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Longitudinal Analysis of Biochemical, Imaging, and Adenoma Size Changes in Primary Hyperparathyroidism

Authors

Berçem Ayçiçek[1], Mazhar Müslüm Tuna[2], İsmail Engin[3], Asena Gökçay Canpolat[4], Ekin Yiğit[5], Sevde Nur Fırat[6], Yusuf Kır[7], Ali Yeşiltepe[8], Neşe Çınar[9], Kenan Sakar[9], Çiğdem Tura Bahadır[10], Şevkican Güneş[11], Ayse Kubat[11], Ceren Tufan[12], Emre Sedar Saygili[13], Dilek Kılınç Candemir[14], Aysenur Karahan[15], Ahmet Görgel[16], Ziynet Üç Alphan[17], Yudum Yaprak Usda Konak[18], Semin Fenkci[19], Mustafa Aydemir[20], Kadircan Karatoprak[21], Özge Şahin Kimyon[22], Oğulcan Boz[6], Alper Gürlek[23], Özden Uzun[24], Ümit Nur Özbay[25], Gülşah Elbüken[26]

Affiliations

1 Endocrinology and Metabolism, Istinye University, Istanbul, Turkey
2 Endocrinology and Metabolism Disease, Umraniye Training and Research Hospital, Istanbul, Turkey
3 Endocrinology, Ümraniye Eğitim Ve Araştırma Hastanesi, Istanbul, Turkey
4 Ankara University, Ankara, Turkey
5 Yildirim Beyazit University, Ankara, Turkey
6 Ankara Diskapi Yildirim Beyzat Training and Research Hospital, Ankara, Turkey
7 TC Saglik Bakanligi Ankara Gulhane Egitim ve Arastirma Hastanesi, Ankara, Turkey
8 Dumlupinar University, Kütahya, Turkey
9 Muğla Sıtkı Koçman University, Mugla, Turkey
10 Amasya University, Amasya, Turkey
11 Istanbul University, Fatih, Turkey
12 Canakkale Onsekiz Mart Universitesi, Çanakkale, Turkey
13 Çanakkale Onsekiz Mart University, Çanakkale, Turkey
14 Firat University, Elâzığ, Turkey
15 Hatay Mustafa Kemal University, Antakya, Turkey
16 Selçuk University, Konya, Turkey
17 Usak University, Usak, Turkey
18 Trabzon University, Trabzon, Turkey
19 Pamukkale University, Pamukkale, Turkey
20 Endocrinology, Akdeniz Universitesi Tip Fakultesi, Antalya, Turkey
21 Bursa Uludag University, Nilüfer, Turkey
22 Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital, Istanbul, Turkey
23 Hacettepe University, Ankara, Turkey
24 Tekirdag Namik Kemal University, Tekirdağ, Turkey
25 Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey
26 Department of Endocrinology and Metabolism, Tekirdag Namik Kemal University, SÜLEYMANPAŞA, Turkey

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Correspondence

Prof. Berçem Ayçiçek
Endocrinology and Metabolism, Istinye University
Istanbul
Turkey
bercemay@gmail.com

ABSTRACT

Background Primary hyperparathyroidism (PHPT) is a prevalent endocrine disorder characterized by disrupted calcium–phosphorus homeostasis. Accurate biochemical assessment, including albumin-corrected calcium, and preoperative localization of parathyroid adenomas are essential for optimal management. This study aimed to evaluate temporal changes in imaging detectability, biochemical markers, and adenoma size, and to assess novel biochemical indices in patients with asymptomatic PHPT (aPHPT).

Methods In this multicenter retrospective study, 416 aPHPT patients underwent clinical, biochemical, and radiological evaluation at three time points. Biochemical parameters included albumin-corrected calcium, phosphorus, parathyroid hormone (PTH), 25-hydroxyvitamin D, alkaline phosphatase (ALP), and 24-hour urinary calcium. Novel indices—calcium/phosphorus (Ca/P), PTH/phosphorus (PTH/P), and calcium × chloride/phosphorus (Ca × Cl/P)—were calculated to evaluate diagnostic and predictive value. Imaging included high-resolution neck ultrasonography, 99mTc-sestamibi SPECT/CT, and four-dimensional CT to assess adenoma detectability and size changes. Statistical analyses included repeated-

measures ANOVA or Friedman tests for temporal comparisons, correlation analyses, logistic regression for predictors of adenoma detection, and ROC curves to evaluate diagnostic accuracy. A p-value < 0.05 was considered significant.

Results Among 416 patients (87 % female), ultrasound-detected adenomas decreased over time due to surgery of clearly visible lesions. CT and SPECT/CT initially improved localization, with later decline in CT but continued gains in SPECT/CT. Adenoma size increased, and the PTH/phosphorus ratio changed significantly. Baseline albumin-corrected calcium, phosphorus, and adenoma size predicted radiological detectability, with ROC AUCs of 0.78 for adenoma size and 0.72 for phosphorus. Surgically treated patients exhibited more pronounced biochemical abnormalities and superior CT-based localization.

Conclusion Following imaging and biochemical assessments, including albumin-corrected calcium, improve detection, monitoring, and management of aPHPT. Novel indices such as PTH/phosphorus and Ca/P ratios provide practical, low-cost tools for early disease identification and risk stratification. Integrating dynamic biochemical markers with imaging supports individualized, evidence-based clinical decision-making.

Introduction

Primary hyperparathyroidism (aPHPT) is characterized by excessive secretion of parathyroid hormone (PTH), disrupting calcium and phosphorus homeostasis [1]. Although many patients are clinically asymptomatic, chronic PTH elevation can still lead to subclinical consequences, including decreased bone mineral density and renal complications [2].

Accurate biochemical assessment and optimal management of aPHPT rely on the integration of advanced imaging techniques for localization alongside serial biochemical monitoring. Ultrasonography (US), scintigraphy, and computed tomography (CT) are commonly employed for adenoma localization; however, their diagnostic performance may fluctuate over time, particularly during repeated assessments [3–5].

