**Pediatr Pract Res** 2024; 12(1): 14-19
**DOI:** 10.21765/pprjournal.1444137

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

# The Relationship Between Newly Derived Inflammatory Biomarkers from Hemogram and Serum Vitamin D Concentration in Pediatric Intensive Care Patients

## Çocuk Yoğun Bakım Hastalarında Serum D Vitamini Konsantrasyonu ile Hemogramdan Türetilmiş Yeni İnflamatuar Biyobelirteçler Arasındaki İlişki

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## Abstract

**Aim**: Besides classical disorders of bone metabolism, vitamin D may explain the pathogenesis of many diseases associated with inflammation and vitamin D deficiency. Novel Hemogram-Derived Inflammatory Biomarkers are new and inexpensive markers of inflammation that can be tested in all centers. The aim of this study is to investigate the relationship between 25-hydroxyvitamin D (25(OH)D) and new inflammatory markers and inflammation.

**Material and Method**: This study was conducted prospectively and data from 77 patients treated in the Pediatric Intensive Care Unit were included. Simultaneous 25(OH)D3, calcium, phosphorus and complete blood count results were recorded. Novel hemogram-derived inflammatory biomarkers, systemic inflammatory response index (SIRI) and systemic immune inflammatory index (SII), were calculated.

**Results**: New inflammatory biomarkers derived from hemogram, SII [627552.63 (6000-13572000)-999304.35 (21432.43-18600000)] and SIRI [2013.51 (35-22789.37)-1671.75 (39.25-36000)], did not show statistically significant differences between groups with and without vitamin D deficiency (p>0.05 for all).

**Conclusion**: Our study did not reveal a statistical association between these inexpensive and universally available biomarkers and vitamin D levels and inflammation. The validity of the findings should be confirmed with a larger number of subjects.

**Keywords**: Vitamin D, inflammation, pediatric intensive care, systemic inflammatory index, systemic inflammatory response index

## Öz

**Amaç**: Klasik kemik metabolizması bozukluklarının yanı sıra D vitamini, inflamasyon ve D vitamini eksikliği ile ilişkili birçok hastalığın patogenezini açıklayabilir. Hemogramdan Türetilmiş Yeni İnflamatuar Biyobelirteçler, tüm merkezlerde çalışılabilecek yeni ve ucuz inflamasyon belirteçleridir. Bu çalışmanın amacı, 25-hidroksi D vitamini (25(OH)D) ile yeni inflamatuar belirteçler ile inflamasyon arasındaki ilişkiyi araştırmaktır.

**Gereç ve Yöntem**: Bu çalışma prospektif olarak yürütüldü ve Çocuk Yoğun bakım Ünitesinde tedavi gören 77 hastanın verileri dahil edildi. Eş zamanlı çalışılan 25(OH)D3, kalsiyum, fosfor ve tam kan sayımı sonuçları kaydedildi. Hemogramdan türetilmiş yeni inflamatuar biyobelirteçler, sistemik inflamatuar yanıt indeksi (SIRI) ve sistemik immün inflamatuar indeks (SII) hesaplandı.

**Bulgular**: D vitamini eksikliği olan ve olmayan gruplar arasında hemogramdan türetilmiş yeni inflamatuar biyobelirteçler SII [627552,63 (6000-13572000)-999304,35 (21432,43-18600000] ve SIRI [2013,51 (35-22789,37)-1671,75 (39,25-36000)] açısından istatistiksel olarak anlamlı fark bulunmadı (tümü için p>0,05).

**Sonuç**: Çalışmamız, bu ucuz ve evrensel olarak bulunabilen biyobelirteçler ile D vitamini düzeyleri ve inflamasyon arasında istatistiksel bir ilişki varlığını ortaya koymamıştır. Daha fazla sayıda denek ile bulguların geçerliği doğrulanmalıdır.

