RESEARCH

Diagnostic performance of the calcium/phosphate ratio for primary hyperparathyroidism in southwest China

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Abstract

Background: The diagnosis of primary hyperparathyroidism (PHPT) remains a challenge because of increased asymptomatic PHPT or patients with normocalcaemic PHPT (NPHPT). In addition, some primary hospitals in China have no equipment to measure parathyroid hormone (PTH) levels. Therefore, an additional, simple, and inexpensive laboratory biochemical marker is urgently needed. The calcium/phosphate (Ca/P) ratio and chloride/phosphate (Cl/P) ratio have been proposed as suitable tools to diagnose PHPT in Europe; however, the Ca/P ratio has never been tested in China. We aimed to conduct a confirmatory study to explore the diagnostic performance of the Ca/P ratio for PHPT in China.
Methods: From January 2015 to December 2020, a total of 155 patients who underwent parathyroidectomy (143 PHPT patients and 12 NPHPT patients) and 153 controls were enrolled in this single-center , retrospective study. Serum calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin vitamin D (25(OH) vitamin D), chloride, alanine transaminase (ALT), aspartate aminotransaminase (AST), estimated glomerular filtration rate (eGFR), and creatinine levels were recorded for all the study participants. Pairwise comparisons were made between groups, and the diagnostic performance of the Ca/P ratio was determined using receiver-operating characteristic (ROC) analysis.
Results: Patients with PHPT had a higher Ca/P ratio than controls ($P < 0.001$). A Ca/P ratio above 2.94 with a sensitivity of 95.5% and specificity of 98.7% can distinguish PHPT patients from healthy individuals. This index was positively correlated with the PTH level ($r = 0.875$, $P < 0.001$).
Conclusion: The Ca/P ratio is an ideal and inexpensive indicator for diagnosing PHPT in China when using a cut-off value of 2.94.

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disease caused by parathyroid dysfunction, with a prevalence of approximately 1/1000–7/1000 in the general population (1). Approximately 80% of PHPT cases are caused by a single parathyroid adenoma and less than 1% by parathyroid adenocarcinoma (2). Traditionally, patients with PHPT typically have hypercalcemia and elevated parathyroid hormone (PTH) levels (3, 4). Dysregulation of PTH, the most important metabolic hormone required for the maintenance of the homeostasis of calcium and phosphate, can lead to skeletal, renal, and cardiovascular complications, including hypercalcemia, hypophosphatemia, osteoporosis, fragility fractures, bone pain, nephrolithiasis, ventricular hypertrophy, and

myocardial calcification (5, 6). Parathyroidectomy (PTX) is the only beneficial treatment modality for all individuals with symptomatic PHPT and asymptomatic patients who meet any of the guideline criteria for surgical intervention (6). At present, the mainstay of the diagnosis of PHPT is the clinical manifestations and routine serum calcium and PTH detection (6, 7, 8). However, the prevalence of asymptomatic PHPT increased by approximately 50% in China between 2007 and 2010 (9), and cases of normocalcaemic PHPT (NPHPT) characterized by inappropriately elevated PTH levels in the setting of normal serum calcium after the exclusion of secondary hyperparathyroidism, including vitamin D deficiency and chronic kidney disease have already been confirmed. The hypotheses regarding the pathogenesis of NPHPT are as follows: (1) the normocalcaemic phenotype may represent an early or mild stage of traditional PHPT (10, 11); and (2) renal tubular resistance to PTH (12). Some primary hospitals in China have no equipment capable of measuring the PTH levels. All of these have brought about a challenge in the diagnosis of PHPT. Therefore, we need to look for an additional, simple, and inexpensive laboratory biochemical marker to diagnose PHPT. Considering the pathogenesis of the condition, there have been studies focused on the utility of the calcium/phosphate ratio (Ca/P) and the chloride/phosphate ratio (Cl/P). Madeo *et al.* reported that a cut-off of 2.71 for the Ca/P ratio has a better predictive value than serum calcium or PTH levels for PHPT, especially in NPHPT, with a sensitivity and specificity of 86 and 87%, respectively (13). Wright *et al.* also reported an AUC of 0.813 for the Ca/P ratio with a sensitivity of 95.6% and specificity of 63.6%, when using a cut-off value of 2.55 (14). Reeve *et al.* revealed that a Cl/P ratio of >33 can be used for PHPT with a sensitivity of 94% and specificity of 96% (15). Recently, a study confirmed that a Cl/P ratio of >33 for NPHPT had a sensitivity of 73.7% and a specificity of 80.0% in the Chinese population (16). Meanwhile, a comparison between Ca/P and Cl/P suggested that Ca/P was more sensitive than Cl/P (14). Therefore, given that no study has tested the Ca/P ratio in Europe since previous studies were all focused on European cohorts, we aimed to conduct a confirmatory study to explore the diagnostic performance of the Ca/P ratio in China and make a comparison between the diagnostic accuracies of the Ca/P and Cl/P ratios.