Emerging evidence highlights the dynamic interplay between biochemical markers—such as vitamin D, creatinine, and the PTH/phosphorus (PTH/P) ratio—and adenoma growth [6, 7]. Building on these insights, the present study evaluates longitudinal changes in radiological localization across sequential assessments, aiming to clarify how imaging positivity, biochemical indices, and adenoma progression converge in the clinical management of aPHPT [4–8].

In addition, derived biochemical ratios—including calcium/phosphorus (Ca/P), PTH/phosphorus (PTH/P), and calcium × chloride/phosphorus (Ca × Cl/P)—have demonstrated utility as adjunctive diagnostic tools. Yin et al. [9] reported high sensitivity and specificity for the Ca/P ratio, particularly in settings where direct PTH assays may be limited. Guo et al. [10] demonstrated that the PTH/P ratio effectively distinguishes primary from secondary hyperparathyroidism, emphasizing the diagnostic value of integrating phosphate levels with PTH. Early studies by Broulík and Pacovský [11] on the chloride/phosphate (Cl/P) ratio laid the foundation for derivative indices, such as Ca × Cl/P, which may further enhance diagnostic accuracy. Collectively, these findings support the use of biochemical ratios alongside imaging to improve detection and management of aPHPT.

In this study, we focused on patients with aPHPT who had not undergone parathyroidectomy in order to analyze the natural disease progression and longitudinal changes. We aimed to assess changes in radiological detectability of parathyroid adenomas over at least three sequential measurements (baseline, approximately 6 months, and ≥ 1 year), identify biochemical predictors of imaging positivity and adenoma detectability, including novel biochemical indices, evaluate the diagnostic value of derived biochemical ratios—such as Ca/P, PTH/P, and Ca × Cl/P—in predicting PTH elevation, and characterize temporal trends in both imaging and biochemical markers to provide insight into disease evolution.

Materials and Methods

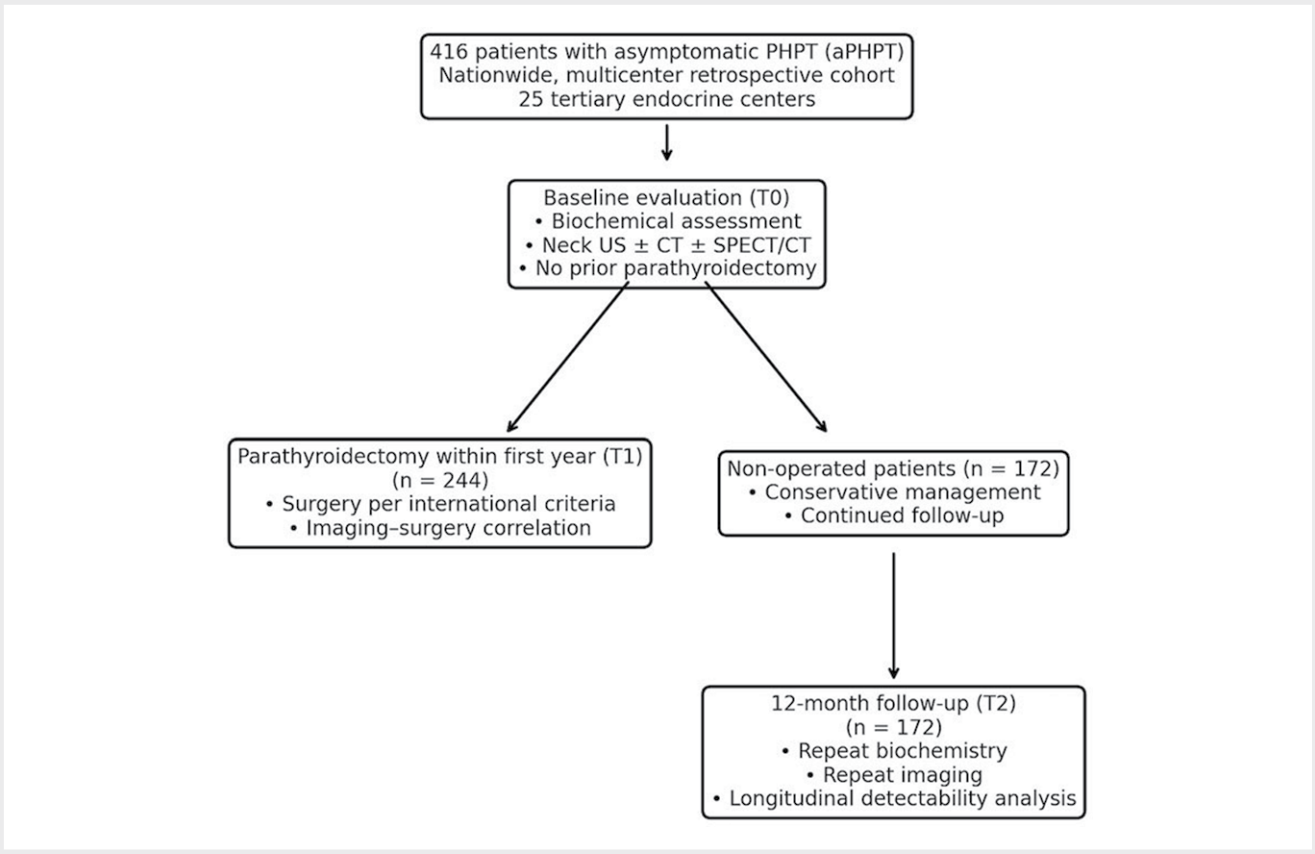
Study Design and Patients

This was a nationwide, multicenter, observational, retrospective cohort study including 416 patients with asymptomatic primary hyperparathyroidism (aPHPT), recruited from 25 tertiary endocrine centers across Turkey over a 6-year retrospective period. Inclusion criteria for centers required an adequate number of aPHPT patients, careful diagnosis according to established guidelines [1, 2] and regular follow-up with systematic monitoring for complications. Centers with insufficient case numbers or inadequate follow-up duration were excluded.

Patients were included if they had biochemically confirmed persistent hypercalcemia with elevated or inappropriately normal PTH levels. Patients with secondary or tertiary hyperparathyroidism were excluded. The terminology for asymptomatic PHPT was adopted from Bilezikian et al., Fifth International Workshop.
The cohort included:

- Patients who refused surgery despite surgical indications,
- Patients awaiting surgery, and
- Patients managed conservatively, including those receiving bisphosphonates or denosumab for osteoporosis.