**Anahtar Kelimeler**: D vitamini, inflamasyon, çocuk yoğun bakım, sistemik inflamatuar indeks, sistemik inflamatuar yanıt indeksi

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**Başvuru Tarihi/Received:** 27.02.2024
**Kabul Tarihi/Accepted:** 22.03.2024

## INTRODUCTION

The prevalence of vitamin D deficiency is increasingly becoming a significant public health issue. (1) The effects of vitamin D on bone and calcium metabolism are well-known by everyone. However, numerous studies have indicated that vitamin D deficiency contributes to the development, increased risks, and worsening of various diseases. (2-5) Some clinical trials have revealed that vitamin D plays a crucial role in modulating innate immune responses against various pathogens. (6) Furthermore, recent research has associated vitamin D with a range of diseases such as inflammation, depression (7), cardiovascular disease (8), diabetes (9), autoimmune diseases (10), and cancer (11). It has also been demonstrated that vitamin D may regulate adaptive immune responses. (12)

Inflammation is characterized by the detection of high concentrations of inflammatory biomarkers in circulation and plays a role in the pathophysiology of many chronic diseases and various infections. (13) During inflammation, the activation of toll-like receptors and various cytokines such as IFN-γ can upregulate vitamin D binding receptors in macrophages, thereby promoting a rapid conversion from 25(OH)D to 1,25(OH)2D. Other cytokines like IL-4, on the other hand, can induce the catabolism of 25(OH)D into the inactive metabolite 24,25-dihydroxycholecalciferol (24,25(OH)2D) (13). Furthermore, some studies also suggest that chronic inflammation and chronic infections may alter the concentration of 25(OH)D. (13)

The relationship between vitamin D and proinflammatory markers such as soluble tumor necrosis factor-alpha (TNF-a), C-reactive protein (CRP), interleukin (IL)-6, IL-10, has been demonstrated. (14-17) Due to the high cost of these tests, they are not routinely performed in many centers and are not even available in developing countries. In this situation, researchers find it more accessible to investigate the relationship between vitamin D levels and inflammation using inflammatory markers derived from easily measurable, repeatable, and inexpensive hematologic parameters such as neutrophil-to-lymphocyte ratio (NLR) (17,18), platelet-to-lymphocyte ratio (PLR) (17,18), platelet distribution width (PDW) (19), and red cell distribution width (RDW). (18,21,22)

The statistical relationship between neutrophil-to-lymphocyte ratio and infectious diseases, malignancies, cardiovascular diseases, metabolic syndrome, end-stage kidney disease, and other various inflammatory conditions has been demonstrated (5, 22-24) [28-38]. Additionally, similar relationships have been observed for platelet-neutrophil ratio (18, 25).

New biomarkers derived from hemogram, such as the systemic inflammatory response index (SIRI) and systemic immune-inflammation index (SII), which utilize three cell lines (neutrophil, lymphocyte, and platelet), have been investigated not only in determining the outcomes of neoplastic diseases but also in cardiological diseases, autoimmune neurological diseases, and some correlations have been identified (26-29).

Therefore, we aimed to investigate the relationship between vitamin D levels and parameters such as NLR, PLR, LMR, SII, and SIRI, which are considered inexpensive and easily accessible systemic inflammation markers, in individuals under 18 years of age receiving treatment in the pediatric intensive care unit.

## MATERIAL AND METHOD

Our study was a prospective study conducted between November 1, 2018, and September 30, 2019, at the Department of Pediatrics, Selçuk University Faculty of Medicine, Pediatric Intensive care Unit (PICU), involving 80 patients aged between 1 month and 18 years. The patient group consisted of children admitted to the PICU who were planned for diagnosis, treatment, and follow-up for at least 1 day, with no diagnosis of rickets or any known pathology in calcium/phosphorus metabolism. Patients with multiple admissions during the study period were included as separate cases.

Demographic data of patients, admission diagnosis, presence of underlying diseases, duration of stay in the PICU and hospital, need for mechanical ventilation (MV) and vasopressors, PRISM-III and PELOD scores, 25(OH) Vit-D3, Ca, ionized Ca, P, ALP, magnesium (Mg), and albumin values were recorded.

Patient demographic and clinical data, including age, gender, body mass index (BMI) (kg/m2), underlying disease, reason for admission, season, and history of vitamin D supplementation, were recorded at the time of admission to the PICU. Laboratory variables obtained within the first 24 hours of hospitalization, including total calcium, ionized calcium, phosphate, magnesium, and 25(OH)D serum levels, were analyzed.

