Hungry Bone Syndrome (HBS) in Patients Operated for Primary Hyperparathyroidism (PHPT): A Six-Year Experience

Rhoda Zyra M. Padilla-Baraoidan, MD
Maria Jocelyn Capuli-Isidro, MD
Beinjerinck Ivan B. Cudal, MD
Ayezl A. Embestro-Pontillas, MD

Department of Medicine
Section of Endocrinology
Diabetes, and Metabolism
Makati Medical Center

ABSTRACT

Objective: To review cases of adult patients who develop Hungry Bone Syndrome (HBS) after parathyroidectomy for Primary Hyperparathyroidism (PHPT) in a tertiary care center in the Philippines and describe the clinical features, pre-operative preventive measures done and risk factors for HBS.

Methods:

Design: Retrospective Case Note Review

Setting: Tertiary Private Hospital

Participants: Chart review of adult Filipino patients who underwent parathyroidectomy for PHPT at Makati Medical Center from January 2011 to December 2016 was conducted and evaluated according to the inclusion and exclusion criteria. Medical information obtained included clinical parameters, biochemical results, operation performed, pathology, length of hospital stay and complications if with any.

Results: From among 20 adult Filipino patients (mean age 55 years; 13, 65% female) who underwent parathyroidectomy for PHPT, HBS was found in 7 (35%). Most common pre-operative symptoms of hypercalcemia were musculoskeletal complaints. To prevent HBS, all were hydrated prior to surgery while some were given bisphosphonates and diuretics. The most common parathyroid gland imaging used for pre-procedure localization was Tc 99m Sestamibi scan with single photon emission computed tomography (SPECT) and 19 (95%) had parathyroid adenoma on post-operative histopathologic report. Among biochemical and clinical factors that may be risk factors for HBS, those with HBS had significantly lower pre-operative 25-hydroxyvitamin D, higher BUN, phosphate and alkaline phosphatase (ALP) than those without HBS. Of these, only ALP showed significant association with HBS (OR = 107.17, p = <0.0001). Length of hospital stay was longer among those with HBS although not statistically significant.

Conclusion: Knowledge on post-parathyroidectomy HBS for PHPT may aid clinicians on pre-operative prevention and post-operative monitoring. Thirty-five percent (7) of our patients presented with HBS post-parathyroidectomy for PHPT from 2011 to 2016. An abnormal ALP level pre-operatively may be a risk factor in developing HBS post-parathyroidectomy for PHPT.

Correspondence: Dr. Rhoda Zyra M. Padilla-Baraoidan
Department of Medicine - Section of Endocrinology, Diabetes and Metabolism
Makati Medical Center
#2 Amorsolo St., Legaspi Village, Makati City 1229
Philippines
Phone: +63-917-598-2520
Email: rzpadillamd@gmail.com

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Primary hyperparathyroidism (PHPT) is the most common etiology of hypercalcemia with a reported prevalence of 21 per 100,000 in Minnesota between 1999 – 2001.[1] It is caused by excessive and uncontrolled secretion of parathyroid hormone (PTH) by an abnormal parathyroid gland. Parathyroidectomy remains the treatment of choice for PHPT but it is not without risks.[1] One common complication of parathyroid surgery is the development of hypocalcemia post-operatively.[2] When hypocalcemia is severe, defined as serum total calcium concentration below 2.1 mmol/L and lasts for more than 4 days post-parathyroidectomy, patients are deemed to have Hungry Bone Syndrome (HBS).[3] A 2016 study in Turkey noted the incidence of HBS post parathyroidectomy for PHPT was 13.4%.[2] Another 2012 study in Thailand reported the HBS incidence post-parathyroidectomy for PHPT was 22%.[4] Identified risk factors for the development of HBS include parathyroid hyperplasia and presence of osteoporosis. Identified biochemical predictors for HBS were higher preoperative PTH, ALP and BUN values. Moreover, HBS was more common in patients who had thyroidectomy together with parathyroidectomy.[2]

A search of local (HERDIN) and international databases (PubMed - MEDLINE, Google Scholar and ScienceDirect) using the following keywords: hungry bone syndrome, primary hyperparathyroidism and Philippines revealed only one reported case in 2010 of PHPT with classic and severe skeletal involvement who underwent parathyroidectomy and developed HBS 7 days post-operatively[5] but yielded no other articles on the incidence and risk factors of HBS post parathyroidectomy for PHPT in our country. Increasing identification of hypercalcemia from primary hyperparathyroidism and the importance of equipping clinicians with knowledge on pre-operative prevention and post-operative monitoring of HBS after parathyroidectomy prompted this study.

