JBMR Plus, 2024, **8**, ziae065
https://doi.org/10.1093/jbmrpl/ziae065
Advance access publication: May 13, 2024
Research Article

Secular trends in the incidence and treatment patterns of primary hyperparathyroidism in Korea: a nationwide cohort study

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Abstract

Data on epidemiology and secular trend in primary hyperparathyroidism (PHPT) in adults are relatively limited in Asian countries. This study aims to provide an overview of the secular trends in incidence, clinical characteristics, and treatment patterns of PHPT in South Korea. We used Korea's National Health Insurance Claim database (2005-2020) to identify newly diagnosed PHPT cases. Individuals with age below 19, fewer than 2 E21.0 diagnoses, fewer than 2 PTH measurements, secondary hyperparathyroidism, undergoing dialysis or kidney transplantation within a year of diagnosis, parathyroidectomy (PTX) within a year prior to the diagnosis code, and diagnosis of multiple endocrine neoplasm or parathyroid carcinoma were excluded from the analysis. A total of 6837 patients with PHPT (PTX, $n=2989$; non-surgery, $n=3848$) were compared with 1:10 age- and sex-matched controls ($n=68\,370$). The mean age of patients with PHPT was 56.0 years, with 77.4% being women. The annual incidence of PHPT increased from 0.23/100 000 persons in 2005 to 1.75 in 2020, with higher rate in women than in men. Compared with 2005-2010 ($n=675$), the number of newly diagnosed PHPT cases increased up to 3.1-fold ($n=2119$) in 2011-2015 and 6.0-fold ($n=4043$) in 2016-2020 periods. Among all patients with PHPT, 43.7% of patients underwent PTX, with decrement of proportion of bilateral surgery among PTX group across time (11.9% in 2005-2010 to 8.9% in 2016-2020, *P* for trend .033). Among all patients with PHPT, non-surgery group increased from 41.6% in 2005-2010 to 58.0% in 2016-2020 (*P* for trend <.001). Patients with PHPT had higher odds of osteoporosis (odds ratio [OR] 7.03), renal stones (OR 10.55), chronic kidney diseases (OR 7.42), and cardiovascular, metabolic, and neurological conditions after adjustment for comorbidity index. In summary, the incidence of PHPT increased from 2005 to 2020 with predominance of non-surgical treatment, which calls for research focus on improving non-surgical management.

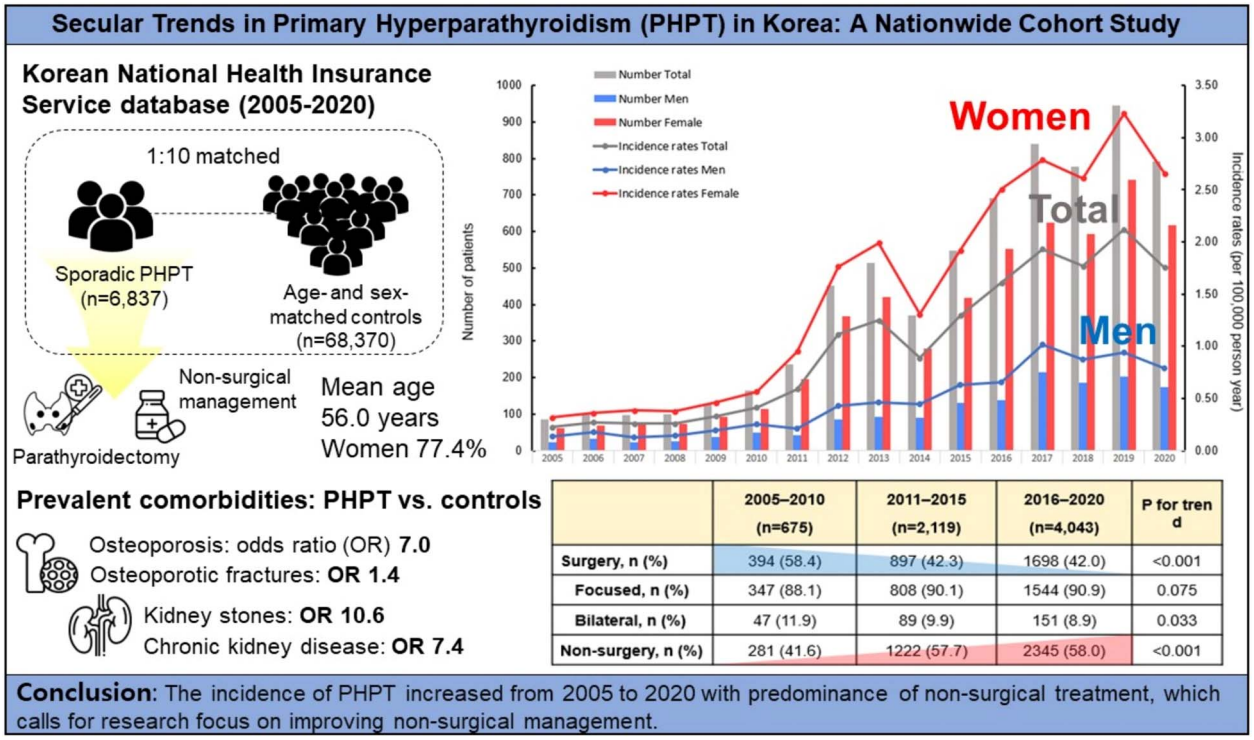
Keywords: parathyroid-related disorders, general population studies, epidemiology, hyperparathyroidism, incidence