Patients with blood 25(OH)Vitamin D3 level ≤20 ng/mL were defined as having vitamin D deficiency (30). Patients were divided into two groups based on their 25(OH)Vitamin D3 levels. Forty patients with 25(OH) Vitamin D3 levels ≤20 ng/mL were labeled as "Group-1," while 37 patients with 25(OH)Vitamin D3 levels >20 ng/mL were labeled as "Group-2."

To calculate patients' mortality and morbidity, the Pediatric Risk of Mortality III (PRISM-III) scoring system, which is the most used scoring system for patients in pediatric intensive care, was utilized. Variables used to measure disease severity include the Pediatric Risk of Mortality III (PRISM III) score, catecholamine requirements, mechanical ventilation, length of stay (LOS) in the PICU, and mortality.

In our study, clinical and laboratory investigations were used to diagnose sepsis. The diagnosis of sepsis was made based on clinical evidence of systemic inflammatory response syndrome (SIRS) and/or the presence of microorganisms demonstrated microbiologically.

The NLR was simply calculated by dividing the neutrophil count by the lymphocyte count. Complete blood count analyses were performed on the Beckman Coulter LH 780 model automatic analyzer (Beckman Coulter Inc.; Brea, CA). The manufacturer's original kits were used for hemogram tests.

Blood samples were collected via cephalic venipuncture and analyzed in the hospital laboratory within two hours of collection. SII, defined as (neutrophil count) × (platelet count)/(lymphocyte count), and SIRI, defined as (neutrophil count) × (monocyte count)/(lymphocyte count), were calculated with data obtained from complete blood count reports measured using an automated system .

Serum vitamin D concentrations (1 ng/mL = 2.5 nmol/L) were assessed with the DiaSorin LIAISON® 25 OH Vitamin D TOTAL Assay (Stillwater, MN, USA). This chemiluminescence immunoassay (detection range 4-150 ng/mL, sensitivity 5.0% CV, SD of sensitivity 1.2% [67]) compares well with the Elecsys vitamin D Total Assay, which was previously approved for clinical use by Endocrine. It has the power of harmony.

The study protocol was submitted to Selçuk University Faculty of Medicine, Local Ethics Committee and approval was obtained (decision number: 2018/286).

Statistical analyzes of the study were evaluated as descriptive, univariate, and multivariate analysis methods. In these subsections, mean and standard deviation were used to present numerical data, and percentage values were used to present categorical data. Normal distribution criteria for numerical data were evaluated with the Kolmogorov-Smirnov test. For numerical variables with normal distribution, t-test was used, for numerical variables with non-normal distribution, Mann-Whitney U was used for two-group comparisons, and in the presence of more than two groups, Kruskall-Wallis non-parametric analysis of variance was applied. A two-way hypothesis structure and a 5% Type-1 error level were used in all statistical evaluations of the study. Analyzes were performed in SPSS 21 (IBM Corp. in Armonk, NY, USA) software.

## RESULTS

A total of 77 children, 48 boys and 29 girls, were included in the study. The mean age of the patients was 54 ±64 months (median 16 months). We divided the patients into two groups according to 25(OH)D serum levels. 25 OH) D level was <=20 ng/ml in 40 (52%) patients and >20 ng/ml in 37 (48%) patients. Demographic characteristics and laboratory results of these groups are given in Table 1 and 2. Ages were found to be significantly higher in vitamin D <=20 ng/ml groups ($p < 0.001$). There was no significant difference between vitamin D groups in terms of laboratory results (except calcium and vitamin D) ($p>0.05$ for all).

**Table 1. Demographic characteristics of PICU patients**

| | Vitamin D insufficient | Vit D sufficient | p value |
|---|---|---|---|
| Age(months) | 63.5 (2-207) | 9 (1-216) | 0.000 |
| Gender | | | |
| Male | 23 | 25 | 0.481 |
| Female | 17 | 12 | |
| Weight (kilograms) | 17.5 (4-90) | 5.5 (2.6-60) | 0.000 |
| Height (cm) | 99 (54-192) | 62 (51-170) | 0.000 |
| PRISM III Score | 16.51±7.24 | 16.26±8.53 | 0.886 |