Our aim was to review the cases of adult patients who developed HBS after parathyroidectomy for PHPT in a tertiary care center in the Philippines and to describe the clinical features, pre-operative preventive measures done and risk factors for HBS.

METHODS

Study Design and Subjects

This retrospective case note review considered Filipino adults 18-years-old and above, admitted under or referred to the Section of Endocrinology, Diabetes and Metabolism of the Makati Medical Center in the Philippines between January 2011 to December 2016 who underwent parathyroidectomy for primary hyperparathyroidism. Primary hyperparathyroidism was defined as a primary abnormality of parathyroid tissue that leads to inappropriately high serum concentration of PTH with hypercalcemia, hypophosphatemia, loss of cortical bone and hypercalciuria. Discharge diagnoses in the chart included all possible terms that could include parathyroidectomy in our institution, coded as either primary hyperparathyroidism, neck exploration, parathyroidectomy or parathyroid biopsy. Patients diagnosed to have secondary hyperparathyroidism due to end-stage renal disease, sarcoidosis, familial hypocalciuric hypercalcemia, tertiary hyperparathyroidism or recurrent or persistent hyperparathyroidism after parathyroidectomy (as these patients would have been previously diagnosed with PHPT and may have undergone parathyroidectomy but have persistently elevated post-operative calcium and PTH levels and re-operation increases their risk for permanent hypocalcemia and not just HBS) were excluded.

This study was approved by the Institutional Review Board of the Makati Medical Center (protocol number MMCIRB 2016-109).

Data Collection

The General Endocrine Cases census from the Annual Reports of 2011-2016 of the Section of Endocrinology, Diabetes and Metabolism of Makati Medical Center were retrieved. All related medical information were obtained including the following: demographic data, clinical presentation, comorbidities, method of localization used to identify the abnormal parathyroid gland, preoperative medications given to prevent HBS, preoperative and postoperative blood chemistry results, operation performed with operative findings, pathology, length of hospital stay and post-operative complications, if any. Demographic data consisted of gender, age, and other comorbidities. Clinical presentation was divided into the effect of calcium on the organ systems: skeletal, renal, neuromuscular, neuropsychiatric, gastrointestinal, and nonspecific symptoms. Chemistry findings included pre-operative and post-operative serum calcium (total or ionized), albumin, magnesium, phosphate, alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), BUN, creatinine and serum 25-hydroxyvitamin D. Postoperative blood chemistry was recorded until discharge. Imaging modalities for localization was accounted for and its volume was computed using the ellipsoid model formula (length x width x height x 0.52).

Normal range of the laboratory parameters were established as follows: iPTH: 15-65 pg/mL, Total Calcium: 8.6 – 10.2 mg/dL, Ionized Calcium: 1.12 – 1.32 meq/L, phosphorus: 2.75 – 4.5 mg/dL, albumin: 3.5 – 5.2 g/dL, magnesium: 1.6 – 2.6 mg/dL, Alkaline Phosphatase: 30 – 130 IU/L, BUN: 6 – 20 mg/dL, TSH: 0.27 – 4.2 uIU/mL, fT4: 12 – 22 pmol/L, 25-

OHD: 30 – 100 ng/mL, TSH-IRMA (nuclear medicine): 0.27 – 3.75 uIU/mL, fT4-RIA (nuclear medicine): 8.8 – 33 pmol/L.

Calcium levels were calculated with the corrected calcium formula based on the patient's albumin levels if with abnormal albumin results. The formula used was as follows: Corrected Calcium (mg/dL) = [0.8 x (4 – patient's albumin)] + Serum Calcium level.

Statistical Analysis

Data encoding, processing and analysis were performed using Microsoft Excel for Mac 2015 version 15.13.3 (Microsoft Corporation, Washington, USA). Continuous data were presented as means and standard deviation (SD) while categorical data were presented as frequencies and SD or 95% confidence intervals (CIs) as appropriate. Fisher exact test was used for assessment of association of categorical data and Student t-test for two-group comparison of continuous variables. Risk factors associated with hungry bone syndrome were determined with exact logistic regression analysis using the software Stata 15 (StataCorp LLC, Texas, USA). Significance level was set at 5%.

