Residual Risks of Comorbidities after Parathyroidectomy in a Nationwide Cohort of Patients with Primary Hyperparathyroidism

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Research Article

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Abstract

Purpose: Primary hyperparathyroidism (PHPT) is a common endocrine disorder with increasing incidence, while epidemiologic data in Asian population has been lacking. Therefore, we aimed to identify the incidence, prognosis, and prognostic factors of PHPT patients who underwent parathyroidectomy in Korea.

Methods: In this retrospective nationwide cohort, patients with PHPT were defined as those with diagnostic codes of PHPT and procedural codes for parathyroidectomy, excluding chronic renal failure or secondary hyperparathyroidism based on National Health Insurance Services database in Korea in 2002-2018. Main primary outcomes were all-cause mortality, cardiovascular, and cerebrovascular events.

Results: A total of 5,561 patients were diagnosed with PHPT and had parathyroidectomy. The mean age was 54.5 years, and 71.8% were women. The age-standardized incidence was 10.1/ 100,000 person-year in 2018, rising from 1.7/100,000 person-year in 2002. During a mean of 5.9 years, history of cardiovascular disease, mood disorder, and genitourinary stone had increased risks of mortality with hazard ratios (HRs) of 1.59 (95% confidence interval [CI] 1.10-2.29), 1.43 (CI 1.14-1.80), and 1.40 (CI 1.09-1.80), respectively. History of hypertension, cerebrovascular disease, diabetes mellitus, and mood disorder were risk factors for cardiovascular events with HRs of 1.42 (CI 1.22-1.66), 1.29 (CI 1.05-1.58), 1.22 (CI 1.07-1.40), and 1.14 (CI 1.00-1.29), respectively. Mood disorder was a significant risk factor for cerebrovascular events (HR 1.30, CI 1.11-1.52).

Conclusion: The incidence of PHPT patients who underwent parathyroidectomy has been rising in Korea as reported in other countries. Patients with complications, especially mood disorder, had increased cardiovascular and cerebrovascular events and mortality risks.

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder following diabetes mellitus and thyroid disorders and is the most common cause of hypercalcemia diagnosed in the outpatient setting [1]. Recent data suggest that the incidence of PHPT is increasing worldwide and that the phenotype is not as severe as it was in the past [1]. The increasing incidence could be mainly due to measurements of serum calcium levels during routine check-ups [2]. This practice changed both the epidemiology and manifestations of PHPT, as it was incidentally detected before the symptoms manifested. In the United States, the incidence of PHPT was 17.4/100,000 person-years in 1974, which rose to 50.4/100,000 person-years in 2010 after the introduction of routine measurements of calcium levels [2, 3]. In addition, a 3-fold increase in incidence from 1998 to 2010 was observed in the Danish population [4]. However, epidemiological data on PHPT in the Asian populations have not yet been reported.

In addition to epidemiology, the prognostic factors for mortality and cardiovascular outcomes are crucial for the management of PHPT. Previous studies have reported an increased risk of cardiovascular

diseases, cerebrovascular diseases, and mortality in patients with PHPT [5, 6]. The risks are reported to decrease after parathyroidectomy [7] but remain higher than those in the general population [5, 8]. Therefore, it would be helpful to identify the contributing factors for major outcomes and actively manage patients at high risk for cardiovascular and cerebrovascular diseases, even after they undergo parathyroidectomy. However, only a few studies have reported the prognostic factors for outcomes in patients with PHPT who underwent parathyroidectomy [5].

To accurately measure mortality and complications, data without follow-up loss are required. Therefore, a nationwide approach to identifying the incidence and prognostic factors is essential for understanding the disease. However, previous studies have been insufficient to understand the current status and prognostic factors of the disease, especially in the Asian populations. Therefore, we aimed to identify the incidence, prognosis, and prognostic factors for PHPT in this nationwide cohort study.

Materials And Methods

Data sources

This was a retrospective nationwide study using data from the National Health Insurance Services (NHIS) database in Korea between 2002 and 2018. The insurance system established by the Korean government covers approximately 97.2% of the Korean residents in all age groups. The database contains data on healthcare services reimbursed by the insurance system, including demographics, diagnoses, prescriptions, diagnostic or surgical procedures, and medical costs. Diagnostic codes were classified using the 10th version of the International Classification of Diseases (ICD-10). The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. 2019-022-1114). The requirement for informed consent was waived because of the anonymized database.