Data were collected until parathyroidectomy was performed or the patient was lost to follow-up for any reason (▶ **Fig. 1**). Although data were collected retrospectively over a 6-year period across multiple centers, the follow-up for each individual patient spanned 12 months, corresponding to baseline (Timepoint 0), 6 months (Timepoint 1), and 12 months (Timepoint 2). A total of 244 patients underwent parathyroidectomy within the first year after diagnosis (Time point 1), while the remaining patients continued clinical and radiological follow-up without surgery. Some patients contributed data at multiple time points due to repeated imaging during follow-up visits, resulting in partial overlap of cases between the time points. Imaging results in non-operated patients were used to assess longitudinal detectability trends and were not intended as a



▶ **Fig. 1** Flowchart of patient inclusion and follow-up in asymptomatic primary hyperparathyroidism (aPHPT). Retrospective flowchart illustrating patient selection, longitudinal follow-up, sequential imaging (USG, CT, and/or 99mTc-sestamibi SPECT/CT), biochemical assessments, and clinical management in a nationwide, multicenter cohort of 416 patients with asymptomatic primary hyperparathyroidism (aPHPT) recruited from 25 tertiary endocrine centers. Evaluations were performed at three predefined time points: baseline (T0), 6 months (T1), and 12 months (T2). The diagram depicts patient progression during follow-up, imaging positivity, and the timing of parathyroidectomy, which was performed according to internationally accepted guideline-based indications, while the remaining patients continued conservative monitoring. Abbreviations: USG, ultrasound; CT, computed tomography; SPECT/CT, single-photon emission computed tomography/computed tomography; PHPT, primary hyperparathyroidism.

diagnostic gold standard. Retrospective data included biochemical and radiological assessments performed locally; data management and albumin-corrected calcium calculations were performed at the coordinating center (Ümraniye Training and Research Hospital).

Biochemical and Clinical Measurements

All patients underwent serial biochemical and radiological assessments at three predefined time points (baseline, 6 months, and 12 months). Standard laboratory parameters included serum calcium, phosphate, magnesium, alkaline phosphatase (ALP), 25-hydroxyvitamin D, albumin, creatinine, and 24-hour urinary calcium.

PTH levels were measured using an intact PTH chemiluminescent immunoassay (Immulite 2000 analyzer), and plasma 25-hydroxyvitamin D was measured by radioimmunoassay. Vitamin D deficiency was defined as ≤ 20 ng/mL, consistent with the IOM definition. Serum calcium was albumin-corrected using: Corrected calcium = serum calcium + 0.8 × (4 − albumin)\text{Corrected calcium} = \text{serum calcium} + 0.8 \times (4 - \text{albumin})Corrected calcium = serum calcium + 0.8 × (4 − albumin)

eGFR was calculated using the CKD-EPI equation [12]. Hypercalcemia was defined as a serum calcium level > 10.2 mg/dL. In addition, novel biochemical indices were calculated, including the calcium/phosphorus ratio, PTH/phosphorus ratio, and calcium × chloride/phosphorus ratio.

Finally, parathyroidectomy status and the use of osteoporosis treatments (denosumab or bisphosphonates) were recorded.

Imaging Modalities and Radiological Localization

Imaging modalities included neck ultrasonography (US), 99mTc-sestamibi SPECT/CT, and contrast-enhanced computed tomography (CT). In this multicenter cohort, all patients had asymptomatic primary hyperparathyroidism (aPHPT) and had not undergone parathyroidectomy, allowing assessment of natural disease progression. Each patient was evaluated using one or more imaging modalities depending on availability at the corresponding center, as some centers did not perform SPECT/CT. Ultrasound was employed as the first-line imaging tool, and all patients underwent at least three US evaluations; however, baseline US data were missing for some patients, as indicated in the flowchart (▶ **Fig. 1**).

Adenoma dimensions were measured on US in up to three planes (Adenoma Size 1, 2, and 3), while in some cases only two-plane measurements were available, and all available measurements were included for longitudinal analysis. Radiological localization was retrospectively assessed at three predefined time points (Timepoints 0, 1, and 2), with positivity defined as the definitive identification of a parathyroid adenoma by any imaging modality (coded as "1") or absence of a visible lesion (coded as "0"). Changes in detectability over time were analyzed to evaluate potential fluctuations in imaging sensitivity.

High-resolution B-mode ultrasonography (7.5–15 MHz linear transducer) was used to examine the thyroid and parathyroid regions.

Parathyroid scintigraphy was performed using dual-phase 99mTc-sestamibi SPECT/CT, enabling combined functional and anatomical localization. Contrast-enhanced CT was performed with dual-phase protocols of the cervical and upper mediastinal regions to optimize detection of ectopic or deep-seated adenomas.

While intraobserver standardization was not feasible in this multicenter retrospective study, comparisons were made longitudinally within the same patients, reflecting routine clinical practice and allowing for reliable assessment of adenoma size changes over time.

As some patients underwent serial imaging at more than one visit, the total number of imaging assessments at different time points exceeded the total number of participants.

Surgical Indications

Parathyroidectomy was performed only in patients who fulfilled internationally accepted surgical criteria [3, 4], including:

- Age below 50 years,
- Serum calcium level > 1.0 mg/dL above the upper limit of normal,
- Presence of osteoporosis or fragility fractures,
- History of nephrolithiasis or nephrocalcinosis, and/or
- eGFR < 60 mL/min/1.73 m².

Surgical decisions were made by a multidisciplinary endocrine surgery team.

Statistical Analysis

All statistical analyses were conducted using Jamovi software (version 2.6.19), with a significance threshold set at $p < 0.05$. Continuous variables were assessed for normality using the Shapiro-Wilk test and presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Categorical variables were summarized as frequencies and percentages. To evaluate the trend of radiological detectability over three time points, McNemar's test was applied for binary categorical comparisons, while Cochran's Q test and Friedman test were used to analyze repeated categorical data. The association between radiological detectability and biochemical/demographic variables was examined using chi-square tests for categorical predictors and logistic regression analysis for numerical predictors, with ROC curve analysis assessing the discriminative ability of biochemical markers. Correlations between PTH levels and biochemical indices were determined using Pearson or Spearman correlation analysis, and multivariate regression was conducted to adjust for confounders. The diagnostic performance of US, SPECT/CT, and CT in adenoma detection was compared using chi-square or McNemar's tests, and Cochran's Q test was employed for repeated measurements. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated, while logistic regression was performed to estimate odds ratios (ORs). Additionally, ROC curve analysis, Youden's index and logistic regression models were used to improve the localization accuracy of the biochemical marker most predictive for PTH elevation.