Lay Summary

Primary hyperparathyroidism (PHPT) is a condition where the parathyroid glands secrete excess hormone, leading to fracture, kidney stones, and loss of kidney function. We aimed to investigate the long-term secular trends in the incidence and treatment patterns of PHPT using a nationwide claim database in South Korea. Compared with 2005-2010, the annual incidence of PHPT increased up to 6-folds in 2016-2020, with higher rate in women than in men. In overall patients with PHPT, less than half underwent surgical treatment, with decreased proportion of bilateral surgery across the time. The proportion of non-surgical group increased from 41.6% in 2005-2010 to 58.0% in 2016-2020. Compared with age- and sex-matched controls, individuals with PHPT had higher odds of having low bone mass, kidney stones, chronic kidney diseases, cardiovascular, metabolic, and neurological conditions at the time of diagnosis. These findings reveal the secular trend toward increased detection of PHPT with predominance of non-surgical treatment in South Korea.

Received: March 9, 2024. **Accepted:** May 10, 2024

Graphical Abstract



	2005–2010 (n=675)	2011–2015 (n=2,119)	2016–2020 (n=4,043)	P for trend
Surgery, n (%)	394 (58.4)	897 (42.3)	1698 (42.0)	<0.001
Focused, n (%)	347 (88.1)	808 (90.1)	1544 (90.9)	0.075
Bilateral, n (%)	47 (11.9)	89 (9.9)	151 (8.9)	0.033
Non-surgery, n (%)	281 (41.6)	1222 (57.7)	2345 (58.0)	<0.001

Introduction

Primary hyperparathyroidism (PHPT) has long been recognized as one of the most common endocrine disorders, with an estimated prevalence of 0.5%-0.7% in the general population.[1,2] Moreover, recent studies suggest that the incidence of PHPT has remarkably increased worldwide after routinely measuring calcium serum levels[3,4] More screening for serum calcium contributes to increased detection of various spectrums of PHPT, such as asymptomatic and normocalcemic PHPT, which may affect clinicians' decisions to treat this disease.[5] Although surgical treatment, in the form of parathyroidectomy (PTX), is considered the definitive treatment for PHPT, non-surgical treatment, in the form of conservative or medical therapy, is an alternative option for patients who are not candidates for surgery because they lack definite symptoms or those who decline surgical intervention.[6] However, insufficient studies have investigated the secular epidemiology of PHPT regarding diagnosis and treatment strategies.

PHPT is characterized by hypercalcemia, hypercalciuria, and excessive secretion of PTH caused by autonomous hyperfunction of one or more parathyroid glands.[6] This results in a wide range of clinical manifestations, including skeletal (osteoporosis, fractures) and renal (nephrolithiasis, chronic kidney disease complications) conditions.[7,8] Furthermore, recent studies have reported that patients with PHPT also complain of non-classical manifestations, which are cardiovascular or neurologic abnormalities, although disease causality has not been well established.[9] However, the results have been controversial regarding higher risks of comorbidities in patients with PHPT.[9] In this regard, there is a need for a comprehensive study to understand the risk of comorbidities in patients with PHPT compared with age- and sex-matched controls.

This study aims to provide an overview of the secular trends in incidence, clinical characteristics, and treatment patterns of PHPT in South Korea. Using the well-established Korean National Health Insurance Service (NHIS) database, the primary aim of this study is to conduct a comprehensive epidemiological analysis of PHPT in Korea, extending our focus to associated comorbidities. Although previous Korean research addressed this topic, it was restricted to patients who underwent PTX, leaving a significant gap in the literature.[4] To overcome this limitation, our study includes surgically managed patients who underwent PTX and those who received conservative management, providing an encompassing view of PHPT. We also aim to assess the odds ratios (ORs) of multiple comorbid conditions among patients with PHPT compared with a control cohort.

Materials and methods

Data source

The NHIS covers ~97% of the Korean population to facilitate reimbursements.[10] The NHIS database contains comprehensive health data on patients, including hospitalization data, diagnostic codes (the International Classification of Disease, 10th revision [ICD-10]), prescription claim records (such as medical procedures and drugs prescribed), and death records submitted to the NHIS by institutions. The NHIS database has been widely used for various epidemiological and health-related research studies. We analyzed data from 2005 to 2020, with a 3-year washout period. The Institutional Review Board of Severance Hospital (IRB No. 4-2021-0795) approved the study protocol. The requirement for informed consent was waived because all data were anonymized.

