

## Original article

# Hungry bone syndrome following parathyroidectomy for primary hyperparathyroidism in a developed country in the Asia Pacific. A cohort study

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## ABSTRACT

**Objectives:** We sought to assess the incidence of hungry bone syndrome (HBS) following parathyroidectomy (PTX) for primary hyperparathyroidism (PHPT) in a cohort of multi-ethnic patients from a developed country in the Asia Pacific.

**Methods:** One hundred and sixty-four patients who underwent PTX for PHPT between 2012 and 2019 at the 2 largest public hospitals in Singapore were identified. HBS was defined as serum albumin-adjusted calcium  $\leq 2.1$  mmol/L with normal or raised serum intact parathyroid hormone (iPTH) levels, manifesting on or after the 3rd day, or persisting for more than 3 days post-operatively.

**Results:** Chinese constituted 73.8%, Malays 12.2%, Indians 9.8%, and other races 4.3%. HBS developed in 4 patients (2.4%) (95% CI, 0.8%–6.5%). HBS patients had significantly longer in-hospital stays; 20 days [IQR:15–22] vs 2 days [IQR:1–3];  $P < 0.001$  in those who did not develop HBS. There was no difference in the incidence of HBS stratifying for age, sex, vitamin D status, or use of preoperative anti-resorptive medication use. For every 10 unit increase in iPTH and alkaline phosphatase (ALP) levels, the risk of HBS increased by 14% and 11%; RR (95% CI), 1.14 (1.05–1.21) and 1.11 (1.03–1.18), respectively.

**Conclusions:** The low incidence of HBS in multi-ethnic patients undergoing PTX by multiple surgeons for PHPT at the 2 largest public hospitals that see the most such patients in Singapore, a developed country, is consistent with the asymptomatic/milder form of presentation of PHPT in the developed world.

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## 1. Introduction

Epidemiological studies from the Western world suggest that 80–95% of patients with primary hyperparathyroidism (PHPT), are

best described as asymptomatic. This common presentation has replaced an older phenotype in which PHPT presented in its classic symptomatic form [1,2]. In contrast, reports from less well-developed countries such as India, Thailand, and China, over the past 5–10 years continue to describe symptomatic PHPT, with skeletal and renal involvement as the predominant clinical form [3–5].

Surgery remains the definitive treatment in PHPT. The success rate of surgical treatment of PHPT is above 95% [6]. The hypocalcaemia that can be seen after parathyroidectomy (PTX) is usually mild and transient with the nadir of the serum calcium typically occurring on the 2nd–3rd day post-operatively [7]. In contrast,

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some patients will develop a prolonged period of hypocalcaemia after PTX in the presence of normal or elevated parathyroid hormone (PTH) levels. This phenomenon, termed “Hungry Bone Syndrome (HBS)” is presumed to be secondary to the immediate arrest of bone resorption with continued bone formation and rapid skeletal remineralization following successful PTX. This physiological definition of HBS has been described biochemically in different ways. Some studies have defined HBS simply as hypocalcaemia and normal or high PTH levels [8]. Other studies have included a low serum phosphate level [9]. Yet others have added a time course to the definition stipulating when the hypocalcaemia is experienced and how long the abnormalities persist post-operatively [9–12]. HBS must be differentiated from transient hypoparathyroidism that can occur postoperatively, a situation that is defined by low PTH levels. Data on the incidence rates of HBS after PTX for PHPT still remain scarce and conflicting. Published incidence rates vary from 8.6% to 59% [8–15]. In those with radiographic evidence for hyperparathyroid bone disease, rates for HBS are higher, between 25 and 90%. In those without radiological evidence of hyperparathyroid bone disease, the incidence is much lower, < 6.0% [12]. Clearly, the likelihood of developing HBS after PTX increases if the disease is advanced and symptomatic. Whether the high rates reported in some studies is due to prevalent high rates of vitamin D deficiency in those countries is not clear.

All the studies reported so far have been from single centers. The only available presumably multi-center study that evaluated readmission rates following PTX for both primary and secondary hyperparathyroidism in the United States reported that 4.1% of the readmissions after PTX for PHPT were for HBS [16]. However, this latter number was derived from a sub-analysis. Furthermore, no clear definition of either PHPT or HBS was provided in the study. Hence, whether these cases were truly HBS or simply post-operative hypocalcaemia is debatable [16].

Singapore has a unique multi-ethnic population comprised of Chinese, Malays, Indians, and other races. It is a highly developed country, and its health care system is very advanced. Public hospitals account for majority of hospital beds in the country. We have previously reported on the prevalence of PHPT amongst patients presenting for evaluation for osteoporosis [17] at our institution, as well as the marked change in the presentation, imaging, and surgical landscape for PHPT that has occurred here in the last 2 decades [18].

