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Serum Calcium/Phosphorus Ratio in Biochemical Screening of Primary Hyperparathyroidism

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SUMMARY

OBJECTIVE: Primary hyperparathyroidism is a common endocrine disease and most cases are asymptomatic. Currently, in a hypercalcemic patient, the first laboratory investigation is serum primary hyperparathyroidism measurement. However, the primary hyperparathyroidism level cannot be measured in many primary healthcare centers in our country. In addition, serum calcium levels are normal in normocalcemic primary hyperparathyroidism patients, even if most centers have serum calcium levels measured. Therefore, a simple and inexpensive laboratory biochemical marker is required for the diagnosis of primary hyperparathyroidism. Recently, the calcium/phosphorus ratio has been proposed as a suitable tool for diagnosing primary hyperparathyroidism. This study aimed to investigate the diagnostic value of serum calcium/phosphorus ratio in primary hyperparathyroidism screening.

METHODS: A total of 462 patients followed in our clinic with a diagnosis of primary hyperparathyroidism were reviewed in this retrospective study. Out of these patients, 148 with normal levels of serum parathyroid hormone, calcium, and phosphorus were selected as the control group. Serum calcium, corrected calcium, phosphorus, albumin, parathyroid hormone, 25-hydroxyvitamin D, and creatinine were evaluated. The diagnostic accuracy of the calcium/phosphorus ratio was investigated using receiver operating characteristic curve analysis.

RESULTS: There were 404 (87.4%) females and 58 (12.6%) males in the primary hyperparathyroidism group. Calcium, parathyroid hormone, and calcium/phosphorus ratio were significantly higher in primary hyperparathyroidism than in controls ($p<0.001$ for each). Receiver operating characteristic curve analyses identified a cutoff value of 2.59 (3.35 if calcium and phosphorus are measured in mg/dL) for the calcium/phosphorus ratio, with a sensitivity of 90.5% and specificity of 93.2% ($p<0.001$).

CONCLUSION: The calcium/phosphorus ratio is a simple and inexpensive method for primary hyperparathyroidism screening when a cutoff value of 2.59 is used.

KEYWORDS: Calcium. Hyperparathyroidism. Hypercalcemia. Hypophosphatemia. Parathyroid hormone.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a relatively common endocrine disease caused by overactive parathyroid glands and it is the most common cause of outpatient hypercalcemia[1,2]. It is generally characterized by elevated serum calcium (Ca) levels along with parathyroid hormone (PTH) that are either elevated or inappropriately normal. Prevalence is 0.1–0.4%, being nearly three times more frequent in females than males[3]. In most patients with mild forms of PHPT, serum levels of Ca are mildly elevated, often within 1 mg/dL of the upper limit of normal, while phosphorus (P) levels are in the lower half of the normal range. Only in severe forms of the disease, P might be significantly lower because of increased P excretion[4-6]. Currently, when PHPT is suspected in a patient, the first laboratory investigation is the measurement of serum PTH and 25-hydroxyvitamin D. In many cases, advanced investigations such as 24-h urinary Ca, parathyroid ultrasonography, and sestamibi scanning are required to exclude other causes of hypercalcemia and make the diagnosis clear.

PHPT is often recognized during biochemical screening. Historically, most patients presented with overt symptoms and signs of PHPT. However, with the advent and widespread use of automated blood analyzers, the majority of patients are diagnosed through routine biochemical laboratory testing done for other reasons[7]. Thus, in recent years, clinicians have more frequently come across asymptomatic PHPT and normocalcemic PHPT (NPHPT) cases[8,9]. Accurate screening and early diagnosis are important to prevent untreated clinical progression in this group. In addition, PTH measurement may not be possible in primary healthcare institutions with limited resources.

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Therefore, more practical and inexpensive biochemical markers are needed for the early diagnosis and screening of PHPT.