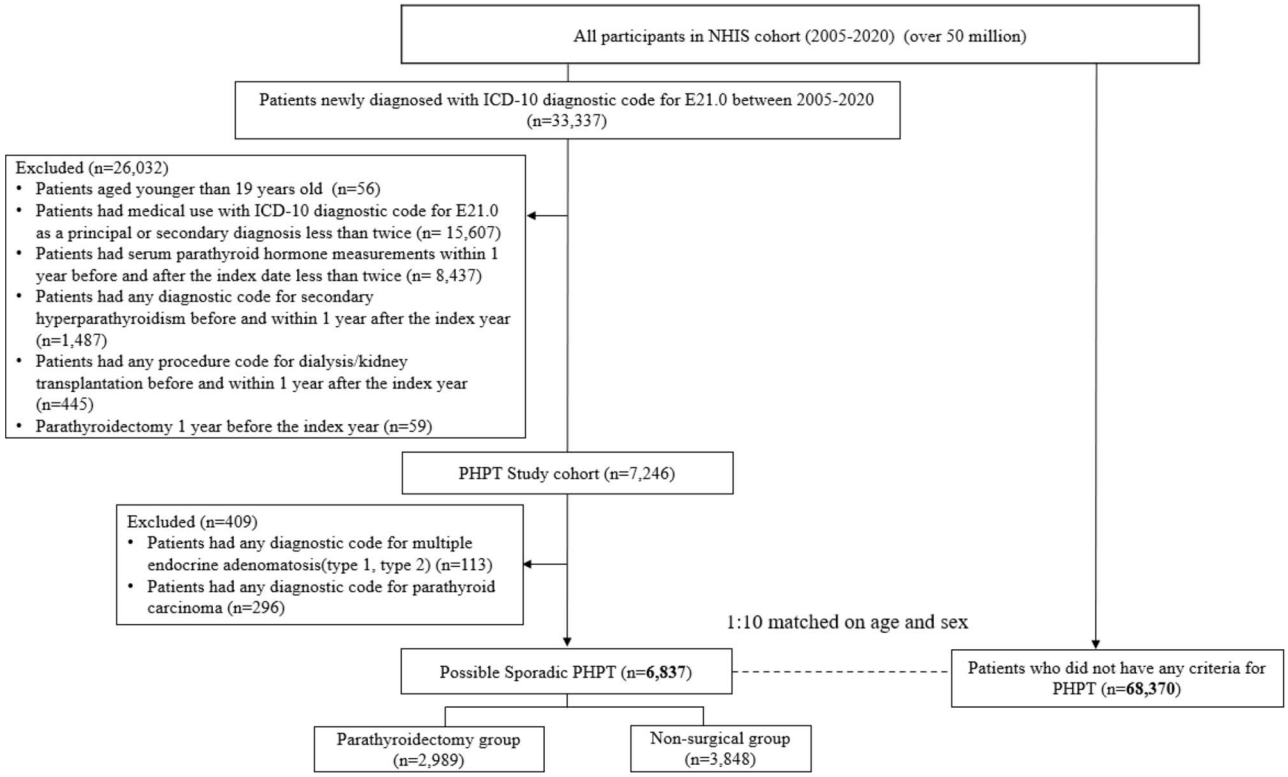


Figure 1. Study flow. NHIS, National Health Insurance Service; ICD-10, International Classification of Disease, 10th revision.

Study population

The process of selecting study participants is demonstrated in Figure 1. From the original NHIS-HEALS database, we identified patients newly diagnosed at least once with PHPT using ICD-10 diagnostic code E21.0. Patients (1) aged <19 years; (2) with fewer than 2 E21.0 ICD-10 codes as a primary or secondary diagnosis; (3) with fewer than 2 serum PTH measurements; (4) with any diagnostic code for secondary hyperparathyroidism; and (5) who had any procedure code for dialysis or kidney transplantation within 1 year before and after the index date were excluded. Additionally, patients who underwent PTX within the first year before the index year were also excluded to rule out secondary, tertiary, or genetic hyperparathyroidism. Furthermore, patients who had any diagnostic codes for multiple endocrine adenomatosis (type 1 or 2) or parathyroid carcinoma were excluded to select actual PHPT cases.

To validate the operational definition of PHPT, we analyzed data from 1466 patients diagnosed with PHPT at Severance Hospital Sinchon center in Seoul, between January 1, 2019, and December 31, 2021. To ensure diagnosis accuracy, a validation cohort of 431 patients (29.4%) had their PHPT diagnosis confirmed through electronic medical record review by 2 independent physicians. We employed operational definitions based on diagnosis and procedure codes to identify confirmed PHPT cases accurately. The criteria were: (1) at least 2 instances of ICD-10 code E21.0, excluding E21.1 and E21.2 codes; (2) 2 or more plasma PTH measurement codes; and (3) no dialysis or kidney transplantation codes within 1 year around the index date. Among 3 operational definitions evaluated, the 1 combining diagnosis and procedure codes showed the highest positive predictive value (PPV, 92%), with modest sensitivity (71%) and the highest specificity (97%). This definition was chosen for its superior accuracy in identifying PHPT cases, prioritizing high PPV to minimize false positives in our nationwide cohort study.

We established a control group to represent the general population and analyze the risk of comorbidities associated with PHPT. Patients who did not meet any criteria for PHPT during the same period were regarded as the control group. Patients with PHPT were compared with their age- and sex-matched controls at a ratio of 1:10.