Methods

Study participants

This was a single-center, retrospective, case–control study. Data were obtained from electronic medical records at the West China Hospital. We enrolled a total of 308 patients, of whom 12 had NPHPT, 143 had PHPT, and 153 were healthy. Patients with NPHPT were defined by serum PTH>6.9 pmol/L (or in the upper range of normal values) but serum calcium levels within the reference range (2.11–2.52 mmol/L) within the 1 year prior to PTX after the exclusion of secondary hyperparathyroidism, including vitamin D deficiency or chronic kidney disease. Patients with NPHPT received vitamin D supplementation for at least 8 weeks to ensure the correctness of the diagnosis. Patients with PHPT were defined as having serum PTH >6.9 pmol/L and serum calcium >2.52 mmol/L. Only patients treated with PTX and confirmed by histopathology were recruited. Plasma albumin-adjusted corrected calcium levels were calculated as follows: corrected calcium (mmol/L)=measured calcium (mmol/L)+0.02×(40-patient's serum albumin concentration (g/L)) (17). Healthy controls should have a normal PTH concentration (reference range: 1.6–6.9 pmol/L). All experimental protocols involving human data were approved by the Medical Ethics Committee of the Sichuan University, which waived the requirement for informed consent. We also ensured that all methods were performed in accordance with the relevant regulations. The selection criteria are shown in Fig. 1.

Study variables

Data on the following parameters were collected in the different groups: age, sex, serum calcium, phosphate, PTH, 25-hydroxyvitamin D (25(OH) vitamin D), chloride, alanine transaminase (ALT), aspartate aminotransaminase (AST), estimated glomerular filtration rate (eGFR), and creatinine. The inclusion criteria for the experimental group were as follows: (1) a diagnosis of PHPT or NPHPT as detailed above; (2) history of parathyroidectomy; (3) histopathological confirmation; and (4) normalization of postoperative calcium. The exclusion criteria were as follows: (1) intake of medications such as hydrochlorothiazide, diuretics, lithium, bisphosphonates, and denosumab; (2) renal insufficiency (eGFR<30 mL/min/1.73 m^2) and abnormal liver function (ALT or AST greater than twice the normal value); and (3) missing data. We chose healthy controls from the Physical Examination Center of the West China Hospital. People with normal biochemical levels and thyroid ultrasound were included in the same time period.

