The relationship between serum vitamin D levels and hematological inflammatory indices in patients with heart failure

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Abstract

Objectives: Recent studies have suggested that chronic systemic inflammation increases the risk of development and progression of heart failure (HF). Vitamin D may contribute to the pathogenesis of HF by modulating inflammatory pathways. Changes in brain natriuretic peptide (BNP) levels are critical for the diagnosis and assessment of HF severity. We aimed to investigate the association between serum vitamin D levels, BNP, and novel hematological systemic inflammation indices in chronic heart failure (CHF) patients.

Methods: In this retrospective study, we report data from 187 participants admitted to the outpatient clinic, with 85 CHF and 102 without CHF (control group). Vitamin D, BNP, and complete blood cell samples were analyzed. Novel hematological systemic inflammation indices—the systemic immune-inflammation index (SII; neutrophil × platelet / lymphocyte), the systemic inflammation response index (SIRI; neutrophil count × monocyte/lymphocyte count), the pan-immune-inflammation value (PIV; neutrophil count × platelet count × monocyte count)/lymphocyte count, monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR)—were calculated.

Results: Binomial logistic regression showed that only MLR was significantly associated with CHF (P < 0.001). A weak, negative, and statistically significant correlation was found between BNP and vitamin D (r=−0.185, p=0.011) levels. There was a weak negative correlation between vitamin D and PLR (r=−0.196, p=0.007), PIV (r=−0.145, p=0.048), and SIRI (r=−0.156, p=0.033).

Conclusion: An independent association between systemic hematological inflammatory indicators and vitamin D with the severity of CHF expressed by elevated BNP levels was revealed.

Keywords: BNP, heart failure, lymphocyte, neutrophil, vitamin D

cardiac contractile dysfunction, hypertrophy, apoptosis, and remodeling [3, 4].

Measurements of blood cell count levels associated with maintaining a subclinical inflammatory environment are inexpensive markers for detecting inflammatory activity. Chronic sterile inflammation plays a critical role in cardiac hypertrophy and cardiac failure [5]. Neutrophilia, lymphocytosis, and thrombocytopenia are common findings in patients with acute or chronic HF, regardless of etiology [6–8]. Circulating inflammatory cells correlate with the severity of CHF [9, 10]. Changes in natriuretic peptide concentrations, either brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), are critical for the diagnosis of HF, accurate assessment of prognosis, and assessment of HF severity [11, 12]. BNP secretion is mainly dependent on ventricular volume expansion and pressure overload. BNP levels provide objective inclusion criteria for clinical trials [12]. Natriuretic peptides are also elevated in inflammation as a protective mechanism to maintain inflammatory homeostasis [13].

In clinical practice, novel systemic inflammatory hematological indices that reflect a balance between the host’s inflammatory and immune responses are used for predicting outcomes in patients with acute HF [14, 15]. Recent research has raised the possibility that inflammatory markers may be complementary biomarkers of CHF [1, 16], which can be simply calculated with the data obtained from the complete blood count. The systemic immune-inflammation index (SII; neutrophil × platelet / lymphocyte), the systemic inflammation response index (SIRI; neutrophil count × monocyte / lymphocyte count), the pan-immune-inflammation value (PIV; neutrophil count × platelet count × monocyte count) / lymphocyte count, and platelet-to-lymphocyte ratio (PLR) based on lymphocyte, neutrophil, and platelet counts, may more comprehensively represent the inflammatory state [14–18].

Vitamin D has effects on the cardiovascular system as well as its well-known effects on bone health and metabolism [19]. Additionally, recent data have revealed the effects of vitamin D on innate and adaptive immunity [19, 20].

An association between an increased risk of developing HF and vitamin D deficiency has been observed in patients [21–23]. It has also been suggested that vitamin D may contribute to the pathogenesis of HF by modulating inflammatory pathways [24].

We aimed to investigate the associations between serum vitamin D levels, novel hematological systemic inflammation, and B-type natriuretic peptide (BNP) levels in CHF patients.

**Materials and Methods**

Our study protocol was approved by the institutional ethics committee (2011-KAEK-25 2022/11-19).

In this retrospective study, we reviewed the medical records of all patients with confirmed CHF diagnoses who were admitted to the outpatient department of Bursa Yuksek Ihtisas Education and Research Hospital between September 1, 2021, and March 30, 2022. Among the 11,000 patients who had blood BNP levels measured, outpatients with simultaneous blood collections for BNP, complete blood cell count, and vitamin D were included. Those with BNP levels between 100 to 500 pg/mL and those with incomplete medical records were excluded.

