Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1721141
J Health Sci Med. 2025;8(4):731-738

Clinical significance of chloride-to-phosphorus and chloride-to-magnesium ratios in primary hyperparathyroidism

Beril Turan Erdoğan[1], Esra Çopuroğlu[2], Gülsüm Karaahmetli[1], Fatma Dilek Dellal Kahramanca[1], Fatma Neslihan Çuhacı Seyrek[2], Hüsniye Başer[2], Oya Topaloğlu[2], Reyhan Ersoy[2], Bekir Çakır[2]

[1]Department of Endocrinology and Metabolism, Ankara Bilkent City Hospital, Ankara, Turkiye
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Turkiye

Cite this article as: Turan Erdoğan B, Çopuroğlu E, Karaahmetli G, et al. Clinical significance of chloride-to-phosphorus and chloride-to-magnesium ratios in primary hyperparathyroidism. *J Health Sci Med.* 2025;8(4):731-738.

Received: 17.06.2025 ◆ **Accepted**: 14.07.2025 ◆ **Published**: 30.07.2025

ABSTRACT

Aims: Primary hyperparathyroidism (PHPT), a well-recognized endocrine disorder, is subclassified into hypercalcemic and normocalcemic forms. Recent studies suggest that biochemical ratios such as the chloride-to-phosphorus (Cl/P) and chloride-to-magnesium (Cl/Mg) ratios may aid in the diagnostic evaluation and risk stratification of PHPT-related complications. This study aimed to investigate the diagnostic and predictive utility of the Cl/P and Cl/Mg ratios in differentiating PHPT subtypes and assessing the risk of osteoporosis and nephrolithiasis.

Methods: This retrospective study included 116 patients who underwent parathyroidectomy for PHPT at Ankara Bilkent City Hospital between 2019 and 2022. All patients met surgical criteria based on international guidelines, and normocalcemic PHPT (N-PHPT) cases were defined by repeatedly normal calcium measurements and exclusion of secondary causes. Preoperative biochemical parameters, imaging findings, and complication profiles were analyzed. Cl/P and Cl/Mg ratios were calculated and evaluated using the Mann-Whitney U test, Spearman correlation, and receiver operating characteristic (ROC) analysis.

Results: The Cl/P ratio was significantly higher in hypercalcemic PHPT than in normocalcemic patients (median 42.4 vs. 38.3, p=0.0125) and was positively associated with bone mineral density. A Cl/P threshold of >43.6 yielded 80.0% specificity in distinguishing PHPT subtypes [area under the curve (AUC): 64.1%]. The Cl/Mg ratio, although not differing between subtypes, was significantly associated with nephrolithiasis risk, with a cut-off value of ≤55 providing 82.4% sensitivity and 66.7% specificity (AUC: 70.5%, p<0.001).

Conclusion: The Cl/P and Cl/Mg ratios show promise as low-cost, accessible biomarkers for enhancing diagnostic evaluation and risk stratification in PHPT. The Cl/P ratio demonstrated utility in distinguishing normocalcemic from hypercalcemic subtypes, while the Cl/Mg ratio effectively identified patients at increased risk of nephrolithiasis. These results are consistent with previous studies and support the potential integration of these indices into clinical assessment algorithms for PHPT.

Keywords: Primary hyperparathyroidism, normocalcemic hyperparathyroidism, chloride-to-phosphorus ratio, chloride-to-magnesium ratio, parathyroidectomy

INTRODUCTION

Primary hyperparathyroidism (PHPT) is among the most common endocrine disorders worldwide, traditionally characterized by elevated parathyroid hormone (PTH) levels along with hypercalcemia.[1,2] Nonetheless, an emerging phenotype known as normocalcemic PHPT has been increasingly recognized, characterized by PTH levels that are elevated despite normal serum calcium.[3,4] Patients with this atypical presentation often exhibit clinical manifestations-such as reduced bone mineral density and nephrolithiasis-comparable to those seen in hypercalcemic PHPT.[5] As a result, timely and accurate differentiation between normocalcemic and hypercalcemic PHPT is clinically critical for guiding surgical versus conservative management strategies.[1,6]

Standard biochemical indices, including serum calcium, phosphorus, and PTH, remain the cornerstone of PHPT diagnosis.[7] However, in recent years, the chloride-to-phosphorus (Cl/P) and chloride-to-magnesium (Cl/Mg) ratios have been proposed as potentially valuable supplementary markers, especially for discriminating nuanced variations in PHPT subtypes.[8,9] Several studies have suggested that altered chloride homeostasis in PHPT may lead to characteristic changes in these ratios, which could, in turn, help predict complications such as nephrolithiasis or osteopenia and osteoporosis.[8,10] Indeed, there is preliminary evidence linking higher Cl/P ratios to deteriorating skeletal integrity in both normocalcemic and hypercalcemic PHPT patients. Likewise,

Corresponding Author: Beril Turan Erdoğan, berilturan@hotmail.com

the Cl/Mg ratio may be informative for identifying individuals at elevated risk of metabolic complications pre- and post-parathyroidectomy.[9]

Despite these promising findings, consensus on the utility of Cl/P and Cl/Mg ratios as routine diagnostic or prognostic tools remains uncertain due to heterogeneous study designs and limited sample sizes.[7,10] Therefore, this study aimed to evaluate the clinical significance of Cl/P and Cl/Mg ratios in the diagnosis of PHPT and to assess their potential role in distinguishing between normocalcemic and hypercalcemic PHPT.