RESULTS

Out of 20 adult Filipino patients who underwent parathyroidectomy for primary hyperparathyroidism at the Makati Medical Center from January 2011 to December 2016, seven (35%) were found to have Hungry Bone Syndrome (HBS).

The 20 participants included in this study had a mean age of 55-years-old with a range of 36 to 69 years and female predominance of 2:1. The most common pre-operative symptoms of hypercalcemia were renal calculi, osteoporosis, myalgia, neck mass, pathologic fracture and constipation. *(Figure 1)* The most common co-morbidities by frequency of mention were hypertension (15; 70%), diabetes mellitus type 2 (8; 40%) and myocardial infarction (5; 25%). To prevent HBS, all were hydrated preoperatively, 7 (35%) were given bisphosphonates and 6 (30%) were given diuretics. A few were given calcitonin (3; 15%) calcimimetics (3; 15%) and vitamin D (3; 15%). *(Figure 2)* The most common parathyroid gland imaging used for pre-procedure localization was Tc99m Sestamibi scan with single photon emission computed tomography (SPECT). *(Figure 3)* All patients with PHPT underwent parathyroidectomy involving removal of only one culprit parathyroid gland. Ninety-five percent (19/20) were found to have parathyroid gland adenoma on post-operative histopathology report. Sixty-percent (12/20) of patients had a concomitant subtotal (3; 15%) or total (9; 45%) thyroidectomy for a separate thyroid pathologic indication. Of the 12 patients that underwent thyroidectomy, 2 had papillary thyroid cancer and the rest had multinodular goiter. None had abnormal thyroid

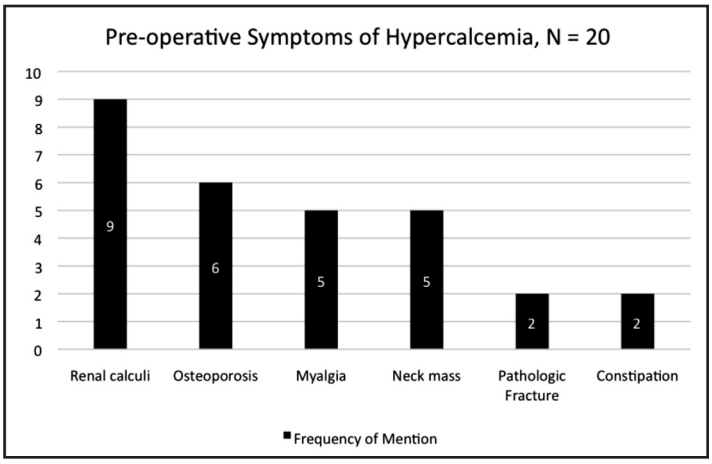

Figure 1. Pre-operative symptoms of hypercalcemia among included patients

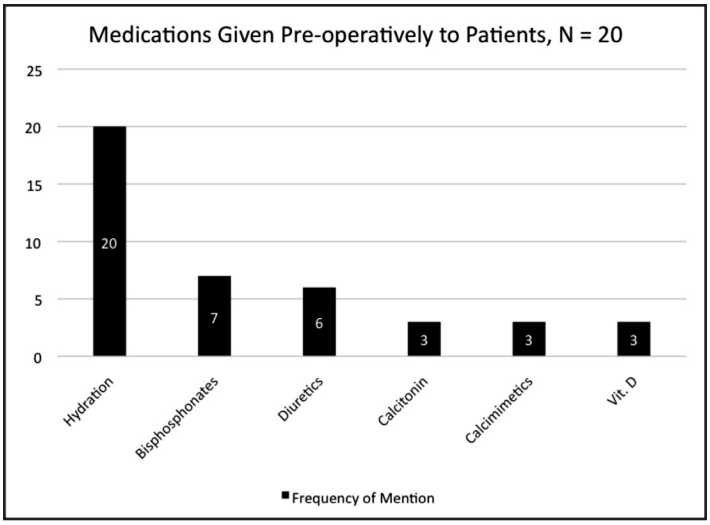

Figure 2. Medications given pre-operatively for hypercalcemia management and HBS prevention