Comorbidities and covariates

Comorbidities such as diabetes, hypertension, dyslipidemia, osteoporosis, Parkinson's disease, and dementia were defined by the ICD-10 diagnostic codes with medical claims for at least one principal or secondary diagnosis and prescription medication use within 3 years before or 6 months after the index date (Supplementary Table S1). Osteoporotic fractures, renal stones, chronic kidney diseases, and cardiocerebrovascular diseases were further defined using the diagnostic and procedure codes related to each diagnosis. To investigate the secular trends of PHPT treatment, PTX was also considered when patients with PHPT had the procedure codes for PTX (P4541 for focused and P4542 for bilateral PTXs) during the study period. In terms of socioeconomic status, we divided patients into 3 groups: the lowest 30%, the middle 40%, and the highest 30% based on the total amount of national health insurance premiums paid by insured individuals.

Statistical analysis

Participants' demographic characteristics are summarized as the means ± SD using Student's t-test or the Mann–Whitney U test for continuous variables. Categorical variables are presented as numbers (%) by performing the $\chi 2$ test. The

annual incidence rates for PHPT, calculated based on the general population of Korea each year, are reported as annual incidences per 100 000 population. To estimate ORs and 95% CIs for the risk of comorbidities, we performed a multivariate logistic regression analysis to adjust for the Charlson Comorbidities Index. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) with 2-sided tests, and a *P*-value of <.05 was considered statistically significant.

Results

PHPT epidemiology in Korea

The overall number of patients with PHPT in South Korea from 2005 to 2020 was 68 737. The mean age was 56.0 ± 13.1 years, and 77.4% of the patients were women (Table 1). As shown in Figure 2, the annual incidence rate in total patients with PHPT was 1.00 per 100 000 and increased from 0.23 per 100 000 persons in 2005 to 1.75 in 2020. Compared with men, the annual incidence rate for women was markedly increased with the highest incidence rate occurring in 2019 (3.23 per 100 000 persons). Table 1 demonstrates the clinical characteristics of patients with PHPT and age- and sex-matched controls. Income distribution significantly differed between the groups ($P < .001$); notably, more individuals in the PHPT group belonged to the upper 30% income percentile (46.2% vs 39.4%). The PHPT group also showed higher prevalence for comorbidities, including diabetes mellitus (16.3% vs 11.0%, $P < .001$), hypertension (44.1% vs 30.9%, $P < .001$), and dyslipidemia (40.2% vs 27.1%, $P < .001$). Osteoporosis was notably more common in the PHPT group (31.8% vs 10.1%, $P < .001$). Other significant disparities were found in rates of osteoporotic fractures, renal conditions, and cardiovascular events (all $P < .001$). Moreover, neuropsychiatric conditions such as depression and dementia were more prevalent in the PHPT group ($P < .001$). With regard to the Charlson Comorbidities Index score, the PHPT group had a higher mean score (3.4 ± 2.8 vs 1.8 ± 2.1, $P < .001$). A significant 74.7% of the PHPT group had a score of ≥2, compared with 45.5% in the control group ($P < .001$).

Treatment modality trends for patients with PHPT

Table 2 shows trends in the treatment strategy for PHPT during the 15-year period in 5-year intervals. In the study population of 6837 patients with PHPT, 2989 (43.7%) underwent surgical treatment, and 3848 (56.2%) were managed non-surgically. The rate of surgical intervention decreased over time, from 58.4% in the 2005-2010 cohort to 42.0% in the 2016-2020 cohort (*P* for trend <.001). Among surgical cases, focused surgeries comprised 90.3% of all procedures. The proportion of focused surgeries remained relatively consistent across the study periods, showing no significant change (*P* for trend = .075). Conversely, the rate of bilateral procedures declined from 11.9% in 2005-2010 to 8.9% in 2016-2020 (*P* for trend = .033). Conversely, non-surgical management increased from 41.6% in 2005-2010 to 58.0% in 2016-2020 (*P* for trend <.001).

Comorbidities of PHPT

We compared the comorbidities risk in patients with PHPT with the age- and sex-matched control population (Figure 3). Patients with PHPT had significantly increased risks of having all comorbidities, especially renal stones (OR 10.55; 95% CI, 9.60–11.59), chronic kidney disease (OR 7.42; 95% CI, 6.53–8.44), osteoporosis (OR 7.03; 95% CI, 6.54–7.57), and major osteoporotic fractures (OR 1.40; 95% CI, 1.23–1.59), which are considered as classical manifestations of PHPT. Heart failure, myocardial infarction, and atrial fibrillation were more commonly observed in patients with PHPT by more than 2-fold. The risk of neurocognitive manifestations such as cerebrovascular disease, depression, Parkinson's disease, and dementia was also higher by less than 2-fold in patients with PHPT compared with the controls. Diabetes mellitus, hypertension, and dyslipidemia as metabolic disorders were more commonly noted in patients with PHPT as well.

Discussion

The NHIS claim database identified 6837 Korean patients with PHPT. The study reported a gradual increase in the annual incidence rate of PHPT in Korea from 2005 to 2015, with a notable rise among women. Our findings regarding changes in treatment modalities for patients with PHPT provided a trend toward minimally invasive PTX and non-surgical treatment. In contrast, the secular trend of traditional bilateral PTX decreased. Considering comorbidity risks, patients with PHPT were more likely to have classic and non-classic manifestations compared with their controls.