Anecdotal observations by us during daily clinical practice are that the incidence of HBS following PTX for PHPT in our population appears to be less than what has been reported elsewhere. The fact that no study has explored its incidence rates in a developed country in the Asia Pacific region prompted us to evaluate this in Singapore. As a secondary aim, we also attempted to elucidate pre-operative factors that could identify the occurrence of HBS in our population.

## 2. Methods

Consecutive adult patients over 18 years of age who underwent parathyroidectomy between Jan 1, 2012 and Jan 1, 2019 at 2 large public hospitals in Singapore - the National University Hospital Singapore (NUH) and Singapore General Hospital (SGH), were identified from the surgical archives of both institutions. These 2 hospitals have the largest annual parathyroidectomy volumes in Singapore. Ethical approval was obtained from the Singhealth Centralised, and the National Health Care Group Institutional Review Boards, (Reference numbers: CIRB 2019/2706 and NHG DSRB Ref:2020/00804), respectively. The parathyroidectomies were performed by multiple surgeons from the centers of General Surgery-Head and Neck, Otolaryngology, and Endocrine Surgery, at these

hospitals. PHPT was identified using the ICD -10 (International Classification of Disease-10th revision) code E21.0. To ensure the accuracy of the identification, the electronic medical records were manually searched and only those with biochemically proven PHPT were included in the final analysis. These were patients with pre-operative serum calcium levels higher than the upper limit of normal (ULN) with a concomitant elevated or inappropriately normal PTH level (based on the ULN of the 2 assays at each respective hospital). Patients who had PTX for secondary hyperparathyroidism (SHPT) were excluded. Tertiary hyperparathyroidism has the same biochemical characteristics as PHPT. However, unlike PHPT, which is mostly due to a single adenoma that would benefit from limited explorative or minimally invasive surgery, the former usually has a preceding long-standing SHPT phase and most often occurs in the setting of end stage renal failure. Other rare congenital and acquired disorders that require long-term phosphate replacement may also be associated with tertiary hyperparathyroidism. Both these group of patients were also excluded. This resulted in a final sample size of 164 subjects. Laboratory data that were assessed included pre-operative serum calcium, phosphate, alkaline phosphatase (ALP), and iPTH levels and post-operative serum calcium and iPTH levels. Serum magnesium levels are routinely checked only in the presence of hypocalcaemia at both hospitals, and so this variable was available only in those who did have hypocalcaemia post-operatively. At SGH, serum calcium, phosphate, and ALP levels were measured using the AU 5800 Clinical Chemistry Analyser (Beckman Coulter Inc, Brea, California, USA) with normal ranges of 2.10–2.60 mmol/L, 0.77–1.38 mmol/L, and 32–103 U/L, respectively. At NUH, these indices were measured using the UniCel Dxl 800 Access Immunoassay (Beckman Coulter Inc, Brea, California, USA) with normal ranges of 2.15–2.55 mmol/L, 0.85–1.45 mmol/L, and 40–130 IU/L, respectively. Serum magnesium levels were measured at both hospitals using the enzymatic colorimetric method (AU 5800 analyser and UniCel Dxl 800 analyser, respectively) with normal ranges of 0.74–0.97 mmol/L and 0.75–1.07 mmol/L, respectively. Serum iPTH levels were measured using a chemiluminescent assay at both SGH and NUH with normal ranges at the 2 hospitals being 0.9–6.2 pmol/L and 1.3–9.3 pmol/L, respectively. Serum calcium levels were adjusted for serum albumin using Payne's formula ( $[\text{Serum calcium} + (4 - \text{albumin (g/L)} \times 0.2 \text{ mmol/L})]$ ). Pre-operative 25-hydroxy-vitamin D (25(OH)D) levels measured using radioimmunoassay at both institutions were also analyzed. Reports of imaging modalities used to localize parathyroid adenoma were reviewed. We also reviewed prescriptions of vitamin D supplements and anti-resorptive medications (bisphosphonates and/or denosumab) up to 6 months pre-operatively. Bone mineral density (BMD) T and Z-scores of the hip and spine assessed by dual-energy X-ray absorptiometry (DXA) and calculated using Singapore male and female, ethnic-specific (as is the practice at the 2 hospitals) reference databases were explored. DXA scans at both centers were performed using the Discovery Wi System (Hologic Inc, Bedford, MA, USA). There are no ethnic-specific normative data for BMD of the forearm in Singapore and hence forearm DXA scanning is seldom performed. One-third radius BMD data therefore were not available. Reports of skeletal X-rays that had been done when patients had complaints of bone pain/tenderness or had history of fractures were studied to record radiographic bone abnormalities. Abdominal X-rays and/or renal ultrasound scans (USS) that had been performed routinely as part of the evaluation of PHPT were analyzed to detect nephrolithiasis. Parathyroid adenoma volume was calculated from the surgical specimens using the ellipsoid volume formula  $[(\text{Length (cm)} \times \text{Width (cm)} \times \text{Thickness (cm)}) \times \pi/6]$  [19]. Mineral metabolic response to parathyroidectomy was assessed by recording daily post-operative values for calcium, phosphate, and on days when