By systematically analyzing both preoperative and postoperative parameters, we sought to clarify whether these ratios can serve as reliable, cost-effective markers for risk stratification and treatment planning in PHPT. Establishing evidence-based cut-off values for Cl/P and Cl/Mg could ultimately enhance precision in clinical decision-making, benefiting patients who present with the heterogeneous biochemical spectrum of PHPT.

METHODS

Study Design and Population

This was a single-center, retrospective observational study conducted among patients diagnosed with PHPT and treated for PHPT at Ankara Bilkent City Hospital between February 2019 and January 2022. The study aimed to evaluate clinical, biochemical, and imaging findings in patients with PHPT and their correlation with surgical and histopathological outcomes.

A total of 677 patients were screened during the study period, and 116 patients (94 females, 22 males) who met the inclusion criteria were included in the final analysis.

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Institutional Review Board approval was obtained from the Ankara Bilkent City Hospital Ethics Committee (Date: 09.03.2022, Decision No: E1-22-2433).

Inclusion and Exclusion Criteria

Inclusion criteria included adult patients (≥18 years) with biochemically confirmed PHPT, characterized by elevated PTH levels. Patients were required to have complete preoperative and postoperative biochemical profiles, including serum calcium (Ca), phosphorus (P), magnesium (Mg), chloride (Cl), albumin, alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-hydroxyvitamin D [25(OH)D]. Renal function was comprehensively assessed through serum creatinine (Cr), estimated glomerular filtration rate (eGFR), 24-hour urinary calcium excretion, and renal ultrasonography or previously documented imaging studies to confirm preserved kidney function. Additionally, all eligible patients underwent imaging studies-such as ultrasonography and scintigraphy-for parathyroid adenoma localization, and they also had their bone mineral density assessed using dual-energy X-Ray absorptiometry (DEXA).

Patients were excluded if they had a history of chronic kidney disease (stage 4 or higher), malignancy, or other endocrine disorders-such as multiple endocrine neoplasia-that could confound biochemical measurements. Secondary causes of elevated parathyroid hormone levels were systematically excluded by assessing renal function (eGFR >60 ml/min/1.73 m^2), the presence of malabsorptive gastrointestinal disorders, and vitamin D status. A 25(OH)D threshold of ≥20 ng/ml was used as the primary cutoff; however, it is recognized that this value lies within a gray zone in clinical practice. Therefore, a limited number of patients with 25(OH)D levels just below 20 ng/ml were included if all other secondary causes had been rigorously excluded and the elevation in PTH levels was persistent. This approach aligns with the 2022 European guidelines[11] and reflects real-world clinical variability, thereby enhancing the generalizability of our findings. Patients who had used medications affecting calcium or bone metabolism, such as bisphosphonates or cinacalcet, within the previous six months were also excluded. Additionally, patients with incomplete medical records or those who were lost to follow-up before postoperative laboratory tests were performed were excluded from the study.

Definition of Normocalcemic and Hypercalcemic PHPT

Serum calcium levels were corrected for albumin using the formula corrected calcium (Ca)=measured Ca+0.8×[4.0-albumin (g/dl)]. Patients were classified as follows: Hypercalcemic PHPT was defined as corrected serum calcium levels above the upper limit of the normal reference range. Normocalcemic PHPT was defined as persistently normal albumin-corrected serum calcium levels, confirmed on at least two separate occasions, accompanied by elevated serum PTH levels. In our institutional laboratory, the upper reference limit for PTH is 80 ng/L; therefore, values above this threshold were considered elevated. Secondary causes of elevated PTH such as vitamin D deficiency [25(OH)D <20 ng/ml], chronic kidney disease (eGFR <60 ml/min/1.73 m^2), and malabsorptive gastrointestinal conditions were rigorously excluded.

Clinical and Biochemical Evaluations

All patients underwent comprehensive biochemical profiling in both the preoperative and postoperative periods. Preoperative laboratory data were collected at the time of diagnosis, prior to surgical planning. Postoperative biochemical parameters were obtained approximately 6 months after surgery, during routine follow-up visits. Blood samples were obtained after an overnight fast and sent for analysis to the institution's central laboratory. The following parameters were measured: Ca, P, and Mg in mg/dL; Cl in mEq/L; albumin in g/L; ALP in U/L; PTH in ng/L; 25(OH)D in ng/ml; Cr in mg/dl; eGFR in ml/min/1.73 m^2; and 24-hour urinary calcium and creatinine excretion in mg/24 h.

Cl/P and Cl/Mg ratios were calculated for each patient as follows: Cl/P ratio=Serum Cl (mEq/L)/serum P (mg/dl); Cl/Mg ratio=serum Cl (mEq/L)/serum Mg (mg/dl)

Bone Mineral Density Assessment

DEXA scans were performed to evaluate the lumbar spine, femoral neck, and total hip bone mineral density. Osteopenia and osteoporosis was defined according to the World Health Organization (WHO) criteria based on T-scores.

Renal Evaluation and Assessment of Nephrolithiasis

Renal involvement was assessed based on three key components: nephrolithiasis, eGFR, and 24-hour urinary calcium excretion. The presence of nephrolithiasis was assessed through clinical history and confirmed by renal ultrasonography or previously documented imaging studies. Patients were classified as having nephrolithiasis only if the diagnosis was confirmed by radiologic imaging.