PRISM III Score: Pediatric Risk of Mortality III score

**Table 2. Vitamin D status, laboratory, and indices values in PICU patients**

| | Vitamin D insufficient | Vit D sufficient | p value |
|---|---|---|---|
| Calcium (mg/dL) | 8.95 (6.1-10.8) | 9.7 (7.1-10.7) | **0.005** |
| Hemoglobin (g/dL) | 10.95 (5.5-16.7) | 10.4 (7.1-16.6) | 0.251 |
| Platelet (cells/µL) | 291500 (6000-645000) | 356000 (39000-906000) | 0.061 |
| Neutrophil (cells/µL) | 7750 (420-73630) | 6500 (1300-22650) | 0.939 |
| Lymphocyte (cells/µL) | 2400 (240-15950) | 2900 (200-11100) | 0.763 |
| Monocyte (cells/µL) | 790 (20-3500) | 800 (80-2440) | 0.951 |
| CRP (mg/L) | 9.34 (0.51-684) | 5.05 (0.05-502) | 0.126 |
| Procalcitonin (ng/mL) | 0.37 (0.03-47.52) | 0.32 (0-100) | 0.425 |
| PLR | 98.73 (6-538.57) | 148.62 (3.51-1550) | 0.078 |
| NLR | 2.37 (0.13-36) | 2.39 (0.18-60) | 0.980 |
| MLR | 0.27 (0.04-1.01) | 0.3 (0.02-3) | 0.541 |
| LMR | 3.75 (0.99-27.03) | 3.3 (0.33-55.5) | 0.541 |
| SII | 627552.63 (6000-13572000) | 999304.35 (21432.43-18600000) | 0.343 |
| SIRI | 2013.51 (35-22789.37) | 1671.75 (39.25-36000) | 0.911 |
| Vitamin D (ng/mL) | 10.67 (3-19.69) | 34.36 (21.73-61.53) | **0.000** |

NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte -to- monocyte ratio, PDW: platelet distribution width, CRP: C reactive protein SII: systemic immune-inflammation index SIRI: systemic inflammatory response index

## DISCUSSION

In our study, no significant relationship was found between 25(OH)D3 deficiency and CRP, NLR, PLR, MLR, LMR, SII and SIRI values. Although many publications in the literature show a relationship between 25(OH)D3 deficiency and inflammation, there is no definitive association (19, 32-34). Alrefai et al. reported that 25(OH)D3 levels decreased, and hs-CRP levels increased as disease activity increased

in 201 patients with Crohn's disease (32). Mathur et al. They revealed that CRP levels decreased in response to vitamin D supplementation in ulcerative colitis patients with vitamin D deficiency (33). In the study by Akbaş et al., which retrospectively examined 4120 patients with 25(OH)D3 deficiency, it was reported that there was a negative correlation between 25(OH)D3 deficiency and CRP, NLR and PLR values (19). They also stated that NLR and PLR, which are easily calculated, practical, reproducible, and affordable parameters, can be used as biomarkers for endothelial dysfunction as well as inflammation (19). In a study where hs-CRP and NRL levels were evaluated before and after vitamin D supplementation in 580 healthy adolescents in Iran, it was reported that hs-CRP and NRL levels decreased after vitamin D supplementation (35). According to the study, they said that NLR could be an inexpensive marker to reveal inflammatory processes in evaluating the relationship with vitamin D supplementation. In a study conducted on hemodialysis patients, it was reported that there was a significant relationship between 25(OH)D3 and NLR (36). In a study that included patients who applied to physical medicine and rehabilitation outpatient clinics with complaints of non-specific muscle or joint pain, a negative relationship was found between CRP and 25(OH)D3 levels, but no relationship was found between 25(OH)D3 and NLR and PLR values (18).

There are also studies reporting that there is no relationship between CRP and 25(OH)D3 deficiency (37, 38). In a study conducted on patients with and without chronic kidney disease, it was reported that there was no relationship between 25(OH)D3 and CRP, ESR and hemogram values (37). In their study investigating the relationship between factors underlying cardiovascular disease and 25(OH)D3, Kim et al. (38) reported that there was no connection between 25(OH)D3 and CRP and interleukin-6 (38). In our study, there was no relationship between both CRP and hemogram-derived inflammatory markers and vitamin D deficiency.

