV and PDW and lower platelet counts in the B12 deficiency groups compared with the control groups. Of note, when we evaluated the B12 deficiency anemia groups according to vitamin D, we found that vitamin D deficiency affected MPV. Our regression analysis also confirmed that vitamin D and B12 levels were significantly associated with MPV levels. We found that B12 was the only anemia group in which vitamin D deficiency was effective on MPV. One reason could be that vitamin D and B12 deficiency are associated with inflammatory processes.[22] B12 and vitamin D deficiency could act synergistically to trigger inflammation and affect MPV, which can be used as a marker of inflammation.[23] Borkataky et al. showed that thrombocytopenia patients with megaloblastic anemia had higher MPV, PDW, and P-LCR than controls.[24] Another study detected high PDW in megaloblastic anemia groups.[25] Consequently, we found that in B12 deficiency anemia, the number of platelets decreased, the mean size of platelets increased, the size varied more, and the proportion of large platelets remained unchanged compared with the control group. We also found that vitamin D deficiency contributed to an increased mean platelet size. In our study, we found lower platelet counts in patients with B12 and B9 anemia. Vitamins B12 and B9 are both required to produce DNA, including that within bone marrow cells responsible for making blood cells. Therefore, B12 and B9 deficiency anemias can lead to a decrease in platelet count and an increase in immature platelets that are not fully functional. Moreover, severe and prolonged B9 and B12 deficiency anemias can cause bone marrow suppression and pancytopenia due to their role in DNA synthesis. Studies have also shown that B9 and B12 deficiency anemias can reduce TPO levels, reducing platelet production.[26] We determined that all three causes of anemia affect PDW and PLT. Considering that these three causes of anemia affect the bone marrow, it is not surprising that variations in platelet count and platelet size are also affected. PDW could be an essential parameter in evaluating platelet morphology in patients with anemia.

Vitamin D crucially plays a role in several bodily functions, including bone health, immune function, and inflammation regulation. Vitamin D is produced naturally by the body when the skin is exposed to sunlight or obtained from diet and supplementation. Vitamin D deficiency is a common condition and causes many problems, such as fatigue, muscle weakness, bone pain, and sleeping problems. In the regression analysis, the change in vitamin D levels not only influenced the anemia groups concerning MPV, P-LCR, and PLT, but also independently affected MPV, P-LCR, and PLT. Our study revealed that vitamin D is essential for platelet morphology and function in patients with anemia. Although the exact mechanisms by which vitamin D deficiency could cause abnormal platelet morphology, platelet activation, and further risk of thrombosis are not entirely understood, studies suggest that vitamin D might affect platelet function and morphology.[27]

Vitamin D deficiency poses significant risks for inflammation and thrombosis. When vitamin D levels are low, there is an increase in inflammatory cytokines, leading to oxidative stress and heightened platelet activation and aggregation, thus raising the risk of thrombosis.[28] Moreover, deficient vitamin D levels impair endothelial function, exacerbating platelet activation and aggregation, further amplifying the risk of thrombosis.[29] Vitamin D receptors (VDRs) in platelet mitochondria play a crucial role in regulating calcium-dependent platelet activation.[30] Additionally, Vitamin D binding protein (DBP), responsible for transporting and regulating vitamin D levels, has multifaceted functions beyond its primary role. Decreased DBP levels due to vitamin D deficiency may lead to less efficient inhibition of platelet activation mechanisms, further increasing thrombotic risk.[31] Cumulatively, this evidence highlights the importance of vitamin D for platelet morphology and function.

Conclusion

In conclusion, our study highlights that vitamin D deficiency, which might occur in anemia patients, affects platelet indices and could consequently cause hemostasis disorders with the potentially fatal complications. Therefore, it is important to screen patients diagnosed with anemia for vitamin D deficiency and to counteract this deficiency to prevent fatal complications.

Disclosures

Ethics Committee Approval: We adhered to the Declaration of Helsinki and obtained Ethics Committee approval from the institution where we conducted our study. (Decision No: AEŞH-EK1-2023-244. Date: 14.06.2023).

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