Glomerular filtration rate was calculated using the Chronic Kidney Disease (CKD)-EPI formula based on serum creatinine levels. An eGFR below 60 ml/min/1.73 m^2 was considered both a surgical indication and a potential marker of disease-related renal impairment. Patients with eGFR <30 ml/min/1.73 m^2 (corresponding to CKD stage 4 or higher) were excluded to minimize inclusion of secondary hyperparathyroidism cases.

All patients underwent 24-hour urinary calcium and creatinine assessments during the diagnostic work-up. In our study, hypercalciuria was defined as 24-hour urinary calcium excretion ≥400 mg/day. Although sex-specific thresholds (≥250 mg/day for women, ≥300 mg/day for men) are proposed in more recent literature, we adopted the ≥400 mg/day cutoff based on several widely accepted clinical and research standards available at the time of data collection. This threshold has been utilized in previous studies on PHPT and nephrolithiasis, where it was associated with adverse bone and renal outcomes.[12] It is also endorsed by the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism as the definition of hypercalciuria in 24-hour urine collections.[13] Moreover, the Mayo Clinic includes this threshold as a criterion for severe hypercalciuria indicating surgical intervention.[14] We would also like to emphasize that all patients in our cohort were evaluated up to January 2022. The most recent international guideline on PHPT was published in November 2022[15] and thus was not available at the time of our surgical decision-making. Therefore, the surgical indications and clinical definitions in this study are based on the consensus criteria and literature available before 2022.

Urinary calcium values were not adjusted for body weight. To avoid confounding effects on calcium excretion, patients using thiazide or loop diuretics were instructed to discontinue these medications prior to 24-hour urine collection. Medication regimens were modified accordingly under physician supervision.

Imaging and Surgical Approach

All patients underwent preoperative imaging with cervical ultrasonography and Tc-99m sestamibi scintigraphy to localize parathyroid lesions. Preoperative imaging was universally performed as part of the standard workup for patients scheduled to undergo parathyroidectomy. In accordance with current international guidelines, surgery was performed on patients with symptomatic hypercalcemia and those who met one or more of the established criteria for asymptomatic PHPT. These criteria include: serum calcium levels exceeding the upper limit of normal by 1.0 mg/dl or more, age younger than 50 years, osteoporosis or low bone mineral density (T-score ≤-2.5), nephrolithiasis confirmed by imaging, hypercalciuria (defined as 24-hour urinary calcium excretion ≥400 mg/day), and reduced glomerular filtration rate (eGFR <60 ml/min/1.73 m^2).[1]

Patients with normocalcemic PHPT were also considered candidates for surgery if they exhibited persistent PTH elevation along with any of the aforementioned end-organ complications, were younger than 50 years, or had radiologically confirmed parathyroid adenomas. Therefore, all patients who underwent imaging had an established indication for surgical intervention based on a combination of biochemical, clinical, and radiological findings.

Postoperative Follow-up

Serum levels of Ca, albumin, P, Mg, Cl, ALP, Cr, eGFR, 25(OH) D, and PTH were re-evaluated within the first postoperative week and during routine follow-up visits. For the purposes of this study, laboratory data from the 6-month follow-up were specifically analyzed. The primary outcomes of interest included changes in the postoperative serum biochemical parameters.

Statistical Analysis

All statistical analyses were performed using MedCalc Statistical Software version 23.0 (MedCalc Software Ltd., Ostend, Belgium). Descriptive statistics were presented as mean±standard deviation (SD) or median (interquartile range, IQR), as appropriate. Normality was assessed using the Shapiro-Wilk test. Comparisons between the normocalcemic and hypercalcemic groups were conducted using student's T test or the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Correlations between continuous variables, such as parathyroid adenoma volume, corrected calcium, Cl/P, and Cl/Mg, were examined using Spearman's rank correlation test. ROC analyses were performed to determine optimal cut-off values for Cl/P and Cl/Mg in differentiating disease subtypes (normocalcemic vs. hypercalcemic) and predicting clinical endpoints, such as nephrolithiasis. Areas under the curve (AUC), sensitivities, and specificities were reported. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 116 patients were included in the study, with a mean age of 52.98±10.8 years. The cohort comprised 94 females (81.0%) and 22 males (19.0%). The descriptive statistics of the study population are summarized in **Table 1**. Based on corrected calcium levels, patients were categorized into two groups: hypercalcemic and normocalcemic. We compared these subgroups based on preoperative and postoperative laboratory parameters.

The Mann-Whitney U test showed no significant difference in the preoperative Cl/Mg ratio between the hypercalcemic

Table 1. Descriptive characteristics of the study population, including demographic, surgical, and preoperative data. Comparisons between normocalcemic and hypercalcemic primary hyperparathyroidism subgroups are presented