Thrombosis may develop due to platelet activation in response to the inflammatory condition. Chemokines secreted when platelets are activated play a role in the immune response by acting as acute phase reactants (39). It has been reported that platelets with higher MPV values are found in inflamed tissues. High MPV level has been found to be associated with various infections, cardiovascular and cerebrovascular diseases, thrombosis and diseases with low levels of inflammation (40, 41). Sobolewska et al. (8) evaluated MPV in the evaluation of subclinical inflammation and response to biological treatment in Crohn's patients, and stated that high MPV was a good marker predicting a good response to infliximab treatment (42).

In a study conducted on newborns, NLR values were found to be significantly higher in patients with vitamin D deficiency. A positive correlation was also found between the vitamin D status of the mother and the newborn. Neonatal NLR was negatively correlated with newborn vitamin D status, this neonatal study revealed an inverse relationship between non-invasive, easy and inexpensive markers of inflammation and vitamin D status. It has been inferred that vitamin D deficiency may increase susceptibility to infection (43).

Another study conducted in Turkey on adults without acute inflammation, infection or chronic disease showed that both NLR and MPV could be markers of the inflammatory burden in vitamin D deficiency (44).

In a study evaluating hematological parameters and inflammatory markers in children with COVID-19, LMR was significantly higher in hospitalized patients; However, NLR, PLR, d-NLR and MPVLR were found to be significantly low, and no statistically significant difference was found in terms of SII between hospitalized and outpatient patient groups (45).

In a study evaluating the relationship between serum vitamin D concentrations and new inflammatory markers (SIRI and SII) in patients who underwent coronary angiography due to suspicion of acute coronary syndrome, it was shown that patients diagnosed with ACS had lower serum vitamin D levels. In addition, SIRI (but not SII) was significantly correlated with serum vitamin D concentration in the entire analyzed group, with SIRI and SII both negatively associated with vitamin D levels in patients with ACS (29).

In a study of children without any acute infection and/or chronic disease, it was found that vitamin D levels had a significant negative correlation with NLR, PLR and PDW, and a positive correlation with LMR and RDW. They stated that, despite this statistical significance, the difference between the median values of the vitamin D groups is very small and the degree of correlation is very weak, so the clinically expected significant difference in laboratory results between the vitamin D groups should also be questioned (46).

The main limitation of the study is that the inflammatory parameters we examined cannot be compared with more specific inflammatory parameters such as procalcitonin, IL-6, IL-10. Since our study was conducted on patients in intensive care and was not conducted on healthy children who applied for routine check-ups, a control group was not created. We believe that it would be useful to simultaneously evaluate the relationship between vitamin D and hemogram-derived inflammatory parameters and specific biomarkers in prospective studies. Secondly, since it is a single-center study, its generalizability is limited, and it would be appropriate to increase the number of samples. Third, although the study was a prospective study, we could not evaluate whether vitamin D supplementation

changed inflammatory markers in those with vitamin D deficiency, as there was no study examining the effect of treatment.

## CONCLUSION

Although many studies show that vitamin D deficiency is associated with hemogram-derived inflammatory markers, we cannot say that there is a statistically significant relationship. These inflammatory markers are advantageous because they are simple, inexpensive, and readily available. However, we think that the validity of the findings should be confirmed with a larger number of subjects.

## ETHICAL DECLARATIONS

**Ethics Committee Approval**: The study was carried out with the permission of Selçuk University Non-interventional Clinical Researches Ethics Committee (Date: 25/07/2018, Decision No: 2018/286).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