Recent studies have focused on the use of serum calcium/phosphorus (Ca/P) ratio for the diagnosis of PHPT, considering the inverse relationship between serum Ca and P in pathogenesis. Madeo et al.[10] examined the Ca/P ratio in the diagnosis of PHPT. They reported a cutoff value of 2.71 (3.5 if Ca and P are measured in mg/dL) for the Ca/P ratio in the diagnosis of PHPT, with a sensitivity of 86% and specificity of 87%. When this ratio was evaluated in 35 patients with NPHPT, the sensitivity decreased to 71%, while the specificity of 88% was maintained. A recent study in the Chinese population confirmed that a Ca/P ratio of over 2.94 can distinguish PHPT patients from healthy controls with a sensitivity of 95.5% and a specificity of 98.7%[11]. In this study, we aimed to investigate the diagnostic value of serum Ca/P ratio in PHPT screening in our patient population with PHPT.

METHODS

In this retrospective, single-center, case-control study, patients diagnosed with PHPT in our clinic between January 2016 and January 2019 were examined. In all, 462 patients with PHPT were included in the study, and 148 healthy control groups who applied to our center in the same period were selected retrospectively. In our series, 396 of 462 patients with PHPT were operated on and the diagnosis was confirmed histopathologically. There was no clinical indication for surgery in 66 patients who did not undergo surgery. All patients operated on had clinical indications for surgery according to criteria established by PHPT guidelines[12]. Exclusion criteria for both cases and controls were less than 18 years of age, severe renal (GFR <30 mL/min) or hepatic failure, secondary (including vitamin D deficiency or chronic kidney disease) or tertiary causes of hyperparathyroidism, metabolic bone disease (such as Paget's disease and osteomalacia), known malignancy of any kind, familial hypocalciuric hypercalcemia (FHH), non-PHPT-related hypophosphatemia, and drugs that interfere with Ca or bone metabolism (steroids, calcitriol, thiazides, phosphate binders, lithium, cinacalcet, bisphosphonates, and denosumab). Biochemical data, including serum Ca (mmol/L), P (mmol/L), albumin (g/dL), PTH (pg/mL), 25-hydroxyvitamin D (µg/L), and creatinine (Cr) (mg/dL) were obtained from medical records. Local ethical committee approval was obtained in accordance with the ethical standards of the Declaration of Helsinki.

Serum total Ca was determined using a reference clinical chemistry laboratory (Roche Diagnostics), with a normal reference range of 2.12–2.62 mmol/L (8.5–10.5 mg/dL). The normal reference range for serum P was 0.81–1.45 mmol/L (2.5–4.5 mg/dL). The reference range for albumin and Cr was 3.5–5.2 and 0.5–1.1 mg/dL, respectively. Plasma intact PTH was measured using the Allegro IRMA (Roche Diagnostics) with a detection limit of 1 pg/mL (normal range, 15–60 pg/mL) and a 2 and 10% intra- and inter-assay coefficient of variation, respectively. 25-Hydroxyvitamin D was measured using liquid chromatography coupled with tandem mass spectrometry (Schimadzu-API LC-MS-MS API 3200, Canada) with lower and upper detection limits of 4 and 150 µg/L (normal range, 20–80 µg/L), respectively. Serum Ca was corrected according to the following formula:

Corrected calcium = Total calcium + [0.8 × (4.0 – albumin)]

Patients with PHPT were subgrouped as hypercalcemic and NPHPT. The diagnosis of hypercalcemic PHPT was based on elevated serum albumin-corrected calcium (>2.62 mmol/L) with high serum PTH concentrations (>60 pg/mL). NPHPT was diagnosed in the presence of elevated serum PTH concentrations (>60 pg/mL) with normal serum albumin-corrected calcium (≤2.62 mmol/L) on two separate occasions. Patients with NPHPT with 25-hydroxyvitamin D3 levels below 30 µg/L received maintenance cholecalciferol (vitamin D3) replacement of 1500–2000 IU/day for at least 8 weeks for accurate diagnosis[13]. After vitamin D3 replacement, serum-corrected Ca levels were within normal limits, but the elevation in PTH level persisted.