	Study population (n=116)	Normocalcemic group (n=40)	Hypercalcemic group (n=76)	p
Age, years	52.98±10.8	53.3±8.3	52.81±11.9	0.800
Gender, female, n (%)	94 (81)	34 (85)	60 (78.9)	0.431
Nephrolithiasis, n (%)	91 (78.4)	33 (82.5)	58 (76.3)	0.620
DEXA, n (%)				
Osteoporosis	31 (26.7)	11 (27.5)	20 (26.3)	0.253
Osteopenia	37 (31.9)	13 (32.5)	24 (31.5)	
Unexpected LBD	7 (6)	0 (0)	7 (9.2)	
Normal	41 (35.3)	16 (40)	25 (32.8)	
Ultrasonographic adenoma location				
Left lobe	4 (3.4)	2 (5)	2 (2.6)	0.253
Right lobe	6 (5.2)	1 (2.5)	5 (6.5)	
Left lobe inferior posterior	42 (36.2)	11 (32.5)	29 (38.1)	
Right lobe inferior posterior	36 (31)	10 (25)	26 (34.2)	
Left lobe superior	8 (6.9)	5 (12.5)	3 (3.9)	
Right lobe superior	5(4.3)	1 (2.5)	4 (5.2)	
None	7 (6)	4 (10)	3 (3.9)	
Mediastinum	1 (0.9)	0 (0)	1 (1.3)	
Left lobe medial posterior	7 (6)	4 (10)	3 (3.9)	
Scintigraphy adenoma location				
Left lobe	2 (1.7)	0 (0)	2 (2.6)	0.322
Right lobe	5 (4.3)	1 (2.5)	4 (5.2)	
Left lobe inferior posterior	40 (34.5)	12 (30)	28 (36.8)	
Right lobe inferior posterior	27 (23.3)	8 (20)	19 (25)	
Left lobe superior	7 (6)	3 (7.5)	4 (5.2)	
Right lobe superior	6 (5.2)	1 (2.5)	5 (6.5)	
Undetected	23 (19.8)	12 (30)	11 (14.4)	
Mediastinum	1 (0.9)	0 (0)	1 (1.3)	
Left lobe medial posterior	2 (1.7)	2 (5)	0	
Right lobe medial posterior	1 (0.9)	0 (0)	1 (1.3)	
Not performed	23 (19.8)	1 (2.5)	1 (1.3)	
Cystic degeneration, n (%)				
Absent	96 (89.7)	34 (97.1)	62 (86.1)	0.026
Present	10 (9.3)	0 (0)	10 (13.9)	
Undefined	1 (0.9)	1 (2.9)	0 (0)	
Echogenicity, n (%)				
Isoechoic	6 (5.6)	0 (0)	6 (8.4)	0.180
Hypoechoic	70 (65.4)	23 (65.7)	47 (65.2)	
Isohypoechoic	31 (29)	12 (34.3)	19 (26.4)	
Pre-op thyroid function, n (%)				
Euthyroid	111 (95.7)	37 (92.5)	74 (97.3)	0.437
Hypothyroid	2 (1.7)	1 (0.02)	1 (0.1)	
Hyperthyroid	3 (2.6)	2 (0.05)	1 (0.1)	
Thyroidectomy type				
Not operated	70 (60.3)	23	47	0.779
Lobectomy	22 (19)	9	13	
Total thyroidectomy	24 (20.7)	8	16	
Number of removed glands, n (%)				
1	99 (85.3)	37 (92.5)	62 (81.5)	0.266
2	16 (13.8)	3 (7.5)	13 (17.1)	
3	1 (0.9)	0 (0)	1 (0.01)	

Data are presented as mean±standard deviation or n (%), as appropriate. Comparisons between groups were performed using the independent samples T test or chi-square test, as applicable. Statistically significant p-values (p<0.05) are shown in bold. DEXA: Dual-energy X-Ray absorptiometry

and normocalcemic groups (p=0.4712). However, significant differences were observed in the Cl/P ratio (median 38.3 vs. 42.4, p=0.0125), PTH levels (median 158.5 vs. 202.5, p=0.0010), and ALP levels (median 101 vs. 113, p=0.0287) between the groups. The detailed comparative analysis of all preoperative continuous variables is presented in Table 2.

ROC curve analysis was performed to evaluate the Cl/P ratio's ability to differentiate hypercalcemic from normocalcemic patients. The Cl/P ratio cut-off value >43.6 was statistically significant (p=0.0096) with an AUC of 0.641, sensitivity of 43.4%, and specificity of 80.0% (Figure 1).

Spearman correlation analyses were conducted to explore associations between biochemical and clinical parameters. No statistically significant correlation was observed between parathyroid adenoma volume and the Cl/Mg ratio (p=0.5804, Rho=0.243). Corrected calcium levels also showed no significant correlation with either adenoma diameter (p=0.1629) or 24-hour urinary calcium excretion (p=0.5645).

Weak but statistically significant correlations were found between corrected calcium levels and the following variables:

- Parathyroid adenoma volume (p=0.0002, Rho=0.355),
- Cl/P ratio (p=0.0017, Rho=0.288), and
- ALP levels (p=0.0191, Rho=0.217).

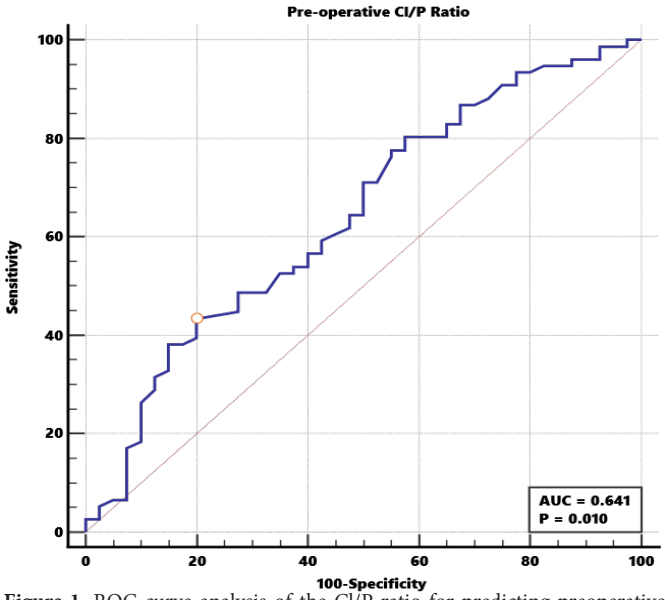

Figure 1. ROC curve analysis of the Cl/P ratio for predicting preoperative hypercalcemic status. The optimal cut-off value was >43.6, yielding 43.4% sensitivity and 80.0% specificity