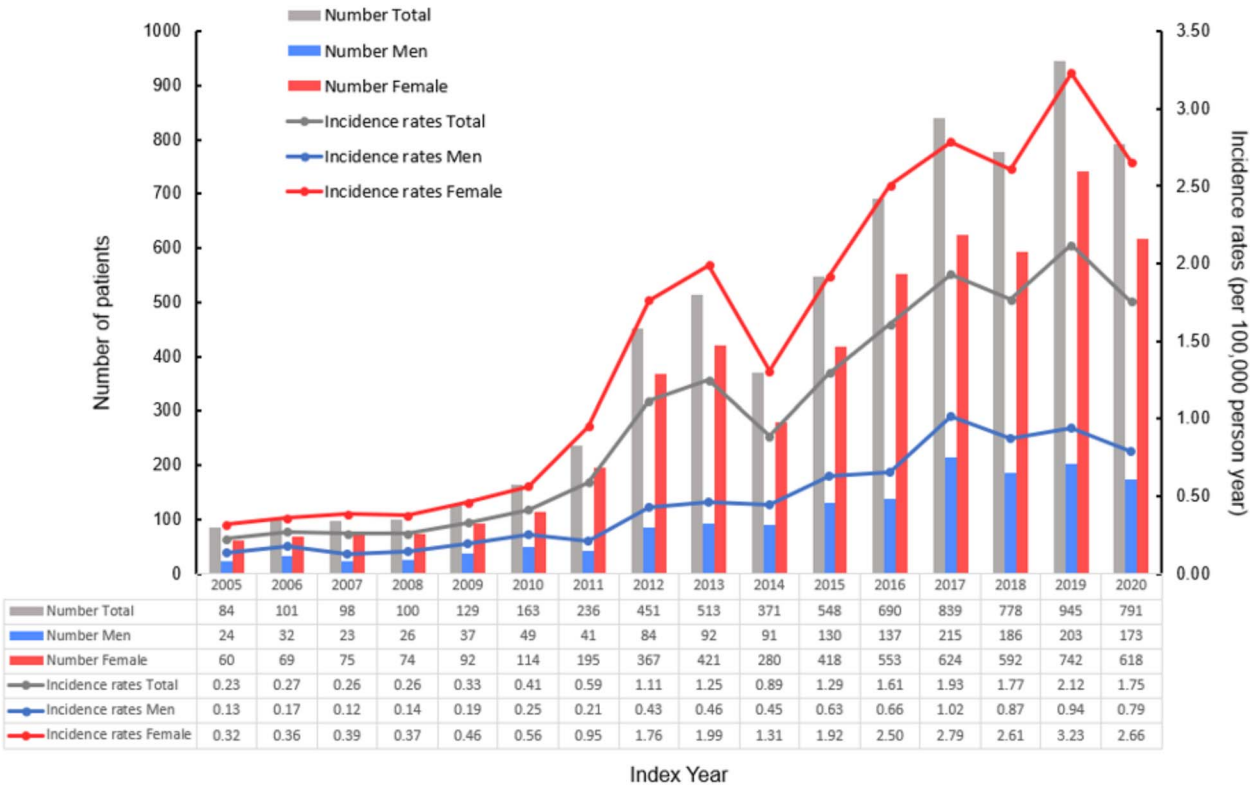
This is the first comprehensive nationwide analysis of PHPT epidemiology in Korea, highlighting an incidence rate from 2005 to 2020 of 0.01% (1.0 per 100 000 person-years), with the rate in women being ∼3 times higher than in men (0.015% or 1.5 per 100 000 person-years vs 0.005% or 0.5 per 100 000 person-years). When compared with global statistics, Korea's PHPT incidence is markedly lower. According to a representative study on racial incidence differences by Michael et al., the incidence of PHPT is highest among Blacks, followed by Whites, Asians, and Hispanics.[1,11] For context, the incidence in the United States presented an increase to 48.3-50.4 per 100 000 person-years around 1998, largely due to proactive osteoporosis screening.[1,3] This figure contrasts with our findings, emphasizing the significant geographical differences in PHPT incidence. Comparatively, other regions report varied incidence rates; Denmark noted a linear rise to 16 per 100 000 by 2010, and the Czech Republic reported 24 cases per 100 000 persons per year, both substantially higher than in Korea.[12,13] These differences suggest the potential role of genetic factors, environmental exposures, and healthcare accessibility in shaping PHPT epidemiology.[11] Our data, indicating lower incidence rates in Korea compared with those reported in Western countries and even within certain Asian and European contexts, call for a deeper investigation into the genetic, environmental, and nutritional factors influencing PHPT. The contrast in incidence rates, especially considering the global trend toward increased biochemical screening, challenges previous assumptions about healthcare access as the primary driver of racial and regional differences in PHPT rates. This study sets the stage for future research into the multifaceted determinants of PHPT across diverse populations.

Considering the epidemiology of the Korean population, Kim *et al.*[14] reported an incidence rate of 0.001% for patients with PHPT who underwent PTX from 2013 to 2016 using the Korean Health Insurance Review and Assessment Service database. This number is much smaller than that reported in

Table 1. Clinical characteristics of individuals with PHPT compared with age- and sex-matched controls.