Statistical analysis

Measurement data on normal distribution were expressed as mean ± S.D.. Abnormal distribution data are
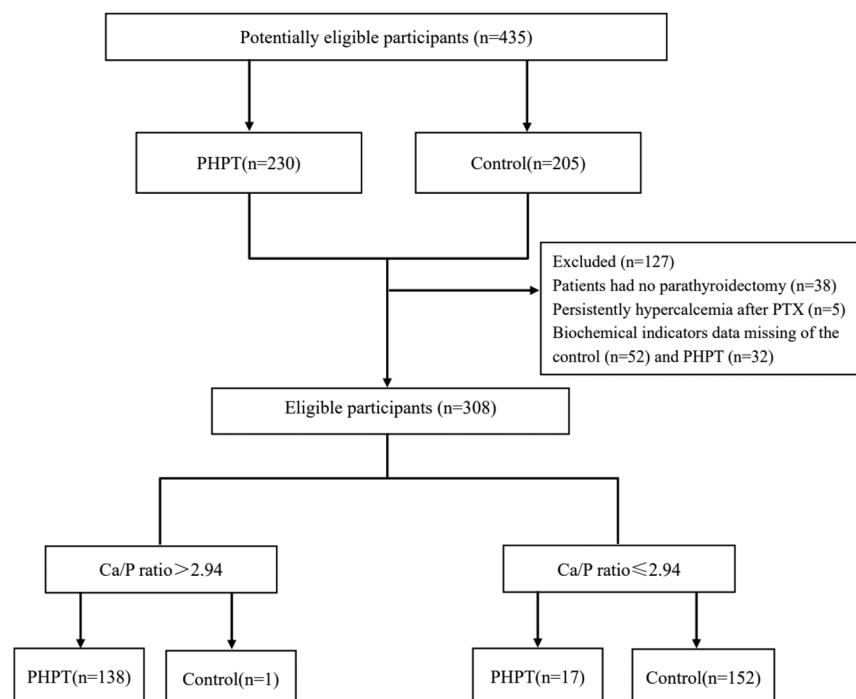
Figure 1
The process of the selection criteria.

expressed as median (interquartile range (IQR)). Except for age, all continuous data were skewed and tested using the Mann–Whitney U test. The analyses were completed using SPSS software (version 25.0). We also calculated the Ca/P ratio of calcium (mmol/L)/phosphate (mmol/L) and Cl/P ratio chloride (mEq/L)/phosphate (mg/100 mL). The evaluation of diagnostic performance is typically based on the receiver-operating characteristic (ROC) curve and the area under the curve (AUC) with 95% CIs. The Spearman correlation coefficient was used in the case of skewed data, while the Pearson correlation coefficient was made in the case of normally distributed data. The sensitivity, specificity, positive and negative predictive values, and their 95% CIs were calculated using MedCalc Software 19 (Mariakerke, Belgium). All *P*-values were two-tailed, and statistical significance was set at $P < 0.05$.

Results

Characteristics of the study cohorts

The clinical characteristics of the cohort are presented in Table 1. Patients with PHPT had higher values of PTH, serum calcium, Ca/P ratio, and Cl/P ratio, but lower serum levels of 25(OH) vitamin D and phosphate than healthy controls ($P < 0.001$). Age, sex, creatinine, and albumin levels did not differ significantly between the two groups ($P > 0.05$).

The diagnostic power for the Ca/P ratio

We analyzed the diagnostic performance of the Ca/P ratio using ROCs. The cut-off point was calculated using Youden's index (sensitivity + specificity – 1). The ROC curve showed that the ROC–AUC was 0.993 (95% CI, 0.976–0.998), sensitivity, and specificity rates of 95.5% (95% CI, 90.0–98.2) and 98.7 % (95% CI, 95.4–99.8), respectively, at a Ca/P ratio of >2.94 (Fig. 2A). The logistic regression model was as follows: logit (P) = −23.847 + 8.342 × Ca/P.

The diagnostic power for the Cl/P ratio

We analyzed the diagnostic performance of the Cl/P ratio through ROCs. The cut-off point was calculated using Youden's index (sensitivity + specificity – 1). The ROC curve showed that the ROC-AUC was 0.966 (95% CI, 0.940–0.983), sensitivity, and specificity rates of 95.5 (95% CI, 90.9–98.2) and 91.5 (95% CI, 85.9–95.4), respectively, at a Cl/P ratio of 32.4 (Fig. 2B).

Correlation between Ca/P ratio and other parameters

We performed a Spearman correlation analysis between the Ca/P ratio and the Cl/P ratio, PTH, and 25(OH) vitamin D3. The Ca/P ratio was positively correlated with the Cl/P ratio ($r = 0.882$, $P < 0.001$) and PTH ($r = 0.875$, $P < 0.001$) and negatively correlated with 25(OH) vitamin D3 ($r = −0.260$, $P < 0.001$).