The SPSS 24.0 software package (IBM Corp., Armonk, NY, USA) was used for statistical analysis. We presented the descriptive statistics as mean±standard deviation for normally distributed variables, median (minimum-maximum) for non-normally distributed variables, and the number of cases and percentages for nominal variables. A comparison between categorical variables was made using the chi-square test. The Student's t-test was used for parametric variables and the Mann-Whitney U test was used for nonparametric variables to investigate the difference between groups. For all comparisons, $p<0.05$ was considered statistically significant. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. The diagnostic accuracies of Ca/P and corrected Ca/P were investigated using receiver operating characteristic (ROC) curves to identify cutoff points that better define affected patients based on their biochemical profiles.

RESULTS

There were 404 (87.4%) females and 58 (12.6%) males in the PHPT group, and the median age of the cohort was 55 (20–82) years. There were 96 (64.9%) females and 52 (35.1%) males in the control group, and the median age was 51 (19–76) years.

The median age was similar in both groups (p=0.059). Serum total Ca, corrected Ca, and PTH were significantly higher, and serum P was significantly lower in PHPT than in controls (p<0.001 for each). 25-Hydroxyvitamin D levels were similar in the two groups (p=0.058). The median serum total Ca/P ratio was 3.32 (1.84–8.61) in the PHPT and 2.10 (1.53–2.91) in the control group (p<0.001). The median-corrected Ca/P ratio was also significantly higher in the PHPT group than in the control group [3.20 (1.71–7.85) vs. 1.94 (1.47–2.77), p<0.001] (Table 1).

Of all the patients, 328 (71%) had hypercalcemic PHPT and 134 (29%) had NPHPT. The mean age was similar in both the hypercalcemic PHPT and NPHPT groups compared to the control group. Serum Ca, corrected Ca, and PTH were significantly higher in the hypercalcemic PHPT group than in the control group, while serum P and albumin levels were significantly lower (p<0.001 for each). Hypercalcemic PHPT patients had a significantly higher serum Ca/P ratio and corrected Ca/P ratio than the controls (p<0.001 for each). 25-Hydroxyvitamin D levels were similar to controls in both groups (p=0.061 and p=0.053, respectively). Similarly, serum Ca, corrected Ca, and PTH were significantly higher in the NPHPT group compared to that in the control group, while serum P was significantly lower (p<0.001 for each). NPHPT had a significantly higher serum Ca/P ratio and corrected Ca/P ratio compared to controls (p<0.001 for each) (Table 1).

The Ca/P threshold of 2.59 (3.35 if Ca and P are measured in mg/dL) obtained by the ROC curve analysis had the highest sensitivity and specificity for the diagnosis of PHPT (90.5% sensitivity and 93.2% specificity, p<0.001) (Figure 1A). In addition, the optimal corrected Ca/P threshold was 2.46 (3.18 if Ca and P are measured in mg/dL) with a sensitivity of 91.8% and specificity of 92.6% for the PHPT diagnosis (Figure 1B).

The cutoff value of 2.59 for the Ca/P ratio was able to accurately identify 418 out of 462 PHPT patients, while only 10 out of 148 controls were incorrectly diagnosed with PHPT. The cutoff value of 2.59 for the Ca/P ratio correctly identified 312 out of 328 hypercalcemic PHPT patients and 106 out of 134 NPHPT patients.

The diagnostic values of serum Ca/P ratio, corrected Ca/P ratio, and PTH for the diagnosis of PHPT are given in Table 2. Accordingly, the accuracy of Ca/P ratio of 2.59 was 94.5% in hypercalcemic and 86.5% in NPHPT patients. Considering the corrected Ca/P of 2.46, the diagnostic accuracy was 95.6% in the hypercalcemic and 86.1% in the NPHPT patients.

Bone mineral densitometry (BMD) was evaluated with dual-energy x-ray absorptiometry (DEXA) in all patients with PHPT. Of the 462 patients, 206 (44.6%) had osteoporosis (T score ≤2.5 in one of three areas), 149 (32.2%) had osteopenia (T score between –1 and –2.5), and 107 (23.2%) had normal scores. Nephrolithiasis was detected in 117 (25.3%) patients on renal ultrasound. Of the 462 patients with PHPT, 396 were operated on for clinical indications and the diagnosis was confirmed histopathologically. In the operated patients, parathyroid adenoma was found in 348 (87.9%), parathyroid hyperplasia in 16 (4%), atypical parathyroid adenoma in 30 (7.6%), and 2 (0.5%) parathyroid carcinoma was detected.