Operational Definition And Validation

PHPT was defined as patients fulfilling all of the following criteria: (i) at least two or more ICD-10 codes of PHPT (E210, E212, E213, or D351); (ii) a procedural code for parathyroidectomy (P4541, P4542, or P4543); (iii) a history of admission. To improve the diagnostic accuracy of PHPT, we included PHPT patients who had underwent parathyroidectomy. The number of patients fulfilling these criteria was 5,680. Patients with a diagnostic code for chronic kidney disease, kidney transplantation, or dialysis were excluded (n = 119). Consequently, 5,561 patients were included in the final analyses (Fig. 1).

To validate the operational definition of PHPT, we evaluated its definition using our institution’s database. From January 2010 to December 2019, 286 patients who fulfilled the definition were identified at Seoul National University Hospital. After reviewing the patients' medical records, 221 were confirmed to have true PHPT (77.2%). To estimate the false-negative rate, we searched for true PHPT patients from our institution’s pathology report database which reported that during the same period, 227 patients were identified as having PHPT. The remaining six patients were not included in the operational definition

because they underwent thyroidectomy instead of parathyroidectomy due to coexisting thyroid cancer. Therefore, the false-positive and false-negative rates for the PHPT definition were estimated to be 22.8% and 2.6%, respectively.

Comorbidities Of Phpt

Cardiovascular events were considered present if one of the following criteria was satisfied: (i) I21 or I22 codes were present for at least two primary or secondary diagnoses during admission or (ii) M6551-6554 or M6561-6567 codes were present. Ischemic stroke was defined as I63, I64, I693, I694, G45, I60-62, or I690-692 codes present for at least two primary or secondary diagnoses. The following comorbid conditions were considered to be present at baseline if the following diagnostic (principal or additional) or procedural codes were present ≥ 2 times within a year of the earliest date of PHPT diagnosis. The comorbidities were diabetes mellitus (E11, E12, E13, E14), hypertension (I10-I13, I15), vertebral fracture (M48, S22, S32), hip fracture (S72, N0601, N0611, N0305, N0981, N0641, N0652, N0654, N0711, N0715), non-vertebral fracture (S42, S52, S72, N0601, N0611, N0305, N0981, N0641, N0652, N0654, N0711, N0715), genitourinary stones (N20), mood disorders (F32, F33, F34), and psychotic disorders other than mood disorders (F20-25, F28-29).

Statistical analysis

Normally distributed data are presented as mean ± standard deviation; non-normally distributed data are reported as median (interquartile range [IQR]); categorical data are reported as number (%). The characteristics of patients in both groups were compared using Student's *t*-test or the Mann–Whitney *U* test for continuous variables, and chi-square test for categorical variables. All incidence rates were reported as the average annual incidence per 100,000 people. The age-standardized incidence rates were calculated each year based on the general population of Korea. Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality, cardiovascular events, and cerebrovascular events. Survival time was calculated as the time from the earliest date of diagnosis until the primary outcome, the date of death if the primary outcome was not mortality, or December 31, 2018, whichever came first. Patients with cardiovascular and cerebrovascular events at baseline were excluded from the analysis. Multivariate HRs were adjusted for significant variables in the univariate analysis. Analyses were performed using Stata version 13.0 (StataCorp, College Station, TX) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA) was used for graph presentation.

Results

Incidence of PHPT

Between 2002 and 2017, 5,561 patients with PHPT underwent parathyroidectomy. Figure 2A demonstrates the increasing incidence of PHPT in patients who underwent parathyroidectomy over time. The crude and age-standardized incidences were 13.2 and 10.1/100,000 person-years in 2018, rising from 1.8 and 1.7/100,000 person-years in 2002 ($p < 0.001$) (Fig. 2A).

Clinical Characteristics Of Patients With Phpt

The clinical characteristics are presented in Table 1. The mean age was 54.5 years, and 71.8% of the patients were women (Fig. 2B). Women were older than men when diagnosed with PHPT. Osteoporotic fractures, including vertebral (4.8%) and non-vertebral (2.3%) fractures, were present in 7.1% of the patients, which were similar between the sexes. At baseline, 52.0%, 54.2%, 29.6%, and 33.2% of the patients were diagnosed with diabetes mellitus, hypertension, mood disorders, and genitourinary stones, respectively. In addition, 27.0% and 16.3% of the patients experienced cardiovascular diseases and cerebrovascular diseases, respectively.