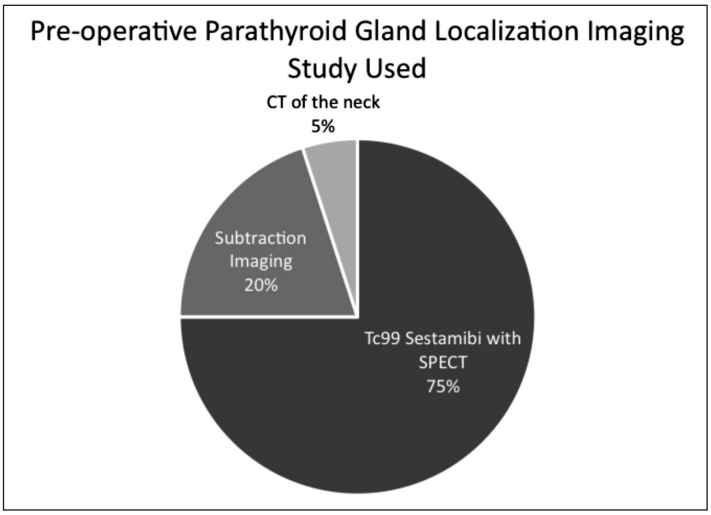

Figure 3. Distribution of pre-operative parathyroid gland localization imaging study used in patients Included in the study

function tests pre-operatively.

Table 1 compares values of selected pre-surgical biochemical and clinical risk factors of HBS. From among these factors, only 4 variables showed significant association with HBS at the 95% confidence level (p <0.05): 25-hydroxyvitamin D, BUN, phosphate and ALP. Those with HBS had significantly lower pre-operative 25-hydroxyvitamin D, higher BUN, phosphate and ALP than those without HBS.

To determine independent risk factors for HBS, we employed exact binary logistic regression for small sample sized data sets. The four variables which showed significant p values from the bivariate analysis were included in logistic regression analysis.

Full model exact binary logistic regression using continuous data did not produce viable estimates. When only ALP was placed in the model, the analysis showed significant results (p <0.0001). Considering only this model, it was found that the odds of having HBS increased by 9% with every unit increase in ALP. (*Table 2A)*

Table 2A shows that viable estimates for ALP were produced when only categorical variables were used. If the full model is considered, the association between HBS and ALP status is shown to be insignificant (p = 0.08). Understandably, when each variable is taken out of the model one by one, the odds ratio (OR) increased. When placed in a model with HBS, ALP showed a significant association with the said outcome variable (p <0.0001). Odds ratio was 107.17, which means HBS was 107.17 times more likely to occur given an abnormal level of ALP than with a normal level. *(Table 2B)*

The length of hospital stay in days was longer among those with HBS with a mean of 10.86 ± 6.15 vs. 6.77 ± 3.98 although the value did not reach statistical significance (p = 0.085).

Table 1. Pre-operative biochemical and clinical risk factors of HBS after parathyroidectomy for PHPT

Risk Factors*	(-) HBS N = 13	(+) HBS N = 7	p Value
Thyroid Stimulating Hormone (TSH) (uIU/ml), Mean, SD	1.66 + 1.12	1.65 + 0.85	0.992
Free Thyroxine (fT4) (pmol/L), Mean, SD	16.55 + 3.21	18.18 +3.32	0.299
Calcium (mg/dL), Mean, SD	10.81 + 1.04	10.73 + 0.87	0.859
Parathyroid Hormone (PTH) (pg/mL), Mean, SD	175.19 + 132.03	441.61 + 603.35	0.136
25-hydroxy Vitamin D(ng/mL), Mean, SD	24.15 + 7.81	11.39 + 2.36	0.00057 (S)
Blood Urea Nitrogen (BUN) (mg/dL), Mean, SD	14.95 +4.36	43.84 + 23.00	0.00029 (S)
Phosphorous (mg/dL), Mean, SD	2.79 + 0. 89	4.03 + 1.71	0.04110 (S)
Magnesium (mg/dL), Mean, SD	2.01 + 0.29	1.99 + 0.46	0.882
Creatinine (mg/dL), Mean, SD	0.94 + 0.32	2.29 + 2.52	0.067
Alkaline phosphatase (IU/L), Mean, SD	79.77 + 24.96	161.86 + 17.37	<0.0001 (S)
Parathyroid gland adenoma volume (cm3), Mean, SD	1.34 + 0.92	3.18 + 3.66	0.097
With thyroidectomy, N (%)	7 (54%)	5(71%)	0.642