Results

Patient Demographics and Follow-up

Among 416 participants, 362 (87.0 %) were women and 54 (13.0 %) were men ($p < 0.001$). The mean age was 55.6 ± 11.5 years.

In the 331 subjects evaluated for ultrasound adenoma detection, the proportion of positive findings significantly decreased over time—from 62.5 % at baseline to 22.7 % at the second and 13.6 % at the third measurement. All patients underwent at least three neck US examinations, with two- or three-dimensional adenoma measurements depending on availability. The apparent decline in US-positive findings likely reflected the selective removal of surgically treated patients with clearly detectable adenomas and the predominance of those with more subtle or equivocal lesions during follow-up.

Bisphosphonate use in 339 subjects dropped from 82.6 % at baseline to 17.4 % at the second measurement, with none on treatment at the third. Denosumab use in 354 subjects and its duration in 184 subjects also decreased sharply, from 95.8 % and 97.3 % at baseline to 4.2 % and 1.6 % at the second measurement, further reducing to 0.5 % at the third. Denosumab use was defined as any patient receiving at least one dose during follow-up; some patients also received bisphosphonates sequentially or concurrently, reflecting real-world combination therapy. Parathyroidectomy rates among 361 subjects were 67.6 % at baseline, decreasing to 32.4 % at the second measurement and to 0.8 % at the third (▶ **Table 1**). The decline reflects both the selective removal of patients with clear surgical indications at baseline and the remaining patients who continued under surveillance without new indications for surgery. Several patients who met surgical criteria (e. g., osteoporosis or serum calcium > 1 mg/dL above the upper limit) initially declined surgery and received antiresorptive therapy instead. Some lacked baseline US or sestamibi imaging and were only imaged later, while others became surgically eligible during follow-up.

Radiological Localization

Radiological localization rates significantly increased from the first (T1) to the second (T2) time point ($p < 0.001$) but declined at the third (T3) ($p = 0.020$). Ultrasound positivity dropped from 62.5 % at baseline to 13.6 % at T3, with the largest decrease observed in patients who later underwent parathyroidectomy (▶ **Table 2, 3**).

Repeated-measures analysis (Friedman test) confirmed a significant difference in CT adenoma detectability across T1, T2, and T3 ($p < 0.001$). Post hoc comparisons demonstrated a marked rise from T1 to T2 ($p = 0.002$), followed by a significant decline from T2 to T3

▶ **Table 1** Descriptive Statistics of Continuous Variables.

Variable (Unit)	Timepoint 0 (Baseline)	Timepoint 1 (6 month)	Timepoint 2 (1 year)	P value
Corrected Calcium (mg/dL)	10.1 ± 0.83 (n = 416)	10.0 ± 0.83 (n = 416)	9.82 ± 0.83 (n = 416)	0.082
Parathyroid Hormone (PTH) (pg/mL)	134.0 (115–149) (n = 416)	140 (120–160) (n = 416)	145 (125–165) (n = 416)	> 0.05
Phosphorus (mg/dL)	2.91 ± 0.58 (n = 414)	2.99 ± 0.58 (n = 414)	1.85 ± 0.58 (n = 414)	**< 0.001**
Magnesium (mg/dL)	1.93 ± 0.40 (n = 337)	1.88 ± 0.40 (n = 337)	-	0.341
Alkaline Phosphatase (ALP) (U/L)	92.4 (67–107) (n = 352)	87.3 (69–110) (n = 293)		> 0.05
Vitamin D (ng/mL)	30.9 (22–37) (n = 402)	28.2 (24–40) (n = 402)		**0.008**
Creatinine (mg/dL)	0.746 ± 0.16 (n = 416)	0.764 ± 0.16 (n = 359)	0.75 ± 0.146 (n = 210)	0.068
Chloride (mEq/L)	104.0 ± 3.32 (n = 256)	104.0 ± 3.32 (n = 256)		0.062
Glomerular Filtration Rate (GFR) (mL/min/1.73 m²)	92.2 ± 17.0 (n = 416)	89.9 ± 17.0 (n = 416)		0.063
Urinary Calcium (mg/24 h)	261.0 ± 156.0 (n = 350)	200.0 ± 156.0 (n = 234)	180.0 ± 156.0 (n = 131)	**0.024**
Urinary Creatinine (mg/24 h)	1020.0 ± 366.0 (n = 266)	829.0 ± 366.0 (n = 174)	718.0 ± 366.0 (n = 170)	0.055
Adenoma Size 1 (mm)	5.68 ± 5.51 (n = 217)	6.23 ± 5.51 (n = 217)		**< 0.001**
Adenoma Size 2 (mm)	4.05 ± 4.6 (n = 206)	3.67 ± 4.6 (n = 206)	4.09 ± 6.52 (n = 105)	0.132
Adenoma Size 3 (mm)	4.79 ± 6.48 (n = 179)	2.77 ± 6.48 (n = 179)	1.53 ± 4.56 (n = 102)	0.593
Corrected Calcium/Phosphorus Ratio	3.46 ± 0.72 (n = 342)	3.50 ± 0.72 (n = 342)	3.55 ± 0.68 (n = 342)	0.287
PTH/Phosphorus Ratio	45.98 ± 9.41 (n = 413)	46.50 ± 9.30 (n = 413)	47.00 ± 9.20 (n = 413)	**0.039**
Corrected Calcium × Chloride / Phosphorus Ratio	38.22 (30.56–46.17) (n = 256)	39.00 (31.00–47.00) (n = 256)	39.50 (31.50–47.50) (n = 256)	0.859
Radiological Localization (n = 331)	198 (59.8 %)	133 (40.2 %)	–	**< 0.001**
Ultrasound Presence (n = 331)	207 (62.5 %)	124 (37.5 %)	–	**< 0.001**
Scintigraphy (n = 143)	130 (90.9 %)	9 (6.3 %)	4 (2.8 %)	**< 0.001**
CT Adenoma (n = 298)	207 (69.5 %)	91 (30.5 %)	–	**< 0.001**
Parathyroidectomy (n = 361)	Baseline: 244 (67.6 %)	Second: 117 (32.4 %)	Third: 1 (0.8 %)	**< 0.001**

▶ **Table 2** Radiological Trends Over Three Time Points.