ROC: Receiver operating characteristic, Cl/P: Chloride-to-phosphorus ratio

Further analyses assessed changes in biochemical parameters between the preoperative and postoperative periods. A weak inverse correlation was identified between the change in Cl/

Table 2. Preoperative biochemical and clinical parameters of patients with normocalcemic and hypercalcemic PHPT

	Study population (n=116)	Normocalcemic group (n=40)	Hypercalcemic group (n=76)	p
Creatinine (mg/dl)	0.7 (0.6-0.8)	0.6 (0.6-0.8)	0.7 (0.6-0.8)	0.214
eGFR (ml/min/1.73m^2)	98 (85-106.5)	99.5 (88-107)	95.5 (83-106)	0.468
Ca (mg/dl)	11.2 (10.8-11.6)	10.6 (10.4-10.8)	11.5 (11.2-11.7)	<0.001
Albumin (g/L)	45.5 (44-48)	46.5 (45-48)	45 (43-47)	0.003
Ca (Corrected)	10.7 (10.3-11.2)	10.1 (9.9-10.3)	11 (10.7-11.4)	<0.001
PTH (ng/L)	185 (145-267)	158.5 (120-218)	202.5 (155-281)	0.023
25-OH vitamin D (ng/ml)	19 (11-29)	20.5 (13-28)	18 (11–29)	0.006
ALP (U/L)	109.5 (82.5-139.5)	101 (69-133)	113 (87.5-152.5)	0.092
Mg (mg/dl)	2.1 (2-2.2)	2.1 (1.9-2.2)	2.1 (2-2.2)	0.867
P (mg/dl)	2.65±0.46	2.78±0.48	2.59±0.44	0.031
Cl (mEq/L)	108 (106.5-110)	107 (106-109)	109 (107-111)	<0.001
Cl/Mg	51.4 (48.6-55.7)	50.4 (48.1-56)	51.9 (49.1-55.4)	0.444
CL/P	41.1 (36.1-47)	38.3 (34.4-43.6)	42.4 (37.5-48.5)	0.021
24h urine Ca (mg/24 h)	340 (235-466)	361 (217-452)	331 (236-476)	0.365
24h urine creatinine (mg/24 h)	1031 (774-1324)	1098 (793-1509)	1000 (758-1317)	0.249
24h urine volume	2700 (1900-3600)	2900 (2000-3600)	2600 (1850-3680)	0.831
Fractionated urine Ca	0.02 (0.01-0.02)	0.02 (0.01-0.024)	0.02 (0.01-0.03)	0.848
Parathyroid adenoma diameters				
Anteroposterior diameter (mm)	5.5 (4.5-6.2)	4.5 (4.5-4.5)	5.8 (4.8-6.3)	0.033
Transvers diameter (mm)	8.3 (5-9.3)	5.1 (5.1-5.1)	8.6 (5.1-9.5)	0.006
Longitudinal diameter (mm)	0.6 (0.5-1)	0.5 (0.5-0.8)	0.6 (0.5-1)	0.089
Parathyroid volume	355 (164-1240)	270 (129-514)	504.8 (208-1668)	0.010
TSH (mIU/ml)	1.5 (1-2.2)	1.6 (0.9-2.7)	1.5 (1.1-2.1)	0.559

Data are presented as median (min-max). Comparisons between groups were performed using the Mann-Whitney U test. Statistically significant p-values (p<0.05) are shown in bold. PHPT: Primary hyperparathyroidism, Ca: Calcium, P: Phosphorus, Mg: Magnesium, Cl: Chloride, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, TSH: Thyroid stimulating hormone, eGFR: Estimated glomerular filtration rate, Cl/Mg: Chloride-to-magnesium ratio, Cl/P: Chloride-to-phosphorus ratio

Mg ratio (ΔCl/Mg) and calcium levels (p=0.0182, Rho=-0.219) (Figure 2). No statistically significant correlation was found between changes in the Cl/P ratio and calcium levels (p 0.0679). The full comparative analysis of postoperative continuous variables is presented in Table 3.

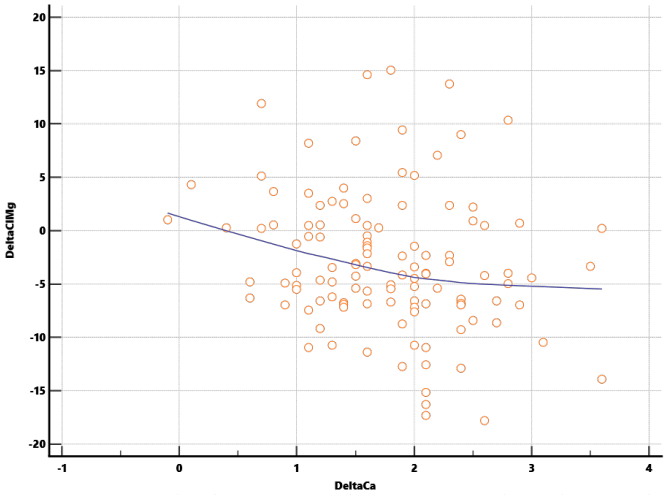

Figure 2. Scatter plot demonstrating the negative correlation between the change in Cl/Mg ratio (ΔCl/Mg) and serum calcium levels (Spearman's ρ=-0.219, p=0.018)

Cl/Mg: Chloride-to-magnesium ratio

The Mann-Whitney U test showed that the Cl/P ratio was significantly higher in patients without osteopenia or osteoporosis compared to those with these conditions (median 42.6 vs. 31.44, p<0.0001). In contrast, the Cl/Mg ratio did not differ significantly between these groups (p=0.8334).