Table 1
Clinical characteristics of patients with primary hyperparathyroidism

	Total (n = 5,561)	Women (n = 3,994)	Men (n = 1,567)	*p*
Age, years	54.5 ± 13.6	55.5 ± 12.9	52.0 ± 14.9	< 0.001
Age ≥ 50 yrs	3,727 (67.0%)	2,828 (71.8%)	899 (57.3%)	< 0.001
Urban residents	3,687 (66.3%)	2,668 (66.8%)	1019 (65.0%)	0.353
Osteoporotic fracture	395 (7.1%)	295 (7.4%)	100 (6.4%)	0.189
Vertebral fracture	268 (4.8%)	201 (5.0%)	67 (4.3%)	0.235
Nonvertebral fracture	127 (2.3%)	94 (2.4%)	33 (2.1%)	0.578
Hip fracture	59 (1.1%)	42 (1.1%)	17 (1.1%)	0.913
Diabetes mellitus	2891 (52.0%)	2011 (50.4%)	880 (56.2%)	< 0.001
Hypertension	3014 (54.2%)	2153 (53.9%)	861 (54.9%)	0.318
Mood disorder	1647 (29.6%)	1196 (29.9%)	451 (28.8%)	0.182
Genitourinary stone	1847 (33.2%)	1350 (33.8%)	497 (31.7%)	0.137
Cardiovascular disease	1503 (27.0%)	1064 (26.6%)	439 (28.0%)	0.298
Acute myocardial infarction	278 (5.0%)	193 (4.8%)	85 (5.4%)	0.362
Cerebrovascular disease	904 (16.3%)	627 (15.7%)	277 (17.7%)	0.072
Ischemic stroke	548 (9.9%)	387 (9.7%)	161 (10.3%)	0.510

Continuous variables are expressed as mean ± standard deviation and categorical variables as numbers (percentages). Comparisons between groups were analyzed by Student *t*-test for continuous variables and χ^2 test for categorical variables.

Over a median of 5.9 years [IQR 4.0–7.6 years] of follow-up, there were 333 (6.0%) cases of mortality, and 461 (8.2%) patients experienced cardiovascular diseases. Among them, 140 (2.5%) experienced acute myocardial infarction. In addition, 347 (6.2%) patients were reported to have cerebrovascular diseases and among them, 225 (4.0%) experienced ischemic stroke.

Factors Associated With Mortality

The prognostic factors for mortality are described in Table 2. In univariate analysis, patients with a history of cardiovascular disease had 1.91 times higher mortality risk than those who did not (95% CI 1.34–2.72, $p < 0.001$). In addition, patients with a mood disorders or genitourinary stones had 1.50- and 1.59-times higher mortality risk, respectively, than those who did not. A history of non-vertebral fracture

was an additional significant risk factor, while a history of vertebral fracture, diabetes mellitus, cerebrovascular diseases, and hypertension, and demographic factors such as sex and age were not relevant.

Table 2
Prognostic factors of mortality in patients with primary hyperparathyroidism

	Univariate		**Multivariate**	
	HR (95% CI)	p	**HR (95% CI)**	p
Cardiovascular disease	1.91 (1.34, 2.72)	< 0.001	1.59 (1.10, 2.29)	0.010
Mood disorder	1.50 (1.20, 1.87)	< 0.001	1.43 (1.14, 1.80)	0.002
Genitourinary stone	1.59 (1.25, 2.02)	< 0.001	1.40 (1.09, 1.80)	0.008
Nonvertebral fracture	1.75 (1.29, 2.36)	< 0.001	1.36 (0.98, 1.88)	0.060
Psychotic disorders other than mood disorder	1.40 (0.86, 2.29)	0.177	-	-
Hip fracture	1.37 (0.77, 2.45)	0.284	-	-
Vertebral fracture	1.28 (0.89, 1.85)	0.187	-	-
Diabetes Mellitus	1.27 (0.99, 1.61)	0.055	-	-
Male (Female as a reference)	1.17 (0.94, 1.46)	0.148	-	-
Cerebrovascular disease	1.11 (0.86, 1.43)	0.431	-	-
Hypertension	1.11 (0.85, 1.44)	0.447	-	-
Age, per year	1.01 (1.00, 1.02)	0.124	-	-

Cox regression analyses were done. Multivariate analyses were adjusted for significant variables from univariate analysis. HR, hazard ratio; CI, confidence interval.

In multivariate analysis adjusted for significant factors from univariate analyses, a history of cardiovascular disease, mood disorders, and genitourinary stones remained to have increased risks of mortality with HRs of 1.59 (95% CI 1.10–2.29), 1.43 (95% CI 1.14–1.80; Fig. 3A), and 1.40 (95% CI 1.09–1.80; Fig. 3B), respectively.