*Student's t-test for test of association of continuous variables (i.e. those with means and SDs); Fischer's exact test for categorical data (i.e. those with frequency count)
(S): significant p value (p <0.05) at 95% confidence interval

DISCUSSION

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by autonomous production of parathyroid hormone. In the United States of America, the estimated incidence of PHPT between 1998-2010 was approximately 50 per 100,000 person years in the general population.[6] The increase in PTH secretion in primary hyperparathyroidism is hypothesized to be secondary to an elevation in set-point with a documented variable shift to the right in the slope of the calcium – PTH curve due to relative non-suppressibility of PTH secretion. The increase in the set-point is the primary determinant of the degree of hypercalcemia.[1]

Parathyroidectomy is the definitive management for PHPT with the aim of removing the culprit abnormal parathyroid gland, however, post-operative severe and prolonged hypocalcemia (HBS) may occur. This is a consequence of the sudden withdrawal of PTH signal post surgery that effects abrupt discontinuation of excessive osteoclastic activity from the hyperparathyroid state.

With the advent of wide availability and utilization of biochemical tests performed even among asymptomatic patients, hypercalcemia from PHPT is now identified with increasing frequency. In our institution, it was noted that there has been a steady increase in the

Table 2A. Results of exact binary logistic regression to determine independent risk factors of HBS pre-operatively using continuous variables

Risk Factors*	Odds Ratio (OR)	Sufficient	Suff.2* Pr(Suff)	95% CI
Alk Phosphatase (ALP)	1.09*	1133	0.0000	1.03 - +Inf

*median unbiased estimates (MUE)

Table 2B. Results of exact binary logistic regression to determine independent risk factors of HBS pre-operatively using binary variables (normal/abnormal)

Variable	Odds Ratio	Sufficient	Suff.2* Pr(Suff)	95% CI
Alk Phosphatase (ALP)	107.17*	7	0.0000	9.91 - +Inf

*median unbiased estimates (MUE)

number of performed parathyroidectomies per year from 2 cases in 2011 to 8 cases in 2016.

In this investigation, 35% (7/20) of patients who underwent parathyroidectomy for PHPT in our institution from 2011 to 2016 were found to have HBS. The mean age was in the fifth decade of life with females comprising the majority at 65% (13/20). These findings are comparable with the results of several authors. One study in 2016 reported an incidence of HBS post-parathyroidectomy for PHPT at 13.4%.[2] Yeh *et al.* in 2013 noted that majority of cases occured in patients over the age of 50-65 years with women being affected twice as often as men.[7] Among Asians in Thailand, the reported HBS incidence post-parathyroidectomy for PHPT was 22%. The subjects had a median age of 49 years (range 15 to 89 years) with female predominance at 3:1.[4]

In terms of clinical pre-operative symptoms of hypercalcemia, since calcium homeostasis is important to normal cellular function, the manifestations of PHPT may present as musculoskeletal, renal, gastrointestinal, cardiovascular, neuromuscular and neuropsychiatric symptoms.[1] The abnormalities directly associated with hyperparathyroidism are nephrolithiasis and bone disease due to prolonged PTH excess. Among our patients included in this study, the most common presenting symptoms were renal, musculoskeletal and gastrointestinal in nature.

PHPT diagnosis is made by biochemical testing. Localization studies are only recommended if the patient will undergo surgery. Commonly used and available imaging methods include neck ultrasound, Tc99m Sestamibi scintigraphy with SPECT or subtraction thyroid scan and MRI of the neck. Sestamibi scintigraphy combined with SPECT has the highest positive predictive value of the available imaging techniques.[8] In our institution, the practice was at par with the recommendations for pre-operative parathyroid gland localization as majority of the patients were likewise subjected to Tc99m Sestamibi scan with SPECT. Even the findings of the parathyroid gland histopathology post-operatively among our patients were consistent with the literature that single adenomas account for up to 80 – 85% of cases of PHPT and mostly consist of parathyroid chief cells.[1]

