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The Relationship Between Hematological Inflammatory Markers and Postoperative Hypocalcemia in Patients with Primary Hyperparathyroidism

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Abstract

Objective

Primary hyperparathyroidism (PHPT) is a common endocrine disease that is characterized by hypercalcemia and commonly associated with parathyroid adenoma (PTA). Hypocalcemia is a common postoperative complication in patients with PHPT. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive hematological inflammatory markers. We aimed to investigate the potential predictive risk factors, including the hemogram-derived inflammatory markers for early postoperative hypocalcemia in patients with PHPT.

Material and Method

Patients diagnosed with PHPT, underwent parathyroidectomy and histopathologically shown to be caused by a single PTA were included.

Results

NLR was significantly correlated with parathormone (PTH), while PLR was related considerably with only NLR. A significant positive correlation was shown between gland weight, volume, calcium (Ca), and PTH levels. A significant correlation of postoperative hypocalcemia with age, preoperative Ca, PTH, and NLR was also demonstrated.

Conclusion

We found that NLR was significantly higher in patients with PHPT who developed postoperative hypocalcemia; however, our regression analysis did not find elevated NLR as a significant predictive risk factor for postoperative hypocalcemia. To the best of our knowledge, this is the first study investigating the relationship between hemogram-derived inflammatory markers and clinical parameters, such as the development of postoperative hypocalcemia and preoperative nephrolithiasis, in patients with PHPT.

Keywords: Hyperparathyroidism, hypocalcemia, neutrophils, lymphocytes, platelets

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Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disease that is presented with hypercalcemia and is commonly associated with a parathyroid adenoma (PTA) (1). Parathyroidectomy has been described as the gold standard therapy for PHPT to normalize serum calcium (Ca) and parathyroid hormone (PTH) levels (2). Hypocalcemia is a common postoperative complication with a 2.3-42% incidence in patients with PHPT (3,4). Even if postoperative hypocalcemia is most commonly temporary, the outcome of this early postoperative complication might be life-threatening; therefore, hospitalization for several days after parathyroidectomy has been recommended by many experienced physicians (5,6). Multiple factors, such as age, PTH, alkaline phosphatase, preoperative serum calcium, osteocalcin, and vitamin D levels, were found to correlate with postoperative hypocalcemia in patients with secondary hyperparathyroidism. At the same time, there was no correlation between laboratory or other clinical factors and postoperative hypocalcemia in patients with primary hyperparathyroidism (4,7–9).

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive hematological inflammatory markers, and these markers are currently in use to indicate the severity of systemic inflammation or infectious complications (10,11). A relationship between PHPT and systemic inflammation has been described by several studies, as a possible consequence of elevated serum calcium levels, which might trigger systemic inflammation (12,13). Furthermore, PTH alone has been shown to stimulate interleukin-6 production and high PTH levels have been reported in septic patients (14,15). In line with these data, NLR has been found significantly related to various parameters, such as serum PTH, Ca, and P levels, white blood cell count, and parathyroid adenoma size (16–18). In this study, we aimed to investigate the potential predictive risk factors, including the hemogram-derived inflammatory markers for early postoperative hypocalcemia in patients with PHPT.

Material and Method

Patients aged >18 years and who were diagnosed with PHPT, underwent parathyroidectomy and histopathologically shown to be caused by a single PTA at our institute between 2010 and 2021 were included in our retrospective study. Demographics, preoperative albumin-corrected serum Ca, phosphorus (P), PTH, 25-hydroxy vitamin D (25OH-D), 24-hour urine calcium (24hr UCa), neutrophil, platelet, and lymphocyte counts, gonadal status of patients, lowest postoperative corrected calcium, the presence of nephrolithiasis demonstrated by any imaging technique and weight of the surgically removed parathyroid gland were recorded. Additionally, lengths of 3 dimensions of PTA given by our pathology department were recorded to calculate the volume of PTA. The volume of a parathyroid adenoma was calculated using the formula for an ellipsoid (Volume = [4/3] π r1r2r3, where r1, r2, r3 are the lengths of the semiaxes in centimeters). Corrected calcium was derived using the following calculation: serum calcium (mg/dL) + 0.8 x (4 - serum albumin [g/dL]). PLR was calculated as the ratio of platelet count to lymphocyte count and NLR as the ratio of neutrophil count to lymphocyte count. Postoperative hypocalcemia was described as a serum calcium level of less than 8.5 mg/dL on the first biochemical test following parathyroidectomy.

The IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. The normality assumption was assessed by using the Kolmogorov-Smirnov and Shapiro-Wilk's tests. Continuous variables were given as either mean standard deviation or median (interquartile range) depending on the distribution pattern. The Mann-Whitney U test was used to perform the comparisons between groups and the Spearman's correlation analysis was used to determine the correlations between continuous variables. The receiver operating characteristics (ROC) analysis was used to determine the area under the curve (AUC) and cut-off values. A p-value <0.05 was considered statistically significant.

Results

A total of 368 patients were included in our study. The basic clinical and demographic features of this population are presented in Table 1. The mean age of the patients was 53.1 ± 12.9, with a female-to-male ratio of approximately 5 to 1. The Spearman's correlation analysis demonstrated that NLR was significantly correlated with PTH and PLR ($p = 0.001$, $r = 0.173$; $p < 0.001$, $r = 0.517$, respectively), while PLR was significantly related to only NLR. A significant positive correlation between gland weight and volume, and Ca and PTH levels was shown (weight and Ca, $p = 0.001$, $r = 0.187$; weight and PTH, $p < 0.001$, $r = 0.370$; volume and Ca, $p < 0.001$, $r = 0.198$; volume and PTH, $p < 0.001$, $r = 0.324$), while there was a significant but very weak negative correlation between gland volume and weight, and P levels (weight and P, $p = 0.044$, $r = -0.119$; volume and P, $p = 0.009$, $r = -0.141$). A very strong correlation between gland weight and volume ($p < 0.001$, $r = 0.831$) was also demonstrated.

Table 1 Demographics and clinical characteristics of patients (n=368)

Characteristic	n (%)
Age (years), median (min-max)	54 (18-84)
Gender	
male	60 (16.3)
female	308 (83.7)
Gonadal Status	
menopausal	158 (52.5)
eugonadal	143 (47.5)
Preoperative Nephrolithiasis	
yes	47 (28.3)
no	119 (71.7)
Postoperative Hypocalcemia	
yes	81 (22.1)
no	286 (77.9)
median (25^{th}-75^{th} percentile)	
Ca (mg/dL)	10.7 (10.3-11.2)
P (mg/dL)	2.6 (2.3-3.0)
PTH (pg/mL)	194 (135-305)
Postoperative PTH (pg/mL)	29 (13-74)
25OH-D (ng/mL)	17 (11-25)
NLR	1.95 (1.52-2.69)
PLR	117.45 (90.93-148.02)
Macroscopic Characteristics of Adenoma	
weight (gr)	1.10 (0.50-2.36)
volume (cm^3)	5.86 (2.51-16.03)

Ca: calcium NLR: neutrophil lymphocyte ratio; P: phosphorus; PLR: platelet lymphocyte ratio; PTH: parathyroid hormone; 25OH-D: 25-hydroxy vitamin D

A significant relationship between postoperative hypocalcemia and age, preoperative Ca, PTH, and NLR was demonstrated ($p = 0.001$, $p = 0.014$, $p = 0.003$, and $p = 0.031$, respectively) by the Mann-Whitney U test (Table 2). NLR values of patients who developed postoperative hypocalcemia were significantly higher than patients without. ROC curve analysis was performed to estimate preoperative predictive levels of Ca, PTH, age, and NLR for postoperative hypocalcemia (Figure 1). The threshold Ca level that would distinguish between patients who developed postoperative hypocalcemia and those who did not was 10.3 with an AUC of 0.589 ($p = 0.02$), 351 for PTH with an AUC of 0.614 ($p < 0.01$), 51 for age with an AUC of 0.623 ($p < 0.01$), and 2.95 for NLR with an AUC of 0.579 ($p = 0.03$). Moreover, there was also a significant association between the preoperative nephrolithiasis and preoperative PLR, P, Ca x P, and 24 hr UCa levels ($p = 0.004$, $p = 0.005$, $p = 0.012$, and $p = 0.039$, respectively).