Factors Associated With Cardiovascular And Cerebrovascular Events

The prognostic factors for cardiovascular events are described in Table 3. In univariate analysis, patients with a history of hypertension, cerebrovascular diseases, diabetes mellitus, mood disorders, or genitourinary stones had a 1.66, 1.39, 1.43, 1.28, and 1.14 times higher risk of cardiovascular events, respectively, than those who did not. In multivariate analysis, a history of hypertension, cerebrovascular diseases, diabetes mellitus, and mood disorders remained to have increased risks of cardiovascular events with HRs of 1.42 (95% CI 1.22–1.66), 1.29 (95% CI 1.05–1.58), 1.22 (1.07–1.40), and 1.14 (95% CI 1.00–1.29; Fig. 4A), respectively, during follow-up.

Table 3
Prognostic factors of cardiovascular events in patients with primary hyperparathyroidism

	Univariate		**Multivariate**	
	HR (95% CI)	p	**HR (95% CI)**	p
Hypertension	1.66 (1.44, 1.91)	< 0.001	1.42 (1.22, 1.66)	< 0.001
Cerebrovacsular disease	1.39 (1.20, 1.62)	< 0.001	1.29 (1.05, 1.58)	0.020
Diabetes Mellitus	1.43 (1.27, 1.62)	< 0.001	1.22 (1.07, 1.40)	0.003
Mood disorder	1.28 (1.14, 1.45)	< 0.001	1.14 (1.00, 1.29)	0.040
Genitourinary stone	1.14 (1.01, 1.29)	0.034	1.12 (0.90, 1.27)	0.070
Psychotic disorders other than mood disorder	1.29 (0.92, 1.82)	0.141	-	-
Nonvertebral fracture	1.11 (0.93, 1.34)	0.244	-	-
Hip fracture	1.10 (0.71, 1.72)	0.662	-	-
Vertebral fracture	1.09 (0.96, 1.38)	0.468	-	-
Age, per year	1.01 (0.99, 1.01)	0.101		
Male (Female as a reference)	1.01 (0.96, 1.41)	0.448		

Cox regression analyses were done. Multivariate analyses were adjusted for significant variables from univariate analysis. HR, hazard ratio; CI, confidence interval.

In univariate analysis, patients with a history of mood disorders, non-vertebral fractures, cardiovascular diseases, diabetes mellitus, or hypertension had a higher risk of cerebrovascular events than those who did not (Table 4). In multivariate analysis, a history of mood disorders only remained significant in increasing the risk of cerebrovascular diseases (HR 1.30, 95% CI 1.11–1.52; Fig. 4B).

Table 4
Prognostic factors of cerebrovascular events in patients with primary hyperparathyroidism

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Mood disorder	1.63 (1.40, 1.89)	< 0.001	1.30 (1.11, 1.52)	0.001
Nonvertebral fracture	1.27 (1.05, 1.54)	0.016	1.19 (0.98, 1.45)	0.090
Cardiovascular disease	1.42 (1.23, 1.65)	< 0.001	1.12 (0.95, 1.31)	0.190
Diabetes Mellitus	1.37 (1.17, 1.61)	< 0.001	1.06 (0.89, 1.27)	0.490
Hypertension	1.43 (1.21, 1.71)	< 0.001	1.04 (0.86, 1.27)	0.680
Age, per year	1.01 (1.00, 1.01)	0.016	-	-
Vertebral fracture	1.26 (0.97, 1.63)	0.079	-	-
Genitourinary stone	1.05 (0.90, 1.22)	0.546	-	-
Hip fracture	0.97 (0.61, 1.55)	0.894	-	-
Psychotic disorders other than mood disorder	0.91 (0.56, 1.47)	0.700	-	-
Male (Female as a reference)	0.81 (0.69, 1.05)	0.120	-	-

Cox regression analyses were done. Multivariate analyses were adjusted for significant variables from univariate analysis. HR, hazard ratio; CI, confidence interval.

Discussion

As PHPT is a common endocrine disorder, a nationwide approach is needed to identify the trend of the incidence and prognostic factors of the disease. In this nationwide retrospective cohort study in Korea, the incidence of PHPT patients who underwent parathyroidectomy increased over time, from 1.7 in 2002 to 10.1/100,000 person-years in 2018. Most patients were diagnosed in their mid-50s, and over two-thirds of the patients were women. During a median of 5.9 years of follow-up, 6.0%, 8.2%, and 6.2% of the patients experienced death, cardiovascular diseases, and cerebrovascular diseases, respectively. Patients with a history of cardiovascular diseases, mood disorders, or genitourinary stones had a higher mortality risk. Patients with a history of hypertension, cerebrovascular diseases, diabetes mellitus, or mood disorders showed an increased risk of cardiovascular diseases. In particular, patients with a history of mood disorders have an increased risk of cerebrovascular diseases.