Variable	1st Time Point	2nd Time Point	3rd Time Point
Radiological Localization (Present, %)	**62.5 %**	**22.7 %**	**13.6 %**
Radiological Localization (Absent, %)	**37.5 %**	**77.3 %**	**86.4 %**
USG Positivity (Present, %)	**62.5 %**	**37.5 %**	**13.6 %**
USG Positivity (Absent, %)	**37.5 %**	**62.5 %**	**86.4 %**
Scintigraphy Positivity (Present, %)	**90.9 %**	**6.3 %**	**2.8 %**
Scintigraphy Positivity (Absent, %)	**9.1 %**	**93.7 %**	**97.2 %**
CT Adenoma (Detected, %)	**69.5 %**	**30.5 %**	**13.6 %**
CT Adenoma (Not Detected, %)	**30.5 %**	**69.5 %**	**86.4 %**
Parathyroidectomy (n, %)	**67.6 %**	**32.4 %**	**0.8 %**

(p < 0.001), with detectability at T1 still higher than T3 (p = 0.018) (▶ **Table 2, 3**).

SPECT/CT showed a non-significant increase from T1 to T2 (mean = 0.229, p = 0.164), but a significant improvement at T3 (mean = 0.500, p = 0.003), likely reflecting learning effects and technological advances. In contrast, CT detectability increased sharply from T1 to T2 (mean = 0.574, p = 0.002) but declined again at T3 (mean = 0.130, p < 0.001), consistent with the selective removal of clearly detectable adenomas and a shift toward more subtle cases at later time points (▶ **Table 2, 3**).

Biochemical Parameters and Adenoma Size

Vitamin D demonstrated significant temporal changes (p < 0.05), whereas PTH, ALP, and magnesium remained stable (p > 0.05). GFR demonstrated a slight decrease over time, without reaching statistical significance (baseline: 92.2 ± 17.0 mL/min/1.73m²; second visit: 89.9 ± 17.0 mL/min/1.73m²; p = 0.063). Adenoma size increased markedly during follow-up (p < 0.001), with the largest effect size ($\eta^2 = 0.246$) for Adenoma Size 1. Among biochemical ratios, the PTH/phosphorus (PTH/P) ratio showed significant temporal change (p = 0.039), while Ca/P and Ca × Cl/P remained unchanged (p > 0.05) (▶ **Table 1**).

Predictors of Radiological Detectability

Logistic regression analysis demonstrated excellent model performance (accuracy = 95.1 %, sensitivity = 97.3 %, specificity = 93.3 %,

▶ **Table 3** Radiological Trends Over Three Time Points (McNemar's Test Results).

Comparison	McNemar's χ^2	p-value	Log Odds Ratio	Interpretation
1st vs. 2nd Time Point (Radiological Localization)	18.8	< 0.001	1.82	Significant increase in radiological localization
2nd vs. 3rd Time Point (Radiological Localization)	5.44	0.020	0.82	Moderate decline in localization consistency
1st vs. 3rd Time Point (Radiological Localization)	8.97	0.003	0.82	Overall increase from baseline, lower than 2nd time point
1st vs. 2nd Time Point (Scintigraphy Positivity)	80.7	< 0.001	−3.14	Highly significant decrease in scintigraphy positivity
CT Adenoma Detection Over Time (1st vs. 2nd)	13.4	< 0.001	1.42	Significant improvement in CT detection
CT Adenoma Detection Over Time (1st vs. 3rd)	13.5	< 0.001	−1.95	Significant reduction in CT detectability at 3rd time point

AUC = 0.990, p < 0.001). Corrected calcium, phosphorus (p = 0.013), and the largest adenoma dimension at baseline (p = 0.005) were significant predictors of detectability, whereas magnesium, vitamin D, the Ca/P ratio, and antiresorptive agent use were not significant (p > 0.05). Smaller adenomas were associated with lower detection rates (p < 0.05). The optimal model probability cut-off was 0.5 (▶ **Table 4**).

ROC curve analysis for biochemical parameters indicated that Ca/P and PTH/P ratios had the highest predictive performance, with AUCs of 0.632 (95 % CI: 0.502–0.759) and 0.661 (95 % CI: 0.536–0.786), respectively (▶ **Fig. 2**). The optimal cut-offs were 3.12 for Ca/P (68.2 % sensitivity, 59.3 % specificity) and 5.91 for PTH/P (71.4 % sensitivity, 64.8 % specificity). Other indices (urinary calcium, serum sodium, serum chloride) had AUC < 0.6. The largest adenoma dimension at baseline (AUC = 0.78, 95 % CI: 0.70–0.85, p < 0.001) and baseline serum phosphorus (AUC = 0.72, 95 % CI: 0.65–0.80, p = 0.002) were also significant predictors (▶ **Table 4**, ▶ **Fig. 3**).

Surgery and Biochemical Profiles

Patients who underwent parathyroidectomy had lower adjusted calcium, higher 24-hour urinary calcium, and lower eGFR compared with those managed conservatively (all p < 0.05). This lower calcium level is likely attributable to the use of antiresorptive agents (e. g., bisphosphonates, denosumab) in a subset of surgically treated patients. Radiological localization and CT-based adenoma detection were significantly more successful in the surgical group, while ultrasound, SPECT, and medical treatment variables did not differ.

Overall, these findings indicate that surgically treated patients had more pronounced biochemical abnormalities and more readily localizable adenomas on imaging, factors likely influencing the decision for surgery.