Table 1. Comparison of demographic, biochemical, and hormonal data in patients with hypercalcemic primary hyperparathyroidism, normocalcemic primary hyperparathyroidism, and controls.

	All patients PHPT (n=462)	Hypercalcemic PHPT (n=328)	Normocalcemic PHPT (n=134)	Control (n=148)	p^1	p^2	p^3
Age (years)	55 (20–82)	55 (20–82)	54 (27–77)	51 (19–76)	0.059	0.062	0.079
Sex, n (%)							
Female	404 (87.4)	283 (86.3)	121 (90.3)	96 (64.9)	**<0.001**	**<0.001**	**<0.001**
Male	58 (12.6)	45 (13.7)	13 (9.7)	52 (35.1)			
Ca (2.12–2.62 mmol/L)	2.80 (2.30–4.02)	2.85 (2.6–4.02)	2.67 (2.30–2.82)	2.34 (2.17–2.62)	**<0.001**	**<0.001**	**<0.001**
P (0.81–1.45 mmol/L)	0.84 (0.36–1.42)	0.82 (0.36–1.26)	0.91 (0.55–1.42)	1.13 (0.81–1.45)	**<0.001**	**<0.001**	**<0.001**
Ca/P ratio	3.32 (1.84–8.61)	3.51 (2.26–8.61)	2.94 (1.84–4.55)	2.10 (1.53–2.91)	**<0.001**	**<0.001**	**<0.001**
Corrected Ca (2.12–2.62 mmol/L)	2.68 (2.19–4.12)	2.75 (2.62–4.12)	2.56 (2.19–2.62)	2.24 (2.10–2.43)	**<0.001**	**<0.001**	**<0.001**
Corrected Ca/P ratio	3.20 (1.71–7.85)	3.39 (2.10–7.85)	2.79 (1.71–4.65)	1.94 (1.47–2.77)	**<0.001**	**<0.001**	**<0.001**
PTH (15–60 pg/mL)	132 (7.60–1210)	144 (7.60–1210)	97 (30.17–494)	54 (21–60)	**<0.001**	**<0.001**	**<0.001**
Creatinine (0.5–1.1 mg/dL)	0.69 (0.30–1.1)	0.69 (0.30–1.1)	0.68 (0.33–0.99)	0.67 (0.41–1.11)	**0.007**	**0.031**	**0.007**
Albumin (3.5–5.2g/dL)	4.56 (3.49–5.78)	4.52 (3.49–5.78)	4.62 (3.70–5.10)	4.50 (4.0–5.20)	**0.035**	**0.001**	**0.459**
25-Hydroxyvitamin D (20–80 µg/L)	16.10 (2–121)	14.70 (2–121)	18.79 (3–67)	23 (8–53)	0.058	0.061	0.053

PHPT: primary hyperparathyroidism; Ca: serum calcium; P: serum phosphorous; PTH: parathyroid hormone. p^1 indicates statistical difference between all primary hyperparathyroidism patients and control group. p^2 indicates statistical difference between hypercalcemic primary hyperparathyroidism patients and control group. p^3 indicates statistical difference between normocalcemic primary hyperparathyroidism patients and control group.

Bold values indicate statistical significance at the p<0.05 level.

DISCUSSION

This study showed that a serum Ca/P value above 2.59 (3.35 if Ca and P are measured in mg/dL) is an ideal indicator for PHPT screening. Our results show that the Ca/P ratio is a simple, inexpensive, and valuable tool in the diagnosis of PHPT and can be used in both normocalcemic and hypercalcemic patients.