The independent risk factors for hypocalcemia were investigated by using a multivariate linear regression analysis (Table 3). After adjusting for the potential

contributors to postoperative hypocalcemia, i.e., age, parathyroid gland weight, preoperative Ca, PTH, PRL, and 25OH-D levels, the significance of the correlation between NLR and the postoperative hypocalcemia disappeared (p = 0.332). In this multivariate regression analysis, younger age, lower preoperative Ca, and higher PTH levels were shown as the only predictive risk factors for postoperative hypocalcemia (p = 0.022, p = 0.029, and p = 0.013, respectively).

Table 2 The comparison between the clinical characteristics and the early postoperative hypocalcemia in patients with primary hyperparathyroidism

	Postoperative Hypocalcemia		
	Yes¶	No¶	p*
Ca	10.7 (10.1-11.0)	10.8 (10.4-11.2)	**0.014**
P	2.7 (2.2-3.2)	2.6 (2.3-2.9)	0.422
Ca x P	27.8 (24.1-31.0)	27.8 (24.0-31.9)	0.844
PTH	227 (148-987)	187 (133-284)	**0.003**
NLR	2.0 (1.7-3.1)	1.9 (1.5-2.6)	**0.031**
PLR	127.6 (94.3-178.9)	115.7 (88.7-144.2)	0.051
24 hr UCa	392 (201-446)	312 (225-445)	0.764
Age	49.0 (36.5-59.0)	56.0 (45.0-63.0)	**0.001**
Gland weight	1.5 (0.5-2.5)	1.0 (0.5-2.2)	0.660
Gland volume	6.0 (2.5-16.2)	5.9 (2.4-16.5)	0.656

Ca, calcium; NLR, neutrophil lymphocyte ratio; P, phosphorus; PTH, parathyroid hormone; PLR, platelet lymphocyte ratio; 24 hr UCa, 24-hour urinary calcium Bold font indicates statistical significance. αData are expressed as mean ± standard deviation ¶Data are expressed as median (25th-75th percentile) *Evaluated by Mann-Whitney U-test

Table 3 Multiple logistic regression analyses of the adjusted factors, correlation with the early postoperative hypocalcemia in patients with primary hyperparathyroidism.

	OR	95% CI for OR	p
Age	0.963	0.993 - 0.994	0.022
Ca	0.558	0.331 – 0.941	0.029
PTH	1.001	1.000 - 1.002	0.013
NLR	1.232	0.808 – 1.878	0.332
PLR	1.006	0.997 – 1.015	0.190
25OH-D	1.000	0.964 – 1.037	0.995
Gland weight	1.000	1.000 – 1.000	0.329

Ca, calcium; CI, confidence interval; NLR, neutrophil lymphocyte ratio; OR, odds ratio; P, phosphorus; PTH, parathyroid hormone; PLR, platelet lymphocyte ratio; 25OH-D, 25-hydroxy vitamin D Bold font indicates statistical significance

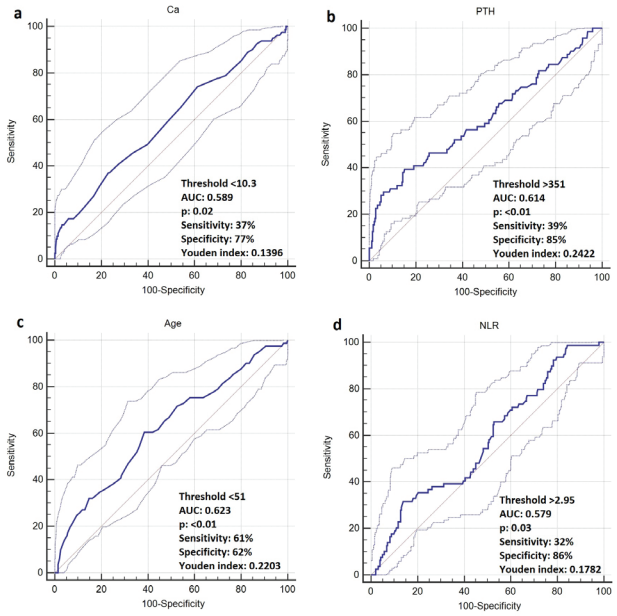

Figure 1:
Receiver operating characteristic curve analysis of preoperative
(a) Ca, (b) PTH, (c) age, and (d) NLR levels for predicting postoperative hypocalcemia.