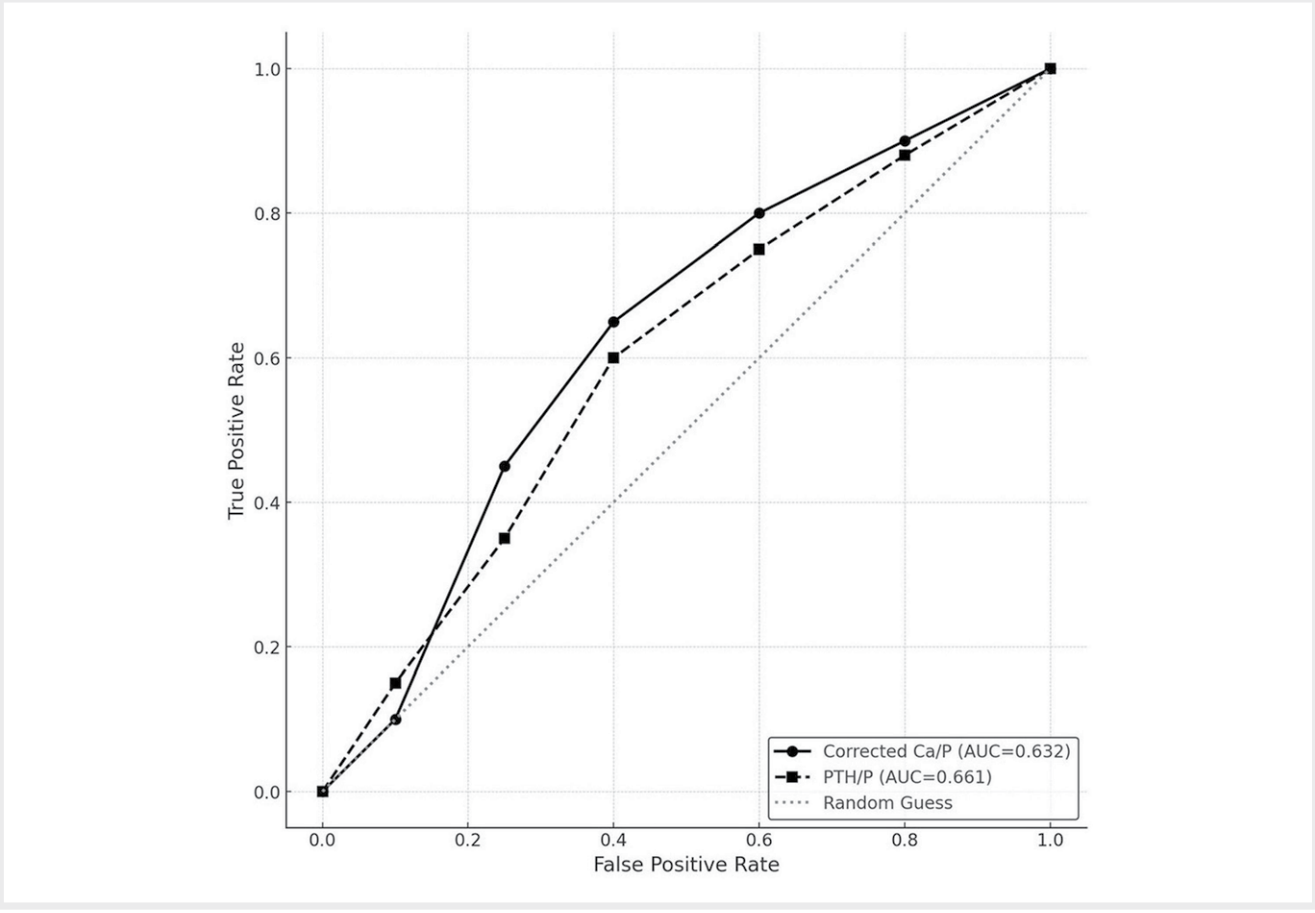
Discussion

Our study highlights temporal changes in radiological localization in primary hyperparathyroidism (aPHPT) across three sequential assessments. Localization rates increased from the first to the second evaluation but declined at the third, a trend consistent across ultrasound, CT, and scintigraphy [3–5]. Ultrasound initially showed stable detection, yet its positivity decreased over time, dropping from 62.5 % at baseline to 13.6 % at the final assessment. The greatest decline occurred among patients who later underwent parathyroidectomy, likely reflecting the surgical removal of easily detectable adenomas. These findings support previous reports that advanced imaging modalities, such as CT and PET/CT, may improve localization, particularly in cases with subtle or inconclusive ultrasound findings [13, 14].

Biochemical analyses revealed significant temporal changes in vitamin D levels; however, the underlying cause of this decline could not be determined in our cohort [6]. While vitamin D decreased over time, parathyroid hormone (PTH), alkaline phosphatase (ALP), and magnesium remained stable, indicating selective temporal variation among biochemical markers. Glomerular filtration rate (GFR) showed a slight decrease from baseline to the second visit (92.2 ± 17.0 to 89.9 ± 17.0 mL/min/1.73 m²) without reaching statistical significance (p = 0.063), suggesting relatively preserved renal function during follow-up. Serum phosphorus declined to 1.85 mg/dL at the final time point, falling slightly below the normal reference range. This decrease may reflect increased renal phosphate excretion or the selective retention of patients with more pronounced biochemical abnormalities during follow-up, suggesting a potential association with disease progression in aPHPT. Concurrently, adenoma size increased significantly, reflecting progressive disease [7]. Adjusted calcium levels were lower in patients who underwent parathyroidectomy, likely influenced by prior antiresorptive therapy in some cases, underscoring the interaction between medical management and surgical selection. Among emerging biochemical indices, the PTH/phosphorus (PTH/P) ratio demonstrated robust temporal changes and appeared superior for monitoring disease progression and predicting adenoma detectability [9, 10]. In contrast, Ca/P and Ca × Cl/P ratios remained stable, suggesting more limited utility in longitudinal assessment. Derived indices, such as the Ca/P and Ca × Cl/P ratios, continue to provide insight into disrupted calcium-phosphorus ho-