The Cl/Mg ratio was significantly higher in patients without nephrolithiasis compared to those with nephrolithiasis (median 55.78 vs. 50.95, p=0.002). No significant difference was observed in the Cl/P ratio in relation to nephrolithiasis status (p=0.2053).

Receiver operating characteristic (ROC) curve analysis revealed that a Cl/Mg ratio cut-off value of ≤55 was statistically significant for predicting nephrolithiasis (p=0.0002), with an area under the curve (AUC) of 70.5%, sensitivity of 82.4%, and specificity of 66.7% (Figure 3).

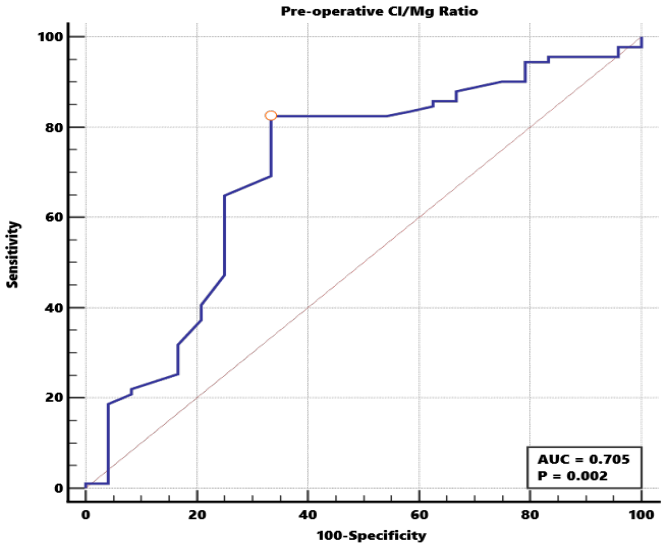

Figure 3. ROC curve analysis of the Cl/Mg ratio for predicting nephrolithiasis. A cut-off value of ≤55 yielded 82.4% sensitivity and 66.7% specificity

ROC: Receiver operating characteristic, Cl/Mg: Chloride-to-magnesium ratio

Additional ROC curve analyses were conducted to assess the diagnostic performance of the Cl/P and Cl/Mg ratios in predicting preoperative hypercalcemic status and nephrolithiasis, respectively. The AUC values, optimal cut-off points, sensitivities, and specificities for both parameters are summarized in Table 4.

Table 4. Diagnostic accuracy of Cl/P and Cl/Mg ratios based on ROC analysis

Parameter	Outcome predicted	AUC	Cut-off	Sensitivity (%)	Specificity (%)
Cl/P ratio	Hypercalcemic PHPT	0.641	>43.6	43.4	80.0
Cl/Mg ratio	Nephrolithiasis	0.705	≤55.0	82.4	66.7

Cl/P: Chloride-to-phosphorus ratio, Cl/Mg: Chloride-to-magnesium ratio, ROC: Receiver operating characteristic, AUC: Area under the curve, PHPT: Primary hyperparathyroidism

Table 3. Postoperative biochemical parameters in patients with normocalcemic and hypercalcemic PHPT

	Study population (n=116)	Normocalcemic group (n=40)	Hypercalcemic group (n=76)	p
Creatinine (mg/dl)	0.75 (0.65-0.91)	0.72 (0.65-0.88)	0.7 (0.64-0.92)	0.323[b]
eGFR (ml/min/1.73m²)	93 (72.5-102.5)	95.5 (79.5-101)	91 (71-103)	0.694[b]
Ca (mg/dl)	9.4 (9.1-9.75)	9.3 (9.05-9.6)	9.5 (9.1-9.8)	0.244[b]
Albumin (g/L)	44.84±2.96	45±3	44.7±2.92	0.684[a]
Ca (corrected)	9.04±0.49	8.97±0.5	9.08±0.46	0.232[a]
PTH (ng/L)	61 (38-81)	66.5 (44-81)	59 (37.5-79.5)	0.530[b]
25OH vitamin D (ng/ml)	23.09±8.90	22.85±9.89	23.22±8.40	0.833[a]
ALP (U/L)	78.5 (65-94.5)	82.5 (65.5-100.5)	77 (65-94)	0.567[b]
Mg (mg/dl)	1.9 (1.8-2)	1.9 (1.8-2)	1.9 (1.8-2)	0.767[b]
P (mg/dl)	3.4 (3.1-3.8)	3.3 (3.1-3.7)	3.4 (3.1-3.8)	0.518[b]
Cl (mEq/L)	106 (104-107)	106 (103-107)	106 (104.5-107)	0.190[b]
Cl/P	31.3 (27.5-33.8)	31.3 (27.6-34.3)	31.1 (27.4-33.8)	0.660[b]
Cl/Mg	55.2 (51-58.6)	54.2 (50.9-58.3)	55.7 (51.2-58.6)	0.386[b]