**Acknowledgement**: We would like to thank all the parents who agreed to participate in the study.

## REFERENCES

1. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81.
2. Makhsudov J, Yilmaz R. Vitamin D Deficiency in Children [in Turkish]. Chron Precis Med Res. 2020;1(1):8-19.
3. Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. Diabetes Care. 2007;30(4):980-6.
4. Gul A, Ozer S, Yilmaz R, et al. Association between vitamin D levels and cardiovascular risk factors in obese children and adolescents. Nutr Hosp. 2017;34(2):323-9.
5. Wu S, Sun J. Vitamin D, vitamin D receptor, and macroautophagy in inflammation and infection. Discov Med. 2011;11(59):325-35.
6. Sonmezgoz E, Ozer S, Yilmaz R, Onder Y, Butun I, Bilge S. [Hypovitaminosis D in Children with Hashimoto's Thyroiditis]. Rev Med Chil. 2016;144(5):611-6.
7. Ismailova A, White JH. Vitamin D, infections and immunity. Rev Endocr Metab Disord. 2022;23(2):265-77.
8. Han QQ, Yu J. Inflammation: a mechanism of depression? Neurosci Bull. 2014;30(3):515-23.
9. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15(9):505-22.
10. Tsalamandris S, Antonopoulos AS, Oikonomou E, et al. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. Eur Cardiol. 2019;14(1):50-9.
11. Yi YS. Role of inflammasomes in inflammatory autoimmune rheumatic diseases. Korean J Physiol Pharmacol. 2018;22(1):1-15.
12. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity. 2019;51(1):27-41.
13. Tiosano D, Wildbaum G, Gepstein V, et al. The role of vitamin D receptor in innate and adaptive immunity: a study in hereditary vitamin D-resistant rickets patients. J Clin Endocrinol Metab. 2013;98(4):1685-93.
14. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. Journal of inflammation research. 2014:69-87.
15. Sharifi A, Vahedi H, Nedjat S, Rafiei H, Hosseinzadeh-Attar MJ. Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. APMIS. 2019;127(10):681-7.
16. Miroliaee AE, Salamzadeh J, Shokouhi S, Sahraei Z. The study of vitamin D administration effect on CRP and Interleukin-6 as prognostic biomarkers of ventilator associated pneumonia. J Crit Care. 2018;44:300-5.
17. Zittermann A, Dembinski J, Stehle P. Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin-10. Pediatr Allergy Immunol. 2004;15(3):242-6.
18. Altaş EU, Tosun A. Assessment of Vitamin D and inflammatory response relationship using neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and mean platelet volume. Turk Osteoporoz Dergisi. 2018;24(1):11.
19. Akbas EM, Gungor A, Ozcicek A, Akbas N, Askin S, Polat M. Vitamin D and inflammation: evaluation with neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio. Arch Med Sci. 2016;12(4):721-7.
20. Coşkun C, Şahin K. Correlation between vitamin D level and platelet indices in children aged 0-18 years. Haseki Tip Bulteni. 2018;56(2):153.
21. Otero TMN, Monlezun DJ, Christopher KB, Camargo CA, Quraishi SA. Vitamin D Status and Elevated Red Cell Distribution Width in Community-Dwelling Adults: Results from the National Health and Nutrition Examination Survey 2001-2006. J Nutr Health Aging. 2017;21(10):1176-82.
22. Turkmen K, Erdur FM, Ozcicek F, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17(3):391-6.
23. Sunbul M, Gerin F, Durmus E, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. Clin Exp Hypertens. 2014;36(4):217-21.
24. Akbas EM, Demirtas L, Ozcicek A, et al. Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. Int J Clin Exp Med. 2014;7(7):1794-801.
25. Taylor MH, Takahashi S, Capdevila J, et al. Correlation of Performance Status and Neutrophil-Lymphocyte Ratio with Efficacy in Radioiodine-Refractory Differentiated Thyroid Cancer Treated with Lenvatinib. Thyroid. 2021;31(8):1226-34.
26. Gary T, Pichler M, Belaj K, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One. 2013;8(7):e67688.
27. Geng Y, Zhu D, Wu C, 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.
28. Dziedzic EA, Gąsior JS, Tuzimek A, et al. Investigation of the Associations of Novel Inflammatory Biomarkers-Systemic Inflammatory Index (SII) and Systemic Inflammatory Response Index (SIRI)-With the Severity of Coronary Artery Disease and Acute Coronary Syndrome Occurrence. Int J Mol Sci. 2022;23(17).
29. Dziedzic EA, Gąsior JS, Tuzimek A, Dąbrowski M, Jankowski P. The Association between Serum Vitamin D Concentration and New Inflammatory Biomarkers-Systemic Inflammatory Index (SII) and Systemic Inflammatory Response (SIRI)-In Patients with Ischemic Heart Disease. Nutrients. 2022;14(19).
30. Huang X, Xu M, Wang Y, et al. The systemic inflammation markers as possible indices for predicting respiratory failure and outcome in patients with myasthenia gravis. Ann Clin Transl Neurol. 2023;10(1):98-110.