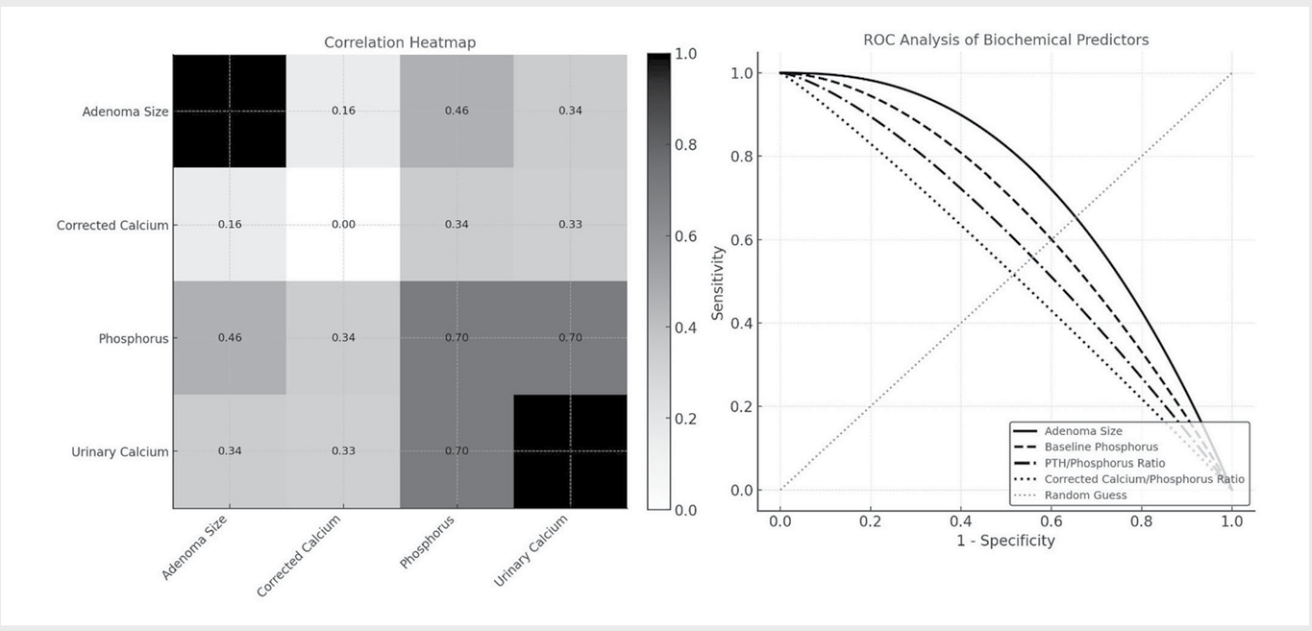
▶ **Table 4** Logistic Regression Analysis for Predictors of Radiological Detectability.

Variable	Estimate (B)	95 % CI (Lower–Upper)	SE	Z	p-value	Odds Ratio (OR)
Intercept	25.959	−2.9659 to 54.8839	14.757	1.759	0.079	1.88 × 10^11
Corrected Calcium	−4.3416	−7.7646 to −0.9186	1.7465	−2.486	**0.013**	0.0130
Magnesium	1.2972	−0.7472 to 3.3416	1.0431	1.244	0.214	3.6590
Vitamin D	0.0365	−0.0292 to 0.1023	0.0335	1.089	0.276	1.0372
Adenoma Size 1	−0.6648	−1.1330 to −0.1967	0.2389	−2.783	**0.005**	0.5144
Adenoma Size 2	−0.1427	−0.6152 to 0.3299	0.2411	−0.592	0.554	0.8670
Adenoma Size 3	0.1254	−0.1457 to 0.3965	0.1383	0.907	0.365	1.1336
Corrected Calcium/Chloride Ratio	−0.0148	−0.0879 to 0.0583	0.0373	−0.396	0.692	0.9853
Corrected Calcium/Phosphorus Ratio	6.3237	−1.9980 to 14.6454	4.2459	1.489	0.136	557.6193
PTH/Phosphorus Ratio	−0.0125	−0.4775 to 0.4524	0.2372	−0.053	0.958	0.9875



▶ **Fig. 2** ROC Curve Analysis for the Corrected Ca/P and PTH/P Ratios. This figure compares the diagnostic performance of the Corrected Ca/P and PTH/P ratios in identifying radiologically detectable parathyroid adenomas, highlighting their respective AUC values and optimal cut-off points. PTH achieved the highest accuracy (AUC = 0.91, 95 % CI: 0.84–0.95, p < 0.001), while urinary calcium (AUC = 0.79) and corrected calcium (AUC = 0.78) also provided significant predictive information. [Abbreviations: ROC = Receiver Operating Characteristic; AUC = Area Under the Curve; pg/mL = picograms per milliliter].

meostasis in aPHPT. Previous studies support their clinical relevance: Yin et al. highlighted the utility of the Ca/P ratio in identifying primary hyperparathyroidism [9], and Guo et al. demonstrated the PTH/P ratio's effectiveness in distinguishing primary from secondary hyperparathyroidism [10], and foundational work by Broulik and Pacovski on the chloride-to-phosphorus ratio, evolving into Ca × Cl/P, underlines the potential value of integrating these measures into routine evaluation [11]. Despite this, our ROC analysis revealed only moderate predictive performance for adenoma detectability for Ca/P (AUC = 0.632) and PTH/P (AUC = 0.661), suggesting



▶ **Fig. 3** Correlation Heatmap and ROC Analysis of Biochemical Predictors for Adenoma Detectability. Abbreviations: PTH = Parathyroid Hormone; Ca = Corrected Calcium; PHPT = Primary Hyperparathyroidism; AUC = Area Under the Curve. Heatmap showing Pearson correlations between adenoma size (largest dimension) and key biochemical parameters including parathyroid hormone (PTH), corrected calcium, phosphorus, and urinary calcium in patients with asymptomatic primary hyperparathyroidism (aPHPT). ROC curves for selected biochemical markers (PTH/phosphorus [PTH/P] and Corrected calcium/phosphorus [Ca/P] ratios, baseline phosphorus, and adenoma size) are overlaid, indicating diagnostic performance: Adenoma Size 1 AUC = 0.78 (95 % CI: 0.70–0.85), baseline phosphorus AUC = 0.72 (95 % CI: 0.65–0.80), PTH/P AUC = 0.661 (cut-off 5.91; sensitivity 71.4 %, specificity 64.8 %), Ca/P AUC = 0.632 (cut-off 3.12; sensitivity 68.2 %, specificity 59.3 %).

that their discriminative power may be reduced in longitudinal follow-up compared with cross-sectional studies [9, 15].