We included a total of 187 participants in the study, all at least 18 years of age. These participants were divided into two groups according to their BNP levels. The BNP concentrations in patients with and without CHF were between 518–8374 pg/ml and <100 pg/ml, respectively. The comparison group was composed of patients admitted to the outpatient clinic for control purposes.

The patients’ demographic characteristics, medical histories, and blood test results were collected from the hospital’s medical records. We excluded patients with acute coronary syndrome, active cancer, end-stage kidney disease, total white blood counts exceeding 1.0×10⁴ cells/μL, active viral or bacterial infections, or any history of hematological diseases.

The complete blood cell samples were analyzed using an automated hematology analysis system (Mindray BC-6000 hematology analyzer; Mindray, Shenzhen, China). The BNP concentrations were measured using an Abbott Architect Analyzer (Abbott, Chicago, Illinois).

SII was calculated as follows: neutrophil × platelet / lymphocyte [17]. SIRI was defined as neutrophil count × monocyte / lymphocyte count [14]. The pan-immune-inflammation value (PIV) included all the immune-inflammatory cells in the peripheral blood count: (neutrophil count × platelet count × monocyte count) / lymphocyte count [18]. Monocyte-to-lymphocyte ratio (MLR), neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red cell distribution width to platelet ratio (RDW to PLT) were calculated from whole blood counts [10,14–18].

Due to the retrospective nature of the study, we could not include other inflammatory markers such as C-reactive protein, fibrinogen, interleukins, and others.

**Statistical analysis**

The statistical software package SPSS 21.0 (SPSS, Chicago, IL) was used to conduct the statistical analysis. The characteristics of the study sample were reported using descriptive statistics. The Kolmogorov-Smirnov test was used to test for normal distribution. Groups were compared using Student’s t-test or Mann-Whitney U test for continuous variables and chi-squared test for categorical variables. Pearson correlation analysis was used to verify the correlation between selected variables. Correlation coefficients (r) were deemed statistically significant when the p-value was <0.05. Binomial logistic regression analysis was performed to quantify the correlation between variables and CHF.

**Results**

The study included 187 patients admitted to the outpatient department, of which 85 had CHF and 102 did not.
mographic, clinical, and laboratory parameters of the two groups are presented in Table 1. The median age of the study sample was 67 years (IQR: 19), and 48% of the patients were male (97 females, 90 males). Vitamin D levels were lower in CHF patients ($p<0.001$), and the inflammatory indices NLR, MLR, PLR, SII, SIRI, PIV, and RDW to PLT were significantly higher in CHF patients than in the control group ($p<0.001$). Binomial logistic regression analysis showed that only MLR was significantly associated with CHF ($p<0.001$), but other hematological indices were statistically insignificant ($p>0.005$), and vitamin D is not an independent risk factor for CHF. Data from the two groups were pooled to analyze the relationships between vitamin D and BNP using other hematological parameters (Table 2). The correlation between BNP and MLR ($r=0.485$, $p<0.001$), SIRI ($r=0.504$, $p<0.001$), and PIV ($r=0.423$, $p<0.001$) was higher than the correlation with other inflammatory indexes. There was a very weak negative correlation between vitamin D and PLR ($r=-0.196$, $p=0.007$), PIV ($r=-0.145$, $p=0.048$), and SIRI ($r=-0.156$, $p=0.033$).

### Discussion

The present study had four main findings. First, we found lower serum vitamin D levels in CHF patients compared to control subjects. This finding is confirmed by a number of previous studies suggesting that insufficient vitamin D status may increase the risk of HF [21–26]. We also found a weak negative correlation between BNP levels and vitamin D levels [25–27]. These patients are at risk of having low serum vitamin D levels due to their limited exercise capacity and inadequate exposure to sunlight. Additionally, we observed a positive relationship between BNP concentration and hematologic inflammatory indices in patients with CHF. There was a very weak negative correlation between vitamin D and PLR ($r=-0.196$, $p=0.007$), PIV ($r=-0.145$, $p=0.048$), and SIRI ($r=-0.156$, $p=0.033$).