PTH is one of the most important hormones that maintain Ca and P homeostasis. It regulates serum Ca and P concentrations through its receptor-mediated, combined actions on the bone, intestine, and kidney. In the kidney, PTH increases the reabsorption of Ca, predominantly in the distal convoluted tubule, and inhibits the reabsorption of P in the renal proximal

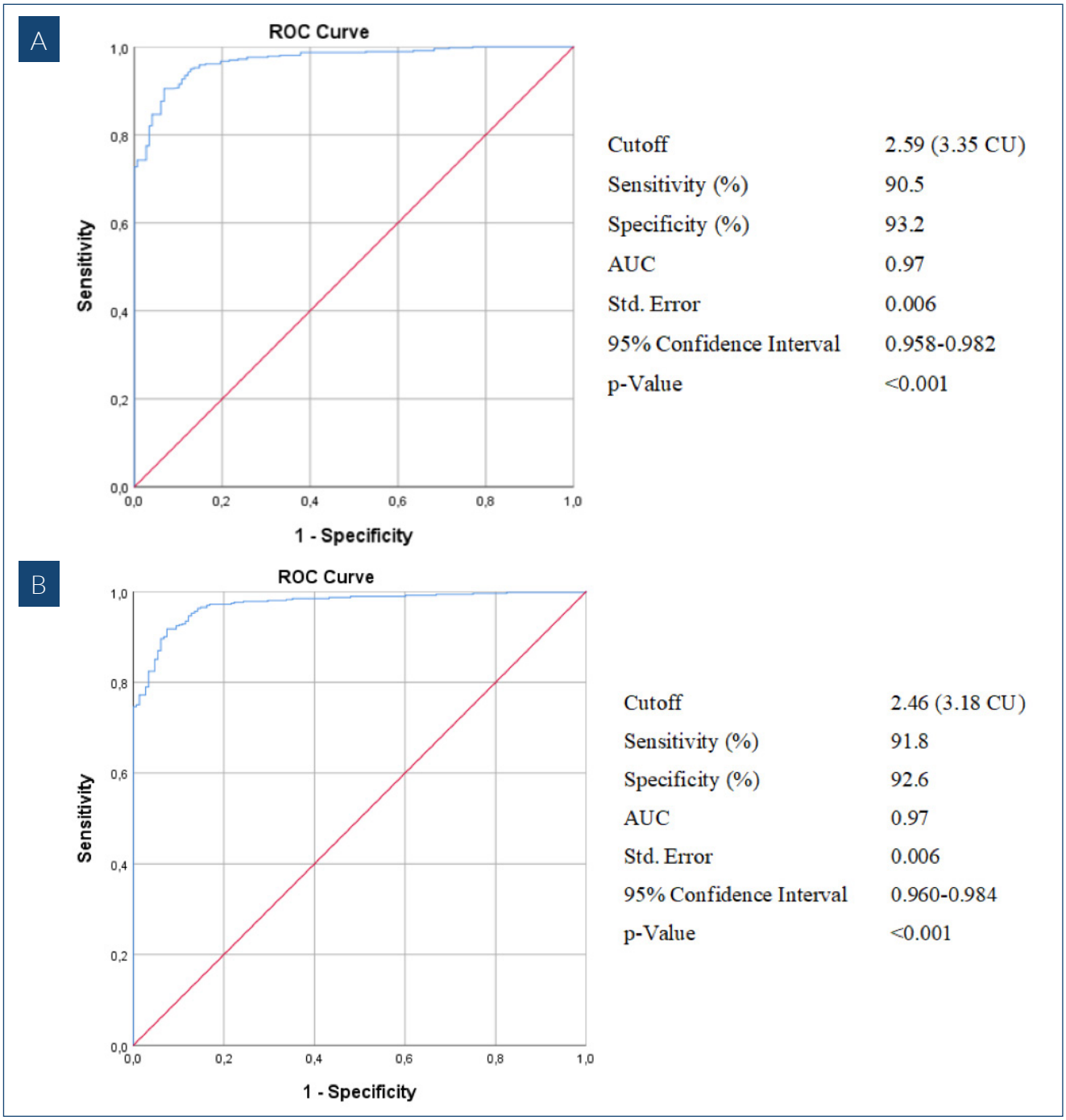

Figure 1. (**A**) Receiver operating characteristic (ROC) curve analysis for calcium/phosphorus with cutoff, sensitivity, specificity, AUC, standard error, and 95% confidence interval values. (**B**) ROC curve analysis for corrected calcium/phosphorus with cutoff, sensitivity, specificity, AUC, standard error, and 95% confidence interval values. CU: conventional units (calcium and phosphorus measured in mg/dL); AUC: area under the curve.