Furthermore, previous studies have emphasized the influence of adenoma size and biochemical markers on localization and surgical outcomes. Lee et al. reported that larger adenomas are more readily localized and associated with improved surgical results [16], a finding consistent with our data. Logistic regression identified adenoma size as a significant predictor of radiological detectability ($p = 0.005$), and ROC analysis demonstrated a strong AUC of 0.78 for the largest adenoma dimension. Similarly, Chen et al. noted that lower serum phosphorus correlates with more severe biochemical and clinical manifestations [17], which aligns with our observation that patients undergoing parathyroidectomy had significantly lower phosphorus levels ($p < 0.001$). Additionally, Patel et al. highlighted that incorporating corrected calcium into biochemical assessment algorithms improves overall accuracy in identifying primary hyperparathyroidism [18]; our results support this, as corrected calcium emerged as a significant predictor of adenoma detectability ($p = 0.013$), highlighting its relevance for predicting preoperative localization rather than for establishing the diagnosis of pHPT. Some patients had calcium levels within the normal range, which may partly reflect the use of antiresorptive therapies (bisphosphonates or denosumab) in the cohort, in addition to the asymptomatic and normocalcemic spectrum of PHPT. This contributed to a robust model with an overall AUC of 0.990.

Given the observed variability in imaging outcomes, our findings underscore the importance of integrating complementary biochemical monitoring alongside conventional imaging.

Standardized longitudinal assessments are critical, as highlighted by the Fourth International Workshop on Asymptomatic PHPT [19, 20]. Our data reinforce these recommendations, demonstrating that imaging alone may be insufficient—particularly given the temporal fluctuations in detectability—and that longitudinal biochemical surveillance provides additional predictive value for both adenoma localization and progression of adenoma size. Combining advanced imaging modalities with robust biochemical indices allows for a more comprehensive approach to monitoring, facilitates timely interventions, and may enhance overall management of aPHPT. Routine re-evaluation using both imaging and biochemical parameters may be particularly valuable in aPHPT, where classical clinical signs are often subtle, yet disease evolution persists.

Conclusion

Concurrently, adenoma size, serum phosphorus, and biochemical indices—particularly the PTH/phosphorus and Ca/P ratios, along with corrected calcium—change significantly over time. These findings emphasize the importance of a comprehensive, longitudinal approach that integrates follow-up imaging with biochemical monitoring to accurately track disease progression and inform clinical decision-making. Novel biochemical indices may aid clinicians in prioritizing patients for repeat imaging or surgical evaluation, particularly when initial imaging is inconclusive, thereby enhancing timely and informed clinical management of aPHPT.

Limitations

This study has several limitations. Although data were collected from multiple centers, heterogeneity in imaging protocols may affect the consistency and reproducibility of the findings. Whenever possible, adenoma sizes were compared using the same imaging modality. However, due to the retrospective nature of the study, uniform imaging techniques and operators across all time points could not be guaranteed.

Due to the retrospective design of this study, patients were not uniformly evaluated with all imaging modalities or at standardized time points. Imaging tests were repeated in routine clinical practice only when clinically indicated, such as when initial localization attempts were inconclusive or discordant. This variability in imaging schedule and modality reflects real-world management of aPHPT and was accepted as part of the study design.

Lastly, while the integration of novel biochemical indices appears promising, further prospective and large-scale multicenter studies are needed to validate these findings and refine biochemical threshold values for broader clinical application.

Tables:

All abbreviations used in this study (e. g., Ca_corr: Corrected Calcium; PTH: Parathyroid Hormone; GFR: Glomerular Filtration Rate; ALP: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; U-Ca: Urinary Calcium; ROC: Receiver Operating Characteristic; AUC: Area Under the Curve) are defined in the Abbreviations section below. Statistical tests used include repeated measures ANOVA (with Greenhouse-Geisser or Huynh-Feldt corrections), logistic regression, correlation analyses (Pearson/Spearman), and ROC curve analysis

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for this multicenter retrospective study was obtained from the central coordinating center, the Ethics Committee of Istanbul University of Health Sciences, Umraniye Training and Research Hospital (Approval No: B.10.1TKH.4.34.H.GP.0.01/501). Additionally, local ethical approval or exemption letters were obtained from the ethics committees of each participating institution, in compliance with national regulations.

Informed Consent

As the study was retrospective in nature, the requirement for informed consent was waived by all ethics committees.

Contributors' Statement

Berçem Ayçiçek: Conceptualization, Formal analysis, Methodology, Writing – original draft. Mazhar Müslüm Tuna: Conceptualization, Data curation, Methodology, Project administration, Writing – review & editing. İsmail Engin: Data curation, Investigation, Supervision. Asena Gökçay Canpolat: Investigation, Supervision. Ekin Yiğit: Data curation, Funding acquisition. Sevde Nur Fırat: Conceptualization, Investigation. Yusuf Kır: Investigation. Ali Yeşiltepe: Data curation, Investigation. Neşe Çınar: Data curation. Kenan Sakar: Data curation, Investigation. Çiğdem Tura Bahadır: Data curation. Şevkican Güneş: Data curation, Investigation. Ayse Kubat: Data curation. Ceren Tufan: Investigation. Emre Sedar Saygili: Data curation, Formal analysis. Dilek Kılınç Candemir: Data curation. Aysenur Karahan: Data curation. Ahmet Görgel: Data curation. Ziynet Üç Alphan: Data curation. Yudum Yaprak Usda Konak: Data curation. Semin Fenkci: Data curation. mustafa aydemir: Data curation. Kadircan Karatoprak: Data curation. Ozge Sahin Kimyon: Data curation. Oğulcan Boz: Data curation. Alper Gürlek: Data curation. Özden Uzun: Data curation. Umit Nur Ozbay: Data curation. Gulsah Elbuken: Data curation, Formal analysis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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