Discussion

In our study, NLR levels were significantly higher in patients with PHPT who developed postoperative hypocalcemia compared to those who had normal postoperative Ca levels. On the other hand, after adjusting for other confounding factors, the results showed elevated NLR was not significantly a predictive risk factor for postoperative hypocalcemia. To date, this is the first study that investigated the correlation between hemogram-derived inflammatory markers and postoperative hypocalcemia in patients with PHPT. We also showed that younger age, lower serum preoperative Ca levels, and higher PTH levels were predictive risk factors for the development of postoperative hypocalcemia in patients with PHPT. A significant, but very weak correlation between NLR and PTH levels was shown in our analysis. Therefore, it can be stated that PTH may play a role as a confounding factor that causes elevated NLRs in patients with postoperative hypocalcemia compared to those without.

The predictive risk factors for postoperative hypocalcemia which were found in our study are newly discovered findings for the literature. Mittendorf et al. have reported that there was no significant association between any of the laboratory values or other clinical factors, and postoperative hypocalcemia in 162 patients with PHPT (4). In another study with similar sample size, the authors found no significant relationship between preoperative PTH, Ca, P, magnesium, albumin, blood urea nitrogen, thyroid stimulating hormone and vitamin D levels, and postoperative early and permanent hypocalcemia in patients with PHPT (9).

A recent study conducted by Liu et al. supports and contradicts some findings of this present study. In line with our findings, the authors found that the patients who were younger than 45 years had higher Ca decreases after parathyroidectomy than the older patients (19). Moreover, it was reported that the weight of the removed parathyroid gland predicted the amount of Ca drop postoperatively in patients with PHPT. The lesions heavier than 2g had a more significant Ca decrease following parathyroidectomy. In contrast with this finding, our results showed that the removed gland weight was not a predictive risk factor for postoperative hypocalcemia.

In our correlation analysis, we demonstrated a significant but very weak correlation between NLR and preoperative serum PTH levels. Our finding is consistent with the results that were presented by a study with a similar sample size (16). Toraman et al. have reported that NLR showed a significant and very weak correlation with serum PTH, vitamin D, and Ca levels in patients with elevated PTH. Similarly, Zeren et al. demonstrated a significant moderate correlation

between NLR and preoperative serum PTH levels in only 32 patients with PHPT (17). In line with this report, a significant medium correlation between NLR and preoperative serum PTH levels was shown by another study which included 37 patients with PHTP (18). The relatively small sample sizes in these two studies might be the main factors that augmented the correlation levels between these two parameters.

Conclusion

In conclusion, we found that NLR was significantly higher in patients with PHPT who developed postoperative hypocalcemia; however, our regression analysis did not find elevated NLR as a significant predictive risk factor for postoperative hypocalcemia. Moreover, the patients with nephrolithiasis had significantly higher PLR than those without any renal stones. To the best of our knowledge, this is the first study investigating the correlation between hemogram-derived inflammatory markers and clinical parameters, such as the development of postoperative hypocalcemia and preoperative nephrolithiasis, in patients with PHPT. Secondly, in this presented study, younger age, higher PTH, and lower preoperative serum Ca levels were shown as the predictive risk factors for postoperative hypocalcemia in patients with PHPT. We believe that our findings are of paramount importance to the literature on the management of primary hyperparathyroidism.

Conflict of Interest Statement
The authors declare no conflicts of interest.

Ethical Statement
Ethics approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Kocaeli University (Date:25.10.2021, No: GOKAEK 2021/18.19 - 2021/305). The study was conducted in accordance with the principles set forth in the Declaration of Helsinki.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data is available on request from the authors.

Authors Contributions
EG: Conceptualization; Formal analysis; Investigation; Validation; Visualization; Writing-original draft.

ÖZ: Data curation; Investigation; Methodology.

BYB: Data curation; Formal analysis; Investigation; Methodology.

AS: Supervision; Writing-review & editing.

BÇ: Supervision; Writing-review & editing.

ZC: Supervision; Writing-review & editing.

DK: Conceptualization; Investigation; Writing-original draft.

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