Table 2. Diagnostic value of Ca/P ratio, corrected Ca/P ratio, and serum parathyroid hormone level for primary hyperparathyroidism diagnosis in the entire cohort, hypercalcemic primary hyperparathyroidism, and normocalcemic primary hyperparathyroidism.

	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
All patients						
Ca/P ratio	2.59 (3.35 CU)	90.5	93.2	97.7	75.8	91.2
Corrected Ca/P	2.46 (3.18 CU)	91.8	92.6	97.5	78.3	92.0
Serum PTH	60	89.0	100	100	74.4	91.6
Hypercalcemic PHPT						
Ca/P ratio	2.59 (3.35 CU)	95.1	93.2	96.9	89.6	94.5
Corrected Ca/P	2.46 (3.18 CU)	97.0	92.6	96.7	93.2	95.6
Serum PTH	60	93.0	100	100	86.6	95.2
Normocalcemic PHPT						
Ca/P ratio	2.59 (3.35 CU)	79.1	93.2	91.4	83.1	86.5
Corrected Ca/P	2.46 (3.18 CU)	79.0	92.6	90.5	83.0	86.1
Serum PTH	60	79.1	100	100	84.1	90.1

PTH: parathyroid hormone; PHPT: primary hyperparathyroidism; Ca: serum calcium; P: serum phosphorus; PPV: positive predictive value; NPV: negative predictive value; CU: conventional units (Ca and P measured in mg/dL).

tubule, with the net result of hypercalcemia and hypophosphatemia[14]. Due to this inverse relationship in Ca and P homeostasis, it was predicted that the Ca/P ratio could be used in the diagnosis of PHPT, and recent studies have focused on this ratio. Madeo et al.[10] published the first study examining the Ca/P ratio in the diagnosis of PHPT. They retrospectively evaluated 97 patients with PHPT and 96 control subjects with normal PTH and Ca. They reported a cutoff value of 2.71 (3.5 mg/dL) for the Ca/P ratio in the diagnosis of PHPT with a sensitivity of 86% and specificity of 87%, and it was confirmed by the independent big database. When this ratio was evaluated in 35 patients with NPHPT, the sensitivity decreased to 71%, while the specificity of 88% was maintained. This study highlights the greater diagnostic power of the Ca/P ratio compared to total or corrected calcium in the diagnosis of PHPT, including the NPHPT form. The authors concluded that the Ca/P ratio could be a valuable and inexpensive method for detecting PHPT in healthcare institutions where PTH measurement cannot be performed. In another study by Madeo et al.[15] involving 142 patients diagnosed with NPHPT, the Ca/P ratio cutoff value of 2.55 showed high sensitivity (71.1%) and specificity (87.9%). Yin et al.[11] recently reported a sensitivity of 95.5% and specificity of 98.7% with a Ca/P ratio cutoff value of 2.94, and this index was positively correlated with the PTH level ($r=0.875$, $p<0.001$). In another study, the cutoff value of 2.55 for the Ca/P ratio served as a reliable predictor for the diagnosis of PHPT with 95.6% sensitivity and 63.6% specificity[16]. These results show that this ratio can be a promising screening method for PHPT diagnosis.

In our study, Ca/P ratio above 2.59 was 90.5% sensitive and 93.2% specific for the diagnosis of PHPT. The cutoff value of 2.59 was able to correctly identify 418 out of 462 PHPT patients, and only 10 out of 148 controls were diagnosed with false PHPT. The sensitivity of the Ca/P ratio was 95.1% and the specificity was 93.2% in the hypercalcemic PHPT group, and as expected, the diagnostic sensitivity of the Ca/P ratio was highest in the hypercalcemic group. Our results were similar to the results of Madeo et al.'s[10] first multicenter study that evaluated the diagnostic value of Ca/P in the diagnosis of PHPT. Our findings support the notion that the Ca/P ratio can be a simple and inexpensive tool for early detection and screening of PHPT. Especially in primary healthcare, it can provide great convenience to general practitioners in diagnosing and guiding patients correctly.