several calcium and phosphate levels were available, the lowest value was the one that was recorded for analysis. Post-operative use of intravenous as well as oral calcium, activated vitamin D, and length of hospital stay (LOHS) were also recorded. HBS was defined as a drop in adjusted serum calcium levels from pre-operative levels to  $\leq 2.1$  mmol/L post-operatively with concurrent normal or high serum PTH levels, manifesting on or after day 3, or persisting for more than 3 days post-operatively and requiring intravenous calcium supplementation.

### 2.1. Statistical methodology

The statistical analysis was performed using R Statistical Software (2019; R Foundation for Statistical Computing, Vienna, Austria).

Demographics and other characteristics are summarized using descriptive statistics. Continuous data are presented as median (interquartile range (IQR)). We used Mann Whitney *U* test to compare continuous variables and Fisher's exact test to compare categorical variables within the HBS and non-HBS groups. We performed univariate logistic regression to estimate odds ratio and 95% confident interval (CI) on the variables that significantly differed between the 2 groups and performed Spearman's rank correlation coefficient rho to measure the relationship between adenoma volume and iPTH levels.

### 3. Results

The clinical and biochemical characteristics of the patient population are shown in Table 1. A majority of the PHPT patients had been diagnosed after a high serum calcium level was incidentally detected on multiphase health screening or after they had been found to have elevated calcium with high or inappropriately normal PTH levels during work-up for osteoporosis. The ethnic distribution of the patients closely approximated the population demographics of Singapore. Of these patients, 65.7% had osteoporosis or low BMD for age, identified by DXA scanning, and 15.8% had nephrolithiasis. Only 1 patient had overt radiographic abnormalities of osteitis fibrosa cystica (OFC) and histologically proven brown tumors. The most common imaging modality employed was ultrasound scan (USS) combined with Sestamibi Tc-99 m scan (72.7%). Of the patients, 12.1% had USS and Sestamibi Tc-99 m scans

**Table 1**  
Comparisons of baseline characteristics between patients with and without hungry bone syndrome (HBS).

	Total (N = 164)	HBS (N = 4)	non-HBS (N = 160)	P-value
Age, median (IQR) years	62 (52, 69)	56 (36.8, 72.2)	62 (52, 68.2)	0.721
Women, N (%)	116 (707)	3 (2.6)	113 (97.4)	1
Men, N (%)	48 (29.3)	1 (2.1)	47 (97.9)	
Chinese, N (%)	121 (73.8)	3 (2.5)	118 (97.5)	0.708
Indian, N (%)	16 (9.7)	0 (0)	16 (100)	
Malay, N (%)	20 (12.2)	1 (5)	19 (95)	
Others, N (%)	7 (4.3)	0 (0)	7 (100)	
No preoperative bisphosphonate or denosumab use, N (%)	127 (77.4)	3 (2.4)	124 (97.6)	1
Preoperative bisphosphonate or denosumab use, N (%)	37 (22.6)	1 (2.7)	36 (97.3)	
No preoperative vitamin D supplement use, N (%)	84 (51.2)	3 (3.6)	81 (96.4)	0.621
Preoperative vitamin D supplement use, N (%)	80 (48.7)	2 (2.5)	78 (97.5)	
Vitamin D dose IU per day, median (IQR)	1000 (1000, 1047.5)	1000 (1000, 1000)	1000 (1000, 1095)	0.924
Preoperative serum iPTH level (pmol/L), median (IQR)	18.8 (11.6, 30.3)	78.4 (54.2, 189.7)	18.7 (11.5, 29.5)	0.022
Preoperative serum corrected Calcium level (mmol/L), median (IQR)	2.7 (2.6, 2.8)	2.8 (2.8, 2.9)	2.7 (2.6, 2.8)	0.222
Preoperative serum Phosphate level (mmol/L), median (IQR)	0.9 (0.7, 1)	1.1 (0.8, 1.1)	0.9 (0.7, 0.9)	0.442
Preoperative serum 25(OH) D level (ng/mL), median (IQR)	20 (15.5, 26.1)	16.3 (10.2, 27.2)	20 (15.7, 25.8)	0.387
Preoperative serum ALP level (IU/L), median (IQR)	112 (85, 146)	212 (160, 268.2)	111 (84, 143)	0.012
Adenoma volume in cm <sup>3</sup> , median (IQR)	1 (0.4, 2)	4.1 (2.5, 7)	0.9 (0.4, 1.9)	0.014
Length of hospital stay in days, median (IQR)	2 (1, 3)	19.5 (14.5, 21.8)	2 (1, 3)	0.001