#### Table 1: Demographic and laboratory parameters in patients with and without CHF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CHF group (n=85)</th>
<th>Control group (n=102)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (23)</td>
<td>64 (19)</td>
<td>0.083</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>58</td>
<td>0.144</td>
</tr>
<tr>
<td>Male</td>
<td>46</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>1288 (1711)</td>
<td>29 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>10.8 (18)</td>
<td>17.3 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total WBC ($\times 10^9$/L)</td>
<td>7.7 (2.8)</td>
<td>7.0 (2.9)</td>
<td>0.068</td>
</tr>
<tr>
<td>Neu ($\times 10^9$/L)</td>
<td>5.5 (1.7)</td>
<td>4.3 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lym ($\times 10^9$/L)</td>
<td>1.1 (0.9)</td>
<td>2.0 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mono ($\times 10^9$/L)</td>
<td>0.49 (0.30)</td>
<td>0.46 (0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLT ($\times 10^9$/L)</td>
<td>237 (119)</td>
<td>253 (90)</td>
<td>0.024</td>
</tr>
<tr>
<td>NLR</td>
<td>4.76 (3.54)</td>
<td>1.94 (0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLR</td>
<td>0.41 (0.40)</td>
<td>0.21 (0.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SII</td>
<td>1078 (1109)</td>
<td>491 (284)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SIRI</td>
<td>2.05 (2.01)</td>
<td>0.92 (0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PIV</td>
<td>531 (594)</td>
<td>214 (226)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RDW to PLT</td>
<td>0.067 (0.032)</td>
<td>0.055 (0.022)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHF: Chronic heart failure; IQR: Interquartile range; BNP: Brain natriuretic peptide; WBC: White blood cell; Neu: Neutrophil; Lym: Lymphocyte; Mono: Monocyte; PLT: Platelet; NLR: Neutrophil to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammatory response index; PIV: Pan immune inflammation value; RDW to PLT: Red cell distribution width to platelet.

#### Table 2: Correlation of BNP and vitamin D and inflammatory indices

<table>
<thead>
<tr>
<th>BNP</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>rho</td>
<td>rho</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>$-0.185$</td>
</tr>
<tr>
<td>Neu</td>
<td>0.409</td>
</tr>
<tr>
<td>Lym</td>
<td>$-0.405$</td>
</tr>
<tr>
<td>NLR</td>
<td>0.368</td>
</tr>
<tr>
<td>MLR</td>
<td>0.485</td>
</tr>
<tr>
<td>PIV</td>
<td>0.423</td>
</tr>
<tr>
<td>PLR</td>
<td>0.361</td>
</tr>
<tr>
<td>SIRI</td>
<td>0.324</td>
</tr>
<tr>
<td>SII</td>
<td>0.504</td>
</tr>
<tr>
<td>RDW to PLT</td>
<td>0.053</td>
</tr>
</tbody>
</table>

*: Correlation is significant at the 0.05 level; **: Correlation is significant at the 0.01 level. PLR: Platelet to lymphocyte ratio.

Recent data also show a correlation between decreased vitamin D and other inflammatory markers, such as C-reactive protein and fibrinogen [37]. However, they usually reflect acute inflammation, whereas complex hematological markers could better reflect the long-term inflammatory state of CHF. These markers could be auxiliary biomarkers of severity and may represent a treatment target [8, 38].
A study by Tabatabaeizadeh et al. [39] demonstrates that high-dose supplementation of vitamin D leads to reductions in NLR levels. However, anti-inflammatory clinical trials have shown limited success in patients with CHF [40]. The complexity of inflammatory responses may partially explain these unsatisfactory results.

**Limitations**

The main limitation of our study is that it was conducted retrospectively at a single center. Second, the study was based on data from patients' medical histories, and other inflammatory markers could not be included. Furthermore, the effects of comorbidities, rheumatological diseases, smoking status, the effects of the drugs patients used, and vitamin D ingestion were not taken into account. The number of patients evaluated is very low, and causal relationships cannot be established from this observational study. Well-designed, larger prospective multicenter studies with more comprehensive data are needed to confirm the findings of this study.

**Conclusion**

An independent association between systemic hematological inflammatory indicators and vitamin D with the severity of CHF expressed by elevated BNP levels was revealed. These results may contribute to a better understanding of how patients' inflammatory responses could be related to vitamin D levels. They could also lead to further studies that will elucidate this relationship.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

**Ethics Committee Approval:** The study was approved by The University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (No: 2011-KAEK 25 2022/11-19, Date: 30/11/2022).

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**References**


11. Maries L, Manitiu I. Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP). Cardiovasc J Afr 2013;24(7):286–9. [CrossRef]


22. Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease will it live up to its hype? J Am Coll Cardiol 2011;58(15):1547–56. [CrossRef]


35. Mongirdiene A, Laukaitiene J, Skipskis V, Kursvietiene L, Lio-bikas J. The difference of cholesterol, platelet and cortisol levels in patients diagnosed with chronic heart failure with reduced ejection fraction groups according to neutrophil count. Medicina Kaunas 2021;57(6):557. [CrossRef]


38. Curran FM, Bhalraum U, Mohan M, Singh JS, Anker SD, Dickstein K, et al. Neutrophil-to-lymphocyte ratio and outcomes in patients with new-onset or worsening heart failure with reduced and preserved ejection fraction. ESC Heart Fail 2021;8(4):3168. [CrossRef]