NPHPT is characterized by persistently increased serum PTH levels in the setting of normal albumin-adjusted and ionized serum Ca. Secondary causes of hyperparathyroidism such as renal failure, vitamin D deficiency, and the use of thiazide diuretics should be excluded from the diagnosis[17-19]. In recent years, the diagnosis of NPHPT has increased due to the widespread use of PTH tests. PTH levels are measured in some patients, even when serum Ca levels are normal. Especially in the comprehensive approach to biochemical evaluation of osteoporosis and metabolic bone diseases, PTH levels are measured despite normal serum Ca levels. In this regard, more individuals are diagnosed with NPHPT. Some patients with NPHPT may progress to a hypercalcemic state or classic conditions that require surgical intervention, such as fractures and kidney

stones. Recent reports showed high rates of osteoporosis (57%), fractures (11%), and nephrolithiasis (14%) in these patients[20]. There are also studies showing an increase in comorbidities in NPHPT[9]. Therefore, it is important to diagnose these patients early. Evaluating the Ca/P ratio in patients with normal serum Ca levels but suspicious of NPHPT can make a significant contribution in terms of early diagnosis. Thus, delays in the diagnosis and treatment of the disease can be prevented and PHPT-related comorbidities can be reduced. In our study, the diagnostic sensitivity of the Ca/P ratio of 2.59 was 79.1% and the specificity was 93.2% in the NPHPT group. Although the diagnostic performance of the Ca/P ratio was better in the hypercalcemic group, our findings suggest that this ratio is a simple but effective tool that can be used for screening and early diagnosis of both classical PHPT and NPHPT.

The serum Ca/P ratio can be used as an accurate tool to differentiate patients with PHPT from healthy subjects. However, although PHPT is the most common cause of hypercalcemia, other disorders of Ca-P metabolism can impair the Ca/P ratio[1,8]. For example, FHH, malignancy hypercalcemia due to parathyroid hormone-related peptide (PTHrP), and hereditary hypophosphatemic rickets with hypercalciuria (HHRH) can all be present with hypercalcemia and hypophosphatemia, and therefore a high Ca/P ratio[21-23]. In addition, hypophosphatemia is frequently observed in patients with human immunodeficiency virus (HIV) infection and receiving highly active antiretroviral therapy (HAART)[24,25]. For all these reasons, it does not seem appropriate to use it alone for a definitive diagnosis without PTH measurement, because there may be other causes of hypercalcemia and/or hypophosphatemia that can be overlooked by using the Ca/P ratio alone. All these conditions should be considered, and the Ca/P ratio should be used in an appropriate clinical context.

The most important limitation of our study is its retrospective design. This also kept us from evaluating the ionized Ca level in the PHPT patient group. Including ionized calcium as a mandatory parameter may change patient categories, but ionized Ca levels are not routinely checked in our center or in many centers. Therefore, we chose our criteria based on serum total Ca because patients would initially be confronted with serum Ca and P levels. In addition, we corrected serum Ca levels according to albumin levels and also did statistical analysis including this parameter. Another limitation of this study was that patients and controls did not match very well by gender.

CONCLUSION

Evaluating serum Ca/P ratio in addition to serum Ca and P level is a very simple, inexpensive, and valuable tool for early diagnosis of PHPT. Moreover, the diagnostic value of this ratio is high in patients with hypercalcemic PHPT as well as with NPHPT. When evaluating a patient for PHPT, the serum Ca/P ratio should also be evaluated instead of just the serum Ca and P level, but the PTH measurement is still required for a definitive diagnosis. The serum Ca/P ratio can be useful in PHPT screening and early diagnosis and can guide clinicians to refer patients for further examination in primary healthcare institutions where PTH measurement cannot be performed.

AUTHORS' CONTRIBUTIONS

NB: Conceptualization, data curation, formal analysis, methodology, writing – original draft, writing – review & editing. **FNC, BP, BEO:** Data curation, formal analysis. **DO:** Conceptualization, formal analysis, methodology, writing – original draft, writing – review & editing. **RE:** Conceptualization. **BC:** conceptualization, writing – original draft, writing – review & editing.

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