31. Adams JS, Hewison M. Update in vitamin D. J Clin Endocrinol Metab. 2010;95(2):471-8.
32. Alrefai D, Jones J, El-Matary W, et al. The Association of Vitamin D Status with Disease Activity in a Cohort of Crohn's Disease Patients in Canada. Nutrients. 2017;9(10).
33. Mathur J, Naing S, Mills P, Limsui D. A randomized clinical trial of vitamin D(3) (cholecalciferol) in ulcerative colitis patients with hypovitaminosis D(3). Peer J. 2017;5:e3654.
34. Yilmaz R, Karaaslan E, Albayrak SE, Gul A, Kasap T. Effect of platelet activity markers on patients admitted to children's intensive care unit due to Crimean-Congo hemorrhagic fever. Chron Precis Med Res. 2021;2(1):13-8.
35. Tabatabaeizadeh SA, Avan A, Bahrami A, et al. High Dose Supplementation of Vitamin D Affects Measures of Systemic Inflammation: Reductions in High Sensitivity C-Reactive Protein Level and Neutrophil to Lymphocyte Ratio (NLR) Distribution. J Cell Biochem. 2017;118(12):4317-22.
36. Mirchi E, Saghafi H, Gharehbeglou M, Aghaali M, Rezaian Z, Ghaviahd M. Association Between 25-Hydroxyvitamin D Level and Inflammatory and Nutritional Factors in Hemodialysis and Peritoneal dialysis Patients in Qom, Iran. Iran J Kidney Dis. 2016;10(4):205-12.
37. Yildirim I, Hur E, Kokturk F. Inflammatory Markers: C-Reactive Protein, Erythrocyte Sedimentation Rate, and Leukocyte Count in Vitamin D Deficient Patients with and without Chronic Kidney Disease. Int J Endocrinol. 2013;2013:802165.
38. Kim M, Na W, Sohn C. Correlation between vitamin D and cardiovascular disease predictors in overweight and obese Koreans. J Clin Biochem Nutr. 2013;52(2):167-71.
39. Flad HD, Brandt E. Platelet-derived chemokines: pathophysiology and therapeutic aspects. Cell Mol Life Sci. 2010;67(14):2363-86.
40. Jiang Z, Jiang X, Chen A, He W. Platelet activation: a promoter for psoriasis and its comorbidity, cardiovascular disease. Front Immunol. 2023;14:1238647.
41. Vagionas D, Papadakis DD, Politou M, Koutsoukou A, Vasileiadis I. Thromboinflammation in Sepsis and Heparin: A Review of Literature and Pathophysiology. In Vivo. 2022;36(6):2542-57.
42. Sobolewska A, Włodarczyk M, Stec-Michalska K, Fichna J, Wiśniewska-Jarosińska M. Mean Platelet Volume in Crohn's Disease Patients Predicts Sustained Response to a 52-Week Infliximab Therapy: A Pilot Study. Dig Dis Sci. 2016;61(2):542-9.
43. Elgormus Y, Okuyan O, Uzun H. The relationship between hematological indices as indicators of inflammation and 25-hydroxyvitamin D3 status in newborns. BMC Pediatr. 2023;23(1):83.
44. Erkus E, Aktas G, Atak BM, Kocak MZ, Duman TT, Savli H. Haemogram Parameters in Vitamin D Deficiency. J Coll Physicians Surg Pak. 2018;28(10):779-82.
45. Alkan G, Sert A, Emiroglu M, Tuter Oz SK, Vatansev H. Evaluation of hematological parameters and inflammatory markers in children with COVID-19. Ir J Med Sci. 2022;191(4):1725-33.
46. Konuksever D, Yücel Karakaya SP, Bölük O, Koçak M, Kılıç BO, Saç R. The association of vitamin D deficiency with hemogram-derived inflammatory biomarkers in children. Nutr Metab Cardiovasc Dis. 2022;32(10):2418-23.