	PHPT ($n=6837$)	Control ($n=68\,370$)	*P*-value[a]
Age, year	56.0 ± 13.1	56.0 ± 13.1	.999
Women, *n* (%)	5294 (77.4)	52 940 (77.4)	.999
Income			<.001
Lower 30%	1592 (23.3)	17 466 (25.6)	
Middle 40%	1973 (28.9)	22 653 (33.1)	
High 30%	3157 (46.2)	26 940 (39.4)	
Comorbidities			
Diabetes mellitus	1114 (16.3)	7501 (11.0)	<.001
Hypertension	3012 (44.1)	21 149 (30.9)	<.001
Dyslipidemia	2745 (40.2)	18 532 (27.1)	<.001
Osteoporosis	2171 (31.8)	6921 (10.1)	<.001
Major osteoporotic fracture	293 (4.3)	2154 (3.2)	<.001
Vertebral fracture	151 (2.2)	1089 (1.6)	<.001
Non-vertebral fracture	157 (2.3)	1129 (1.7)	<.001
Renal stones	957 (14)	1060 (1.6)	<.001
Chronic kidney disease	437 (6.4)	675 (1.0)	<.001
Myocardial infarction	91 (1.3)	364 (0.5)	<.001
Cerebrovascular disease	198 (2.9)	1141 (1.7)	<.001
Heart failure	163 (2.4)	593 (0.9)	<.001
Atrial fibrillation	159 (2.3)	802 (1.2)	<.001
Depression	1026 (15.0)	6855 (10.0)	<.001
Parkinson's disease	50 (0.7)	349 (0.5)	.017
Dementia	176 (2.6)	1300 (1.9)	<.001
Charlson Comorbidities Index			<.001
Mean (SD)	3.4 ± 2.8	1.8 ± 2.1	<.001
0	860 (12.6)	23 106 (33.8)	
1	868 (12.7)	14 134 (20.7)	
≥2	5109 (74.7)	31 130 (45.5)	

[a]Comparisons between groups were analyzed by the Student's *t*-test for continuous variables and $\chi 2$ test for categorical variables. Abbreviation: PHPT, primary hyperparathyroidism.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Number Total	84	101	98	100	129	163	236	451	513	371	548	690	839	778	945	791
Number Men	24	32	23	26	37	49	41	84	92	91	130	137	215	186	203	173
Number Female	60	69	75	74	92	114	195	367	421	280	418	553	624	592	742	618
Incidence rates Total	0.23	0.27	0.26	0.26	0.33	0.41	0.59	1.11	1.25	0.89	1.29	1.61	1.93	1.77	2.12	1.75
Incidence rates Men	0.13	0.17	0.12	0.14	0.19	0.25	0.21	0.43	0.46	0.45	0.63	0.66	1.02	0.87	0.94	0.79
Incidence rates Female	0.32	0.36	0.39	0.37	0.46	0.56	0.95	1.76	1.99	1.31	1.92	2.50	2.79	2.61	3.23	2.66

Figure 2. Annual incidence and number of patients with PHPT according to sex and the index year (2005-2020). Abbreviation: PHPT, primary hyperparathyroidism.

Table 2. Secular trends in treatment modalities for patients with PHPT.

	Overall (*n* = 6837)	2005-2010 (*n* = 675)	2011-2015 (*n* = 2119)	2016-2020 (*n* = 4043)	*P* for trend
Surgery, *n* (%)	2989 (43.7)	394 (58.4)	897 (42.3)	1698 (42.0)	<.001
Focused, *n* (%)	2699 (90.3)	347 (88.1)	808 (90.1)	1544 (90.9)	.075
Bilateral, *n* (%)	287 (9.6)	47 (11.9)	89 (9.9)	151 (8.9)	.033
Non-surgery, *n* (%)	3848 (56.2)	281 (41.6)	1222 (57.7)	2345 (58.0)	<.001