Table 1 Characteristic of subjects in control and PHPT groups.

	PHPT	Healthy	*P* value
Age (years)	48 ± 15	64 ± 13	0.65
Gender (*n* (%))			
Female	51 (32.9)	61 (39.9)	0.61
Male	104 (67.1)	92 (60.1)	
ALT (U/L)	18 (14, 25)	19 (14, 26)	0.23
AST (U/L)	20 (17, 23)	21 (17, 27)	0.04
Creatinine (41–73 mmol/L)	63 (60–73)	68 (60–84)	0.49
eGFR (mL/min)	100.4 (82.5, 115.0)	120.0 (110.9, 141.0)	<0.001
Albumin (g/L)	45.0 (43.0–47.3)	45.2 (44.0–46.8)	0.54
PTH (1.6–6.9 pmol/L)	21.1 (13.7–37.0) *	4.9 (4.1–5.5)	<0.001
25(OH) vitamin D (47.7–144)nmol/L	36.5 (26.4–46.3)*	58.1 (47.3–75.3)	<0.001
Serum calcium (2.11–2.52 mmol/L)	2.75 (2.58–2.95)*	2.36 (2.30–2.41)	<0.001
Serum phosphate (0.85–1.51 mmol/L)	0.75 (0.65–0.82) *	1.01 (0.90–1.12)	<0.001
Chloride (mmol/L)	105.7 (103.3, 108.3)*	101.4 (99.8, 103.0)	<0.001
Ca/P	3.71 (3.27–4.62) *	2.35 (2.10–2.61)	<0.001
Cl/P	39.6 (25.3–89.6) *	26.3 (18.2–45.5)	<0.001

eGFR was calculated by using the following modification of diet in renal disease (MDRD) formula: eGFR = 186 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (1.20 if black) × (0.742 if female).

*$P < 0.001$.

ALT, alanine transaminase; AST, aspartate aminotransferase; Ca/P, calcium/phosphate ratio; Cl/P, chloride/phosphate ratio; eGFR, estimated glomerular filtration rate; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

Discussion

Traditionally, the diagnosis of PHPT relies mainly on clinical manifestations and the routine detection of serum calcium and PTH levels. However, many patients with PHPT are asymptomatic (18, 19, 20). It has been reported that asymptomatic patients account for the vast majority of PHPT cases in the USA and Western Europe, and asymptomatic PHPT has become the most common presentation (21). In China, the proportion of asymptomatic cases also increased to approximately 50% between 2007 and 2010 (9, 18). We can infer that the clinical pattern of PHPT has now entered an era of a more asymptomatic type. Recently, some researchers

Figure 2

Receiver-operating characteristic curves (ROCs) used for PHPT of Ca/P ratio and Cl/P ratio. (A) ROC curve analysis for Ca/P ratio together with AUC, 95% CI values, sensitivity, and specificity. (B) ROC curve analysis for Ca/P ratio together with AUC, 95% CI values, sensitivity, and specificity.