In the present study, we demonstrated that the incidence of PHPT increased over time in Korea, as in other countries. To the best of our knowledge, this is the first nationwide study of PHPT in Asia. Several

nationwide studies of PHPT in the Caucasian population already exist [2, 3]. The representative study of the United States was from the Rochester Epidemiology Project, which showed a rapid increase in disease prevalence after introducing calcium level measurements in general check-ups and in patients with genitourinary stones [2, 3]. A similar increasing trend has been observed in the European countries [4, 9]. A 3-fold increase in incidence was observed in Denmark from 1998 to 2010 (16/100,000 person-years in 2010) [4]. The authors suggested that increasing calcium measurements largely explained the upward trend of the disease. In the same context, the similar rise in PHPT incidence in Korea can be partly explained by the increase in calcium level measurements during check-ups [10]. In addition, the incidence of PHPT in Korea (10.1/100,000 person-years in the present study) was lower than that previously reported in the Caucasian population. Consistent with our results, a previous multi-ethnic study also reported that the incidence of PHPT was lower in the Asian populations [11]. However, because the study only included participants who underwent parathyroidectomy, the actual number of patients may be higher than that reported in the present study. Additional nationwide studies in the Asian populations are required.

In this study, the patients with a history of genitourinary stones had an increased risk of mortality. Genitourinary stones are a common complication of PHPT that 15–60% of patients with PHPT experience at baseline [12, 13]. In the general population, stones are often associated with risk factors of atherosclerosis, such as obesity, diabetes, hypertension, and dyslipidemia [14–16], leading to an increased risk of subclinical atherosclerosis [17]. In line with these results, a large population-based cohort study showed that patients with genitourinary stones had a higher risk of subsequent acute myocardial infarction and stroke than those without stones [18]. In addition, other studies have shown that patients with a history of stones have a significantly elevated risk of coronary heart diseases [19, 20]. However, data on the risk of genitourinary stones on mortality in patients with PHPT, not in the general population, are lacking. It is clinically essential to address the risk of genitourinary stones in patients with PHPT because they already have an increased risk of mortality owing to hypercalcemia and other risk factors [7, 21]. According to the present study, as there is a possibility that genitourinary stones may exacerbate the risk, patients with PHPT and stones could be considered a subgroup that requires prompt treatment. Although the risk of cardiovascular events was elevated, but marginally significant in multivariate analysis in patients with a history of genitourinary stones, further larger nationwide studies with sufficient events may clarify this association.

In contrast, the present study showed that patients with PHPT and mood disorders had a significantly higher risk of cardiovascular diseases, cerebrovascular diseases, and mortality. It has been reported that mood disorders, especially depression, are common in patients with PHPT as one of the nonclassical symptoms of the disease [22]. Although there is still a lack of data on whether mood disorders are related to atherosclerotic diseases in patients with PHPT, it has been consistently reported that mood disorders increase the risk of cardiovascular diseases and cerebrovascular diseases in the general population [23–27]. In a recent Mendelian randomization study, a genetic predisposition to depressive disorder was associated with an approximately 30% higher risk of atherosclerotic diseases [23]. Activation of the hypothalamic-pituitary-adrenal axis in patients with depression has been suggested to induce insulin

resistance and inflammation [28, 29]. In addition, low resilience to psychological stress in patients with depression may play a role in developing cardiovascular or cerebrovascular events [30, 31]. In addition to mood disorders, PHPT itself has been reported to increase insulin resistance and inflammatory signals [32–34]. Therefore, as demonstrated in the present study, mood disorders in patients with PHPT may amplify the tendency to increase the risk of atherosclerotic diseases, which emphasizes the importance of assessing the psychological aspects of patients with PHPT.