Data are presented as mean ± standard deviation or median (min–max), or frequency (%), as appropriate. Comparisons were made using the independent samples t-test (☒) or the Mann–Whitney U test (☒). Statistically significant p-values (p<0.05) are shown in bold. PHPT: Primary hyperparathyroidism, Ca: Calcium; P: Phosphorus; Mg: Magnesium; Cl: Chloride; Cr: Creatinine; ALP: Alkaline phosphatase; PTH: Parathyroid hormone; TSH: Thyroid stimulating hormone; eGFR: Estimated glomerular filtration rate; Cl/Mg: Chloride-to-magnesium ratio; Cl/P: Chloride-to-phosphorus ratio

DISCUSSION

In this study, we evaluated the clinical relevance of the Cl/P and Cl/Mg ratios in PHPT, with a focus on subtype differentiation and complication risk assessment. The Cl/P ratio was significantly higher in hypercalcemic PHPT compared to normocalcemic cases, and a threshold of >43.6 offered 80.0% specificity for this distinction. The Cl/Mg ratio, while not varying across subtypes, was significantly associated with nephrolithiasis, with a cut-off value of ≤55 demonstrating 82.4% sensitivity and 66.7% specificity. Notably, Cl/P was also higher in patients without osteoporosis/osteopenia, while Cl/Mg was lower in patients with nephrolithiasis, indicating potential roles in skeletal and renal risk stratification, respectively.

Our study uniquely demonstrates that the Cl/P ratio can support differentiation between PHPT subtypes and may reflect bone mineral status, while the Cl/Mg ratio can serve as a marker of renal lithogenic risk. These associations were observed even in a normocalcemic cohort, which is often under-recognized due to the absence of overt hypercalcemia.[3,5,16] Moreover, we observed that patients with normocalcemic PHPT had smaller adenomas, consistent with previously reported imaging challenges, and we confirmed significant biochemical normalization post-parathyroidectomy across both subtypes.[17] These insights contribute to refining the diagnostic work-up of PHPT using readily accessible and cost-effective indices.

The Cl/P ratio findings are in line with earlier studies suggesting its utility in PHPT evaluation. Yu et al.[18] proposed the Ca×Cl/P ratio as a sensitive tool for diagnosing PHPT, including normocalcemic variants, while Wright et al.[20] and Johnson et al.[8] noted its moderate diagnostic utility, particularly when classical markers are inconclusive. Our study expands on these by applying a defined Cl/P threshold to differentiate PHPT subtypes and correlating it with skeletal involvement.

Consistent with Khan et al.,[16] who emphasized diagnostic challenges in normocalcemic PHPT, our findings highlight the need for adjunctive markers in ambiguous presentations. Moreover, Wang et al.[21] reported that combining Cl/P with ALP improved PHPT detection in resource-limited settings, a result partially mirrored in our observation of Cl/P's association with bone integrity.

The Cl/Mg ratio, although less studied, emerged in our analysis as a promising marker for nephrolithiasis risk. Saponaro et al.[22] demonstrated that hypomagnesuria predicts nephrolithiasis in asymptomatic PHPT, likely due to the inhibitory role of magnesium on calcium oxalate crystal formation. Although previous studies did not directly evaluate Cl/Mg, our data suggest that it may indirectly capture magnesium status, providing novel support for its predictive role.

Yin et al.[23] reported a Cl/P threshold of 32.4 as highly sensitive and specific for PHPT diagnosis in a Chinese cohort, and Na et al.[24] found that chloride and phosphate imbalance reflected disease severity. Our Cl/P threshold of 43.6 was more specific but less sensitive, likely due to our focus on subtype distinction rather than diagnosis per se.

The anatomical finding of larger parathyroid volumes in hypercalcemic PHPT aligns with Kiriakopoulos et al.,[17] who noted that normocalcemic patients often have smaller adenomas, reducing detectability on imaging. These anatomical differences may reflect disease chronicity or biological aggressiveness.

First, the retrospective, single-center design and modest sample size limit generalizability. Second, normocalcemic PHPT was defined using albumin-corrected calcium, as ionized calcium was not measured-an acknowledged limitation that may lead to misclassification, given that 4-64% of normocalcemic patients show elevated ionized calcium.[11,25]

Limitations

Our study has several limitations. Third, the absence of a control group prevents assessment of Cl/P and Cl/Mg specificity relative to non-PHPT populations. Our 25(OH)D cutoff of ≥20 ng/ml may have allowed inclusion of patients with borderline vitamin D status; however, this threshold was chosen to reflect clinical practice and optimize sample size while still excluding secondary hyperparathyroidism. Finally, the proposed cut-offs may not be universally applicable due to laboratory variability, highlighting the need for external validation.

CONCLUSION

This study suggests that the Cl/P and Cl/Mg ratios can serve as accessible and cost-effective adjunctive markers in the evaluation of primary hyperparathyroidism. The Cl/P ratio may assist in differentiating between PHPT subtypes and reflect skeletal involvement, whereas the Cl/Mg ratio appears to be associated with nephrolithiasis risk and may support preoperative renal risk assessment. While neither ratio is likely to replace traditional diagnostic criteria, they may complement existing tools in selected clinical contexts. Further prospective studies including appropriate control groups are warranted to validate these findings and to explore their potential role in long-term risk stratification and management of PHPT.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Bilkent City Hospital Ethics Committee (Date: 09.03.2022, Decision No: E1-22-2433).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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.