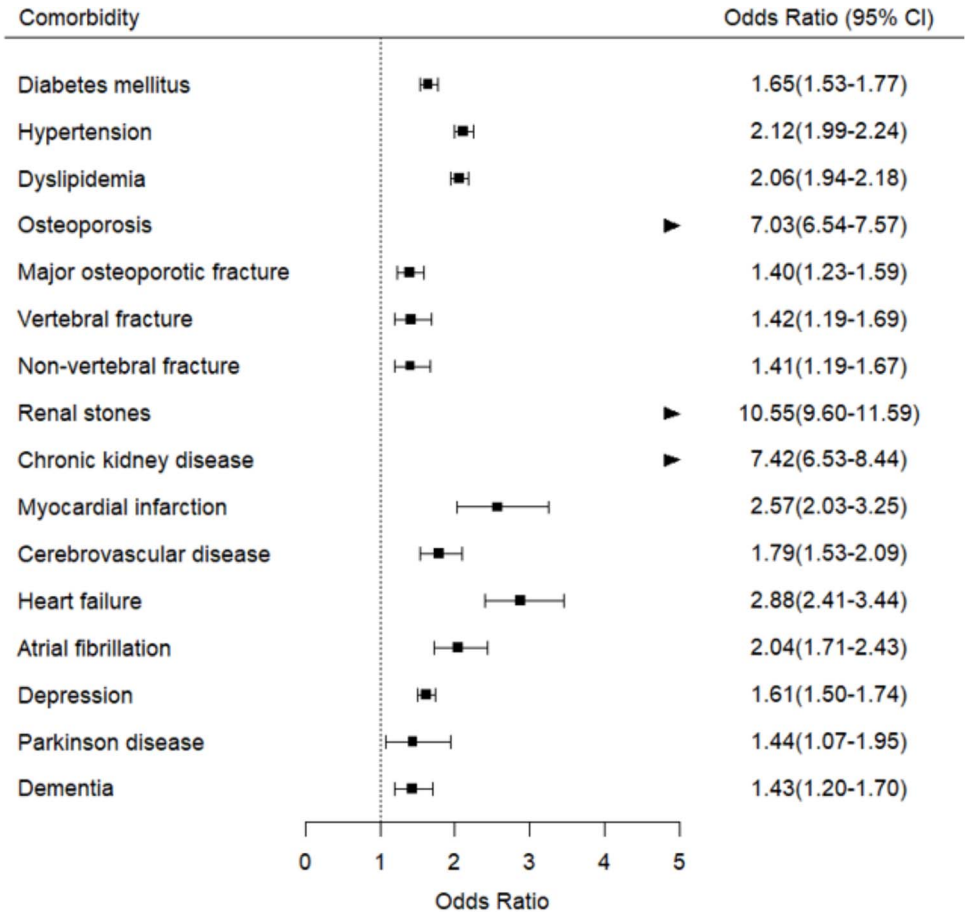


Figure 3. ORs of the comorbidities in the PHPT patient population compared with the control population. OR adjusted for Charlson's comorbidity index was presented. Abbreviation: OR, odds ratio.

our study because their studies did not include non-surgical cases. According to a recent study conducted on Koreans, the number of patients who underwent PTX under the diagnosis of PHPT was 5561, higher than the 2989 patients who underwent PTX among total PTX patients ($N = 6837$) in this study.[4] Their incidence rate of 5.5 person-years over a 17-year period was reported to be higher than that of our study. Differences in the incidence rate of sporadic PHPT within the same population, as demonstrated in the studies by Kong et al. and ours, are primarily due to variations in the operational definitions of sporadic PHPT. Additionally, the discrepancy in results may be attributed to the different population groups analyzed in each study. Kong et al.'s research focused on patients who underwent PTX, whereas our study included a broader spectrum, analyzing diagnosis codes for hyperparathyroidism to encompass surgically and medically treated patients.

Our study showed a marked upward trajectory in the incidence of PHPT in the Korean cohort, a phenomenon corroborated globally in recent studies from the United States and Europe, highlighting a universal escalation in identifying PHPT cases.[2-4,12,15] This upward trend can be explained by the widespread implementation of automated calcium analyses and the incorporation of osteoporosis services in standard health assessments, thereby amplifying the detection of non-surgical, asymptomatic, or normocalcemic PHPT incidences. In contrast, a recent investigation by Soto-Pedre et al. revealed a phase of stabilization in the incidence rates of PHPT over the previous decade in Scotland, offering an alternative perspective that warrants further exploration into the underlying etiological factors influencing these epidemiological trends.[16] This plateau may indicate a maturation and refinement in diagnostic paradigms related to PHPT, depicting forward progress in clinical diagnostic methodologies. In alignment

with these emerging trends, our data demonstrate a discernible shift in the therapeutic changes toward focused PTX and non-invasive techniques despite the escalating incidence outlined in our study. This tendency signifies a paradigmatic shift in the clinical management of PHPT and suggests an advancing understanding of its intricate pathophysiological dynamics.[17] A prospective period where diagnostic precision aligns with therapeutic expertise is indicated, thereby facilitating improved patient outcomes through advanced and targeted treatment protocols.[5]

Our nationwide cohort study showed the evolving trajectory of PHPT treatment in Korea, suggesting its transition from a predominantly symptomatic disorder to one increasingly characterized by asymptomatic phenotypes in recent decades. In concordance with prior studies, we discerned elevated susceptibilities to osteoporosis, renal stones, and chronic kidney disease among patients with PHPT, underscoring the prominent skeletal and renal complications intrinsically associated with this pathology.[9] The data reveal a marked increase in the OR for osteoporosis and fractures, highlighting the crucial role of skeletal alterations. These alterations are evidenced through accelerated bone remodeling, characterized by the elevation of bone turnover markers and the expansion of osteoid and mineralizing surfaces.[18,19] Moreover, our analysis emphasizes the necessity to devise a thorough risk assessment strategy for nephrolithiasis, incorporating urinary, pre-renal, and genetic variables to sufficiently address the elevated risks of renal complications, which are linked to the pivotal roles of PTH and calcium in calcium reabsorption.[20,21] Regarding non-classical manifestations, we identified a higher risk for cardiovascular, neurobehavioral, and neurocognitive disorders. A prevailing consensus regarding the heightened prevalence of aortic vascular stiffness in patients with PHPT, serving as a precursor to increased cardiovascular risk, is noteworthy.[22] Additionally, our study reported the potentially significant impact of PTH on neural functionalities, outlining its substantial influence on cognitive impairments.[23,24]