\*Mann Whitney *U* test was used to compare continuous variables and Fisher's exact test was used to compare categorical variables within the HBS and non-HBS groups. N: number; IQR: interquartile range; iPTH: intact parathyroid hormone; ALP: alkaline phosphatase; 25(OH)D: 25 hydroxyvitamin D.

**Table 2**  
Univariate logistic regression analysis of factors that predicted hungry bone syndrome (HBS).

Variable	OR (95%CI)	P-value
Pre-operative iPTH level	1.02 (1.01, 1.04)	0.011
Pre-operative ALP level	1.01 (1, 1.03)	0.027
Adenoma size (cm <sup>3</sup> )	1.09 (0.93, 1.2)	0.146

OR: odds ratio; ALP: alkaline phosphatase, iPTH: intact parathyroid hormone.

in combination with 4D computerized tomography (CT) imaging. Some patients only underwent a single imaging modality, specifically, 5.5% underwent a parathyroid USS alone, 3% only a Sestamibi Tc-99 m scan, and 6.1% a 4D-CT scan alone.

Most patients did not receive any anti-resorptive agent before surgery with only 22.4% of the 164 patients found to have received an anti-resorptive agent within 6 months prior to surgery. Nineteen (11.5%) of the patients received a bisphosphonate in the month prior to surgery of which 5 patients were given single doses of intravenous pamidronate (n = 3) and/or zoledronic acid (n = 2) for management of hypercalcaemia.

Less than half of the patients were on a form of vitamin D supplementation within the 6 months prior to surgery with a median dose of 1000 International Units (IU) per day.

There was a significant correlation between adenoma volume and pre-operative iPTH levels; Spearman's rank correlation coefficient rho: 0.51, P-value < 0.001.

Four patients (2.4%; 95% CI, 0.8%, 6.5%) developed post-operative HBS based on the criteria defined earlier. There were no significant differences in age, sex, use of bisphosphonates, denosumab, vitamin D supplements, pre-operative 25(OH)D levels, or serum calcium levels between the groups who did or did not develop HBS. Pre-operative serum iPTH and serum ALP levels and adenoma volume differed significantly between the 2 groups (Table 1). On univariate logistic regression, only pre-operative iPTH and ALP levels were significantly associated with a risk of developing HBS; OR (95% CI) of 1.02 (1.01, 1.04, P = 0.007) and 1.01 (1, 1.03, P = 0.023) respectively (Table 2). With every 10 unit increase in iPTH and ALP levels, the risk of post-operative HBS was found to increase by 14% and 11% (risk ratios (95% CI) 1.14(1.05, 1.21; P < 0.001) and 1.11(1.03, 1.18; P = 0.004), respectively). The distribution of ALP and iPTH levels in the Non-HBS and HBS groups are shown pictorially in

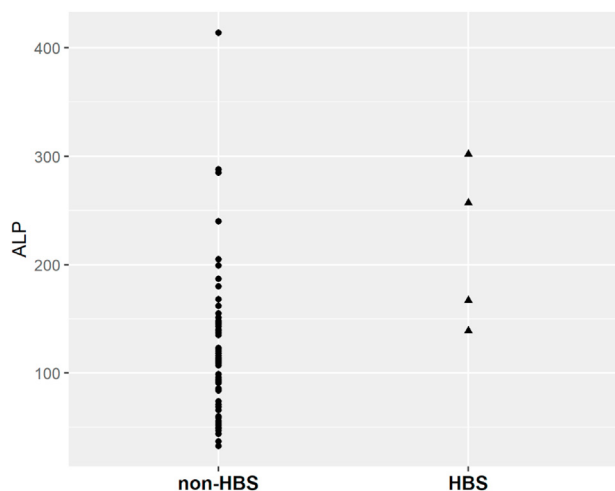


Fig. 1. Distribution of alkaline phosphatase (ALP) levels (IU/L) in hungry bone syndrome (HBS) and non-HBS groups.