have focused on the utility of the Cl/P or Ca/P ratio, and they found that PHPT could be excluded when the Cl/P ratio was <33 or Ca/P ratio >2.55 with a good predictive value (13, 14, 16, 22). We also measured this model in the present study. The ROC–AUC of the Cl/P ratio was 0.966 (95% CI, 0.940–0.983), sensitivity and specificity rates of 95.5% (95% CI, 90.9–98.2) and 91.5% (95% CI, 85.9–95.4), respectively, at a Cl/P ratio of 32.4, which was similar to theirs. The ROC–AUC of the Ca/P ratio was 0.993 (95% CI, 0.976–0.998), and the sensitivity and specificity rates were 95.5% (95% CI, 90.0–98.2) and 98.7 % (95% CI, 95.4–99.8), respectively. A possible explanation is that high levels of PTH in patients with PHPT can inhibit phosphate reabsorption from proximal renal tubules but increase chloride reabsorption from these same tubules. Wright *et al.* compared the Ca/P ratio with Cl/P and found that the AUC for the Cl/P ratio was 0.712, which was inferior to the Ca/P ratio (AUC = 0.813) (14). In our study, we also found that the Ca/P ratio had a better predictive value than the Cl/P ratio in the diagnosis of PHPT (0.993 (95% CI, 0.976–0.998) vs 0.966 (95% CI, 0.940–0.983), $P = 0.005$). In this study, the ratio at a threshold of 2.94 can correctly identify 9 out of 12 NPHPT patients, 138 out of the 143 PHPT patients and only 1 out of the 153 controls were incorrectly diagnosed with PHPT. The mechanism is as follows: (1) PTH directly increases calcium absorption and decreases phosphate reabsorption in the proximal tubule of the kidney; (2) PTH promotes the conversion
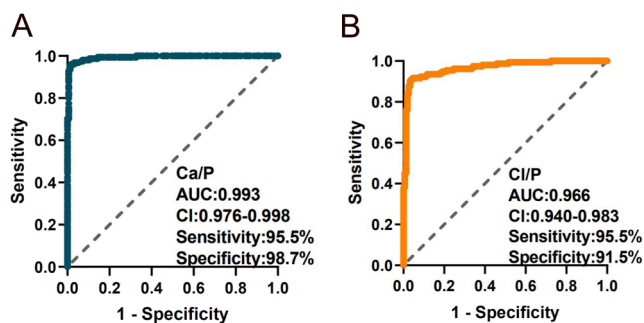
of 25(OH) vitamin D to 1,25-dihydroxyvitamin D by increasing the activity of 1α-hydroxylase in the proximal tubule of the kidney, which promotes gut calcium and phosphate absorption. Although other studies have already investigated the Ca/P ratio in the diagnosis of PHPT, they did not compare the Ca/P ratio with the Cl/P ratio (13, 23, 24, 25). In another study by Madeo *et al.*, the cut-off Ca/P value of 2.55 was able to correctly identify 101 out of 142 NPHPT patients, showing a high sensitivity (71.1%) and specificity (87.9%), which is in line with our findings (13). When using a cut-off of 2.55 in our study, the sensitivity and specificity were 99.4 and 83.1%, respectively. When using a cut-off of 2.55 in our study, the sensitivity and specificity were 99.4 and 83.1%, respectively. We guess that the reason data available in the literature suggested a different cut-off for Ca/P in the diagnosis of PHPT was because of: (1) study cohorts; (2) measuring methods and equipment; and (3) the different proportion of the NPHPT in experimental group. Our results indicated that the Ca/P ratio is an ideal and inexpensive indicator that can be used to diagnose PHPT and has a good correlation with the serum PTH level ($r = 0.875$, $P < 0.001$), which successfully solved the problem of some primary hospitals in remote areas in China not having the required equipment to determine the serum levels of PTH. In summary, the results of this study demonstrate that the Ca/P ratio is an inexpensive and convenient indicator for diagnosing PHPT. Although this index cannot replace the gold standard of imaging, the utility of this ratio may alert clinicians to the possibility of PHPT when patients are asymptomatic Moreover, this ratio is useful for laboratories and clinics with limited resources in low-income geographical areas. There are some limitations to this study. The majority of patients with PHPT were postmenopausal women, however, we did not match age and sex in the selection of the control group. Second, we only included patients with parathyroid adenoma but not those with parathyroid carcinoma, and we excluded patients who did not undergo parathyroidectomy. Although the inclusion of PHPT was defined by serum calcium >2.52 mmol/L together with PHT >6.9 pmmol/L or in the upper range of the normal values, there were no PHPT patients with normal PTH levels in this study. We will focus on this type of PHPT and verify the diagnostic performance of the Ca/P ratio in further research. Meanwhile, no data are available at the moment as far as ethnic differences of the diagnostic performance of Ca/P ratio are concerned, so the results should be confined to the Chinese population.

Conclusion

The Ca/P ratio is an ideal indicator for screening PHPT. PHPT can be identified in healthy individuals when the Ca/P ratio is above 2.94 in the Chinese population.

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