REFERENCES

1. Bilezikian JP, Marcocci C, Khan AA, Potts JT Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014;99(10):3561-3569. doi:10.1210/jc.2014-1413
2. Walker MD, Silverberg SJ. Primary hyperparathyroidism. *Nat Rev Endocrinol.* 2018;14(2):115-125. doi:10.1038/nrendo.2017.104
3. Maruani G, Hertig A, Paillard M, Houillier P. Normocalcemic primary hyperparathyroidism: evidence for a generalized target-tissue resistance to calcium. *Clin J Am Soc Nephrol.* 2010;5(12):2174-2182.
4. Cusano NE, Bilezikian JP. Updates on the skeletal impact of hyperparathyroidism. *Curr Opin Endocrinol Diabetes Obes.* 2016;23(6):410-416.
5. Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014; 99(10):3570-3579. doi:10.1210/jc.2014-1414
6. Chang R, Delgado A, Morales B, et al. The utility of chloride-to-phosphorus ratio in distinguishing normocalcemic from hypercalcemic primary hyperparathyroidism. *Endocr Pract.* 2023;29(5):559-566.
7. Cetani F, Pardi E, Marcocci C. Update on the clinical and therapeutic management of primary hyperparathyroidism. *Endocr Pract.* 2017; 23(10):1153-1166.
8. Johnson TM, He X, Wan J, et al. Elevated Cl/P ratio as a predictor of bone density decline in primary hyperparathyroidism. *J Endocr Soc.* 2024;8(2):122-129.
9. Smith TA, Gupta V, Luo J. Exploring the role of magnesium in primary hyperparathyroidism: a prospective cohort study. *Clin Endocrinol (Oxf).* 2024;91(1):72–80.
10. Filippiadis DK, Reisinger I, Ezziddin S, et al. Imaging and biochemical pitfalls in the diagnosis and follow-up of primary hyperparathyroidism. *Eur Radiol.* 2023;33(3):1920-1927.
11. Bollerslev J, Rejnmark L, Zahn A, et al. European Expert Consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE educational program of parathyroid disorders. *Eur J Endocrinol.* 2022;186(2): R33-R63. doi:10.1530/EJE-21-1044
12. Shariq MA, Inabnet WB, Valderamma S, Shifrin A. Impact of preoperative hypercalciuria on bone mineral density and renal function after parathyroidectomy in primary hyperparathyroidism. *Surgery.* 2020;168(1):149-154. doi:10.1016/j.surg.2020.02.004
13. Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014; 99(10):3570-3579. doi:10.1210/jc.2014-1413
14. Kearns AE, Thompson GB. Medical and surgical management of hyperparathyroidism. *Mayo Clin Proc.* 2002;77(1):87-91. doi:10.4065/ 77.1.87
15. Bilezikian JP, Khan AA, Silverberg SJ, et al. Evaluation and management of primary hyperparathyroidism: summary statement and guidelines from the fifth international workshop. *J Bone Mineral Res.* 2022;37(11):2293-2314. doi:10.1002/jbmr.4677
16. Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporos Int.* 2017;28(1):1-19. doi:10.1007/s00198-016-3716-2
17. Kiriakopoulos A, Petralias A, Linos D. Classic primary hyperparathyroidism versus normocalcemic and normohormonal variants: do they really differ? *World J Surg.* 2018;42(4):992-997. doi:10. 1007/s00268-018-4512-2
18. Yu Y, Qiu J, Chuan F, Feng Z, Long J, Zhou B. The Ca-Cl/P ratio: a novel and more appropriate screening tool for normocalcaemic or overt primary hyperparathyroidism. *Endocr Pract.* 2024;30(3):231-238. doi: 10.1016/j.eprac.2023.12.004
19. Wright C, King D, Small M, Gibson C, Gardner R, Stack BC Jr. The utility of the Cl:PO4 ratio in patients with variant versions of primary hyperparathyroidism. *Otolaryngol Head Neck Surg.* 2021;164(2):308-314. doi:10.1177/0194599820947009
20. Wright C, King D, Silva-Nas J, et al. Post-operative chloride phosphate and calcium phosphate ratios in hyperparathyroidism patients. *J Surgical Endocrinol.* 2022;4(1):129-135.
21. Wang Q, Li X, Chen H, et al. The chloride/phosphate ratio combined with alkaline phosphatase as a valuable predictive marker for primary hyperparathyroidism in Chinese individuals. *Sci Rep.* 2017;7(1):4868. doi:10.1038/s41598-017-05183-6
22. Saponaro F, Marcocci C, Apicella M, et al. Hypomagnesuria is associated with nephrolithiasis in patients with asymptomatic primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2020;105(8):dgaa233. doi:10.1210/clinem/dgaa233
23. Yin M, Liu Q, Wang Q, et al. Diagnostic performance of the calcium/ phosphate ratio for primary hyperparathyroidism in southwest China. *Endocr Connect.* 2021;10(11):1387-1392. doi:10.1530/EC-21-0267
24. Na D, Tao G, Shu-Ying L, et al. Association between hypomagnesemia and severity of primary hyperparathyroidism: a retrospective study. *BMC Endocr Disord.* 2021;21(1):170. doi:10.1186/s12902-021-00838-y
25. Ong GS, Walsh JP, Stuckey BG, et al. The importance of measuring ionized calcium in characterizing calcium status and diagnosing primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2012;97(9):3138-3145. doi:10.1210/jc.2012-1429