The presence of diabetes mellitus and hypertension was an additional risk factor for cardiovascular diseases in patients with PHPT in the present study. Diabetes mellitus and hypertension are common comorbidities, particularly in patients with PHPT [35, 36]. Cardiovascular diseases are a major cause of mortality in patients with diabetes mellitus and hypertension [37, 38]. The main mechanisms have been suggested to be endothelial dysfunction, vascular inflammation, and arterial remodeling, leading to atherosclerosis [39–41]. These mechanisms of diabetes mellitus and hypertension overlap substantially with the effects of PHPT on cardiovascular diseases. It has been reported that parathyroid hormone may cause endothelial dysfunction by inducing reactive oxygen species and inflammatory signals [5, 42]. Therefore, consistent with previous studies, risk of cardiovascular diseases can be exacerbated in patients with PHPT, who also have diabetes mellitus and hypertension. Since patients with PHPT are already at an increased risk of cardiovascular diseases, closer attention is needed to manage these comorbidities. Further population-based studies in Asians with a longitudinal follow-up are needed to validate these findings.

This study has several strengths. First, this is the first nationwide study in Asia to report the incidence and disease course of PHPT. Second, since the study used a national claims dataset, the prevalence of comorbidities was readily identified. In addition, due to the nature of the dataset, there were no cases of follow-up loss. Moreover, this study is the first to report the clinical risk factors of cardiovascular diseases and cerebrovascular diseases, in addition to mortality, in an Asian population. Consequently, we could provide novel insights into the risk of mood disorders and genitourinary stones for cardiovascular events and cerebrovascular events in patients with PHPT. In addition, as this study was based on patients who underwent parathyroidectomy, the study could represent the residual risk even after surgery. Further studies on the effect of mood disorders in patients with PHPT on their outcomes would help in understanding the disease.

This study had some limitations. As this study had a retrospective design, factors that could affect the results, such as the onset of symptoms, family history, and social history of smoking and drinking, could not be obtained from national insurance service records. Additionally, biochemical and histopathological data could not be included in the analysis because of the data source. Therefore, we could not determine the biochemical characteristics of PHPT, especially calcium and parathyroid hormone levels. In addition, patients with comorbidities, such as diabetes mellitus and hypertension, could be overestimated because the operational definitions were based on diagnostic codes. Moreover, without nonsurgical patients, the cohort is biased to include those with symptoms and more severe PHPT. Outcomes in PHPT patients who underwent surgery could be worse than those in overall PHPT patients. Also, patients with secondary

hyperparathyroidism could be included that vitamin D deficiency, GI malabsorption, or thiazide use could be included. Further, we could not assess improvement in the complication of PHPT after parathyroidectomy in this study. Finally, the study results were associations, not causation that the increased or reduced risk of outcomes could be epiphenomena with same common risk factors.

In conclusion, the incidence of PHPT has been increasing over time in Korea, similar to the trends in other countries. Moreover, some novel prognostic factors have been identified, such as mood disorders as prognostic factors for mortality, cardiovascular diseases, and cerebrovascular diseases; genitourinary stones as a prognostic factor for mortality. These results emphasize the importance of close follow-up in patients with renal and psychotic complications, even after surgical treatment. Further nationwide representative studies are required to confirm these findings.

Statements And Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. 2019-022-1114). The requirement for informed consent was waived because of the anonymized database.

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Figures

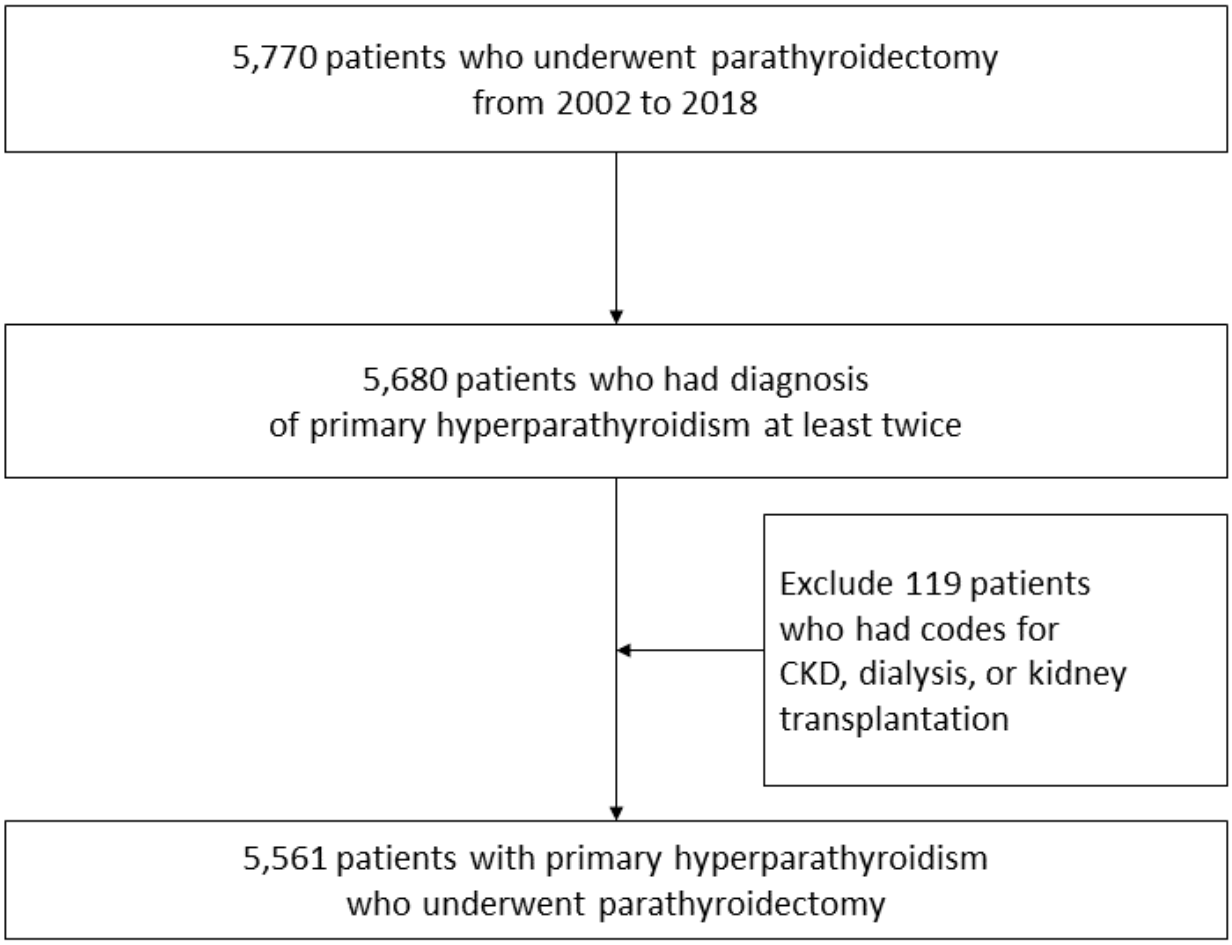

Figure 1

Selection of study participants

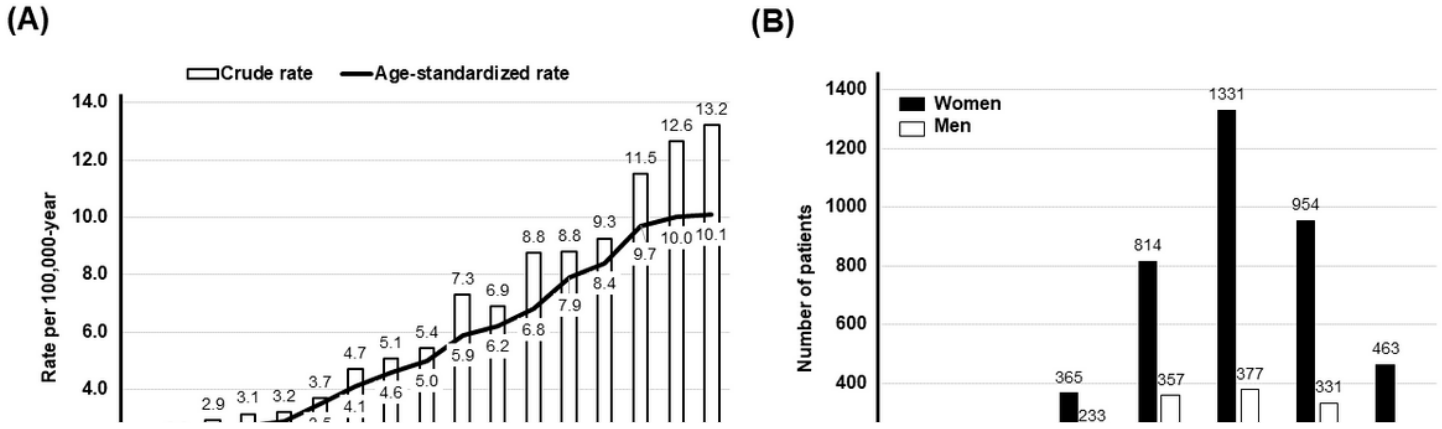

Figure 2

(A) Incidence and (B) age and gender distribution of primary hyperparathyroidism in Korea

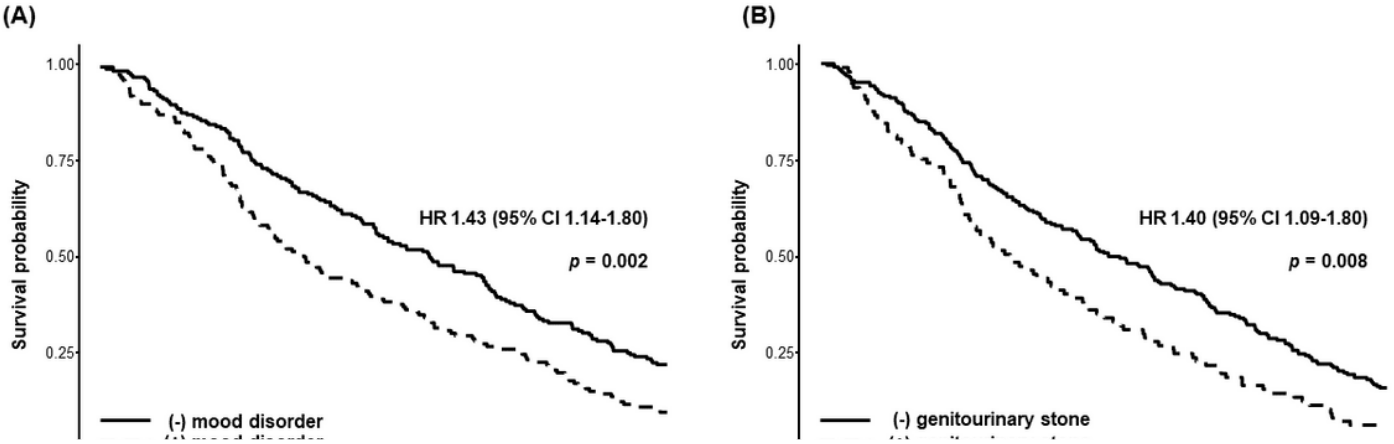

Figure 3

Kaplan-Meier curve illustrating survival probability according to (A) presence of mood disorder and (B) genitourinary stones

HR, hazard ratio; CI, confidence interval.

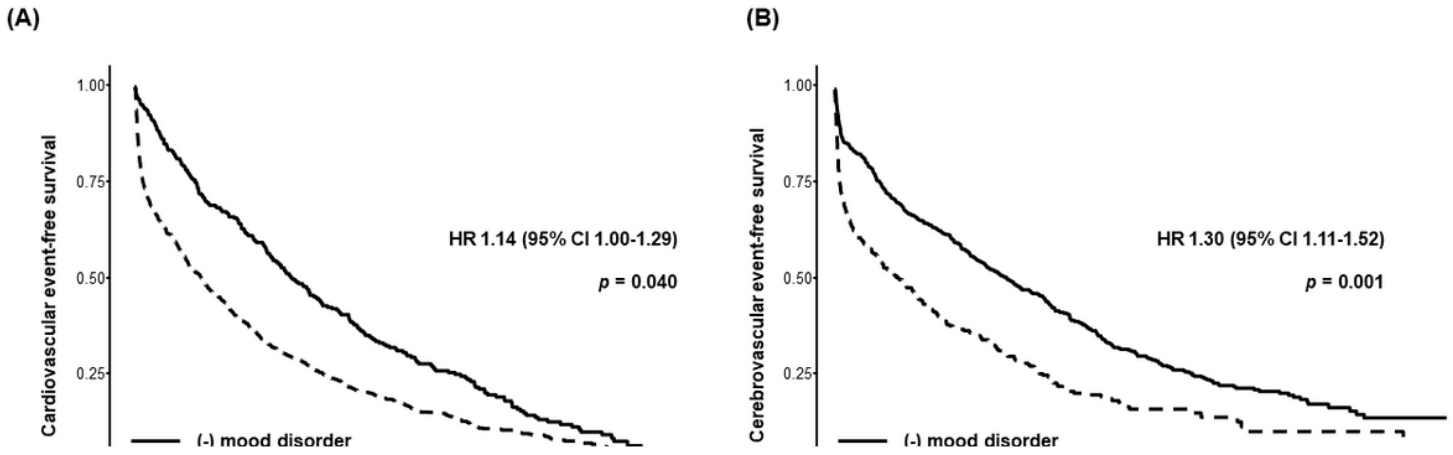

Figure 4

Kaplan-Meier curve illustrating (A) cardiovascular and (B) cerebrovascular event-free survival according to presence of mood disorder

HR, hazard ratio; CI, confidence interval.