Our analysis of Supplementary Table S2 not only identifies significant demographic shifts and evolving comorbidity profiles in patients with PHPT across the time periods 2005-2010, 2011-2015, and 2016-2020 but also suggests a consequential trend toward increased conservative, non-surgical management of PHPT. This trend is particularly noteworthy given the significant aging of the patient population and the higher proportion of female patients over time. Notably, the observed decrease in classical manifestations such as urinary tract stones and osteoporosis, alongside the increase in systemic comorbidities like type 2 diabetes, hypertension, and dyslipidemia, points to a broader health context within which PHPT is being managed.[9] The rise in hospitalizations for heart failure and dementia further complicates the clinical picture, necessitating a more cautious approach to treatment. These dynamics, highlighted by significant *P*-values indicating changes over time, suggest that the shift toward non-surgical management may be in response to the evolving clinical profiles of PHPT patients.[25] This shift likely reflects a growing preference for individualized treatment strategies that prioritize the overall health and quality of life of patients, particularly those with complex comorbidities or who are at increased risk from surgical interventions.[25,26] Our findings underscore the need for continued adaptation in clinical practice, embracing a holistic approach to the management of PHPT in light of these changing demographic and clinical trends.

This study has several strengths, underscoring its pivotal role in medical research. First, utilizing a comprehensive national sample size confers robust statistical power and mitigates selection bias. This allows for a detailed exploration of the epidemiology and clinical features of PHPT across surgically and medically managed patients, a topic not previously explored in Korea. Additionally, given the scarcity of studies specifically addressing the epidemiology of PHPT in Asia, this research fills a significant gap in the existing literature, offering valuable insights that are particularly relevant to Koreans. Furthermore, this constitutes the first study elucidating the secular trends in Korean PHPT epidemiology, encompassing variations in incidence and treatment patterns. The study delineates the spectrum of clinical risks pertaining to classic and non-classic PHPT complications. This underscores the persistent imperative for apt detection and management of this condition, warranting further investigation. Furthermore, this study aligns with and supports the recently published guidelines from the Fifth International Workshop.[9,27,28] Providing empirical data specific to the Korean population addresses an unmet need in these guidelines, offering a culturally and regionally relevant perspective that enhances the applicability and utility of these international standards in the context of PHPT management in Korea. Nonetheless, this study also had limitations. First, identifying patients with PHPT relied upon the Korean NHIS claim datasets rather than on biochemical (calcium, PTH, creatinine, and vitamin D levels) or histopathological data and medical chart reviews, thereby raising the possibility of inaccurate diagnoses. Second, given the retrospective nature of this study, certain influential factors, such as the onset of symptoms, family history, and social history, including smoking and drinking, were not available from this database. Moreover, while recognizing the potential for Berkson bias—where diagnostic processes for PHPT through biochemical tests might disproportionately identify those with comorbidities—this emphasizes that the prevalence of comorbid conditions in PHPT patients is significantly higher. This still suggests a strong association between PHPT and conditions like osteoporosis, kidney stones, and reduced kidney function beyond diagnostic biases. The observed higher prevalence of these comorbidities highlights the clinical significance of our findings, stressing the essential need for healthcare professionals to be attentive to such conditions in PHPT patients. This underscores the value of holistic care in managing PHPT and points to the necessity for further research on PHPT's complex relationship with its comorbid conditions. Additionally, this study encountered limitations in accurately assessing the use of specific medications such as denosumab, teriparatide, romosozumab, and cinacalcet due to NHIS database constraints, which limit visibility to drugs with fewer manufacturers. This notably affects our analysis of treatments for osteoporosis and PHPT, as well as the evaluation of cinacalcet, which is only reimbursed for dialysis patients under current policies. These restrictions highlight important gaps in our findings regarding medication use, emphasizing the need for future research to explore these aspects more thoroughly.

In summary, by utilizing the NHIS claim database, our study identified an increasing incidence of PHPT in Korea, a trend consistent with observations in other countries. A shift in

treatment paradigms was observed, showing a growing preference for minimally invasive PTX and non-surgical modalities. This shift may be related to a potential rise in the incidence of milder forms of PHPT. Patients with PHPT exhibited elevated ORs for various comorbidities such as osteoporosis, renal stones, chronic kidney diseases, and cardiovascular, metabolic, and neurological conditions, indicating a higher predisposition to classic and non-classic manifestations compared with matched controls. Given the observed secular trends, further research is imperative to enhance the outcomes for patients with PHPT.

Author contributions

Kyoung Jin Kim (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Seungjin Baek (Data curation, Investigation, Methodology, Visualization, Writing—original draft), Min Heui Yu (Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization), Sungjae Shin (Data curation, Formal analysis, Investigation, Supervision, Validation), Sung Joon Cho (Data curation, Formal analysis, Investigation, Methodology, Validation), Yumie Rhee (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation), and Namki Hong (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing). Kyoung Jin Kim and Seungjin Baek contributed equally to this work.

Supplementary material

Supplementary material is available at *JBMR Plus* online.

Funding

This study was funded by the Korean Association of Endocrine Surgeons.

Conflicts of interest

None declared.

Data availability

Additional data are available after approval and oversight by the Korean National Health Insurance Service.

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2021-0795). Data from the NHIS-HEALS database did not contain any personally identifiable data. Thus, the NHIS approved the cohort study without needing informed consent from participants.

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