In a 2013 meta-analysis on measures that can be instituted pre-operatively to prevent HBS, it was recommended to supplement vitamin D pre-parathyroidectomy to normalize levels as depleted vitamin D has been postulated as a risk factor for the development of HBS. Other agents that may be used with good level of evidence are bisphosphonates that best address bone resorption. Intravenous pamidronate given 2 days pre-operatively decreased serum calcium pre-surgery and decreased calcium requirements post-procedure while intravenous zoledronate lowered HBS frequency post-operatively by as much as 4%.[3] On one end of the spectrum, preparation for parathyroidectomy in patients is not limited to prevention of HBS but also involves controlling elevated calcium levels to prevent occurrence of hypercalcemic crisis pre-operatively. In 2011, a study enumerated the treatment needed in the correction of hypercalcemia which includes adequate hydration, stimulation of calcium excretion by forced diuresis, inhibition of osteoclast effect on bone resorption through bisphosphonates or calcitonin and use of estrogens in menopausal women or calcimimetics like calcitonin.[9] These were the rationale for the pre-operative preparation of our patients wherein most received hydration, diuretics, anti-resorptive agents, vitamin D and calcimimetics.

Several authors investigated possible risk factors for the development of HBS post-parathyroidectomy for PHPT and in 2016, the following were identified: histopathologic finding of parathyroid hyperplasia and presence of osteoporosis pre-operatively. The HBS biochemical predictors were higher pre-surgery PTH, ALP and BUN values. In addition, HBS was more common in patients who had parathyroidectomy concomitantly with thyroidectomy.[2] Another article presented the following risk factors: older age at the time of surgery, higher pre-operative levels of serum calcium, PTH, ALP, decreased serum levels of magnesium and albumin and depleted vitamin D status.[3] Radiographic evidence of PHPT-associated bone pathology was likewise deemed to be a risk factor for HBS development. It was also reported that the volume and weight of the removed parathyroid adenomas were higher among patients who had HBS than those who had an uncomplicated post-operative course.[3] Apart from the documented increased risk of HBS if parathyroidectomy is performed

with thyroidectomy, it is prudent to include thyroid function tests in the biochemical investigation prior to parathyroidectomy as concomitant Graves' disease or hyperthyroidism can exacerbate the increased bone turnover state in PHPT.[10]

In our investigation, there were 4 identified possible biochemical risk factors that may predict HBS pre-operatively: 25-hydroxyvitamin D, BUN, phosphate and ALP. However, only abnormal ALP showed a significant association with HBS after further analysis.

Serum ALP levels can serve as a marker of bone remineralization. Preoperative serum ALP levels thereby reflect bone turnover status and directly relates to the osteoclastic activity and degree of bone resorption.[2,3] As for the other three risk factors identified but that did not show significant results after exact logistic regression tests, a possible theoretical explanation could be that low vitamin D levels in PHPT could mean more advanced disease reflecting higher bone resorption, reduced bone mineral density, post-operative hypocalcemia and higher PTH levels.[11] Moreover, low serum levels of 25-hydroxyvitamin D cause decreased fractional calcium absorption leading to suboptimal bone mineralization.[3] In HBS, the elevated BUN as a risk factor can develop due to the advanced age of patients and the effects of hypercalcemia on renal blood flow and renal tubular function.[2] While an increased PTH level would theoretically inhibit proximal tubule reabsorption of phosphate leading to hypophosphatemia, the elevated pre-operative levels of phosphate in patients who developed HBS post-parathyroidectomy for PHPT in our cases could be secondary to the effect of high PTH on the bones that influences higher bone turnover releasing calcium and phosphate from the bone matrix into the circulation.[1]

This study has several limitations. The retrospective design did not give the researchers the opportunity to validate the symptoms of hypercalcemia pre-operatively or the hungry bone syndrome manifestations post-operatively. The sample size of 96 that was needed to show accurate estimates of incidence and identify significant predictors was not achieved in this study and potential significant associations among variables could have been masked. Future researchers may consider a prospective study on the outcomes of patients undergoing parathyroidectomy for PHPT or extend the study period to achieve the target sample size. The establishment of a multicenter case registry may provide a means for collaboration among different centers in the country for a more accurate estimate of epidemiology and better understanding of the clinical features of HBS post-parathyroidectomy for PHPT.

In conclusion, our study found that thirty-five percent (7/20) of our patients developed HBS post-parathyroidectomy for PHPT between 2011 and 2016. Our findings suggest that an abnormal ALP level pre-operatively may be a risk factor for developing HBS post-parathyroidectomy for PHPT. Knowledge of post-parathyroidectomy HBS for PHPT may aid clinicians in pre-operative prevention and post-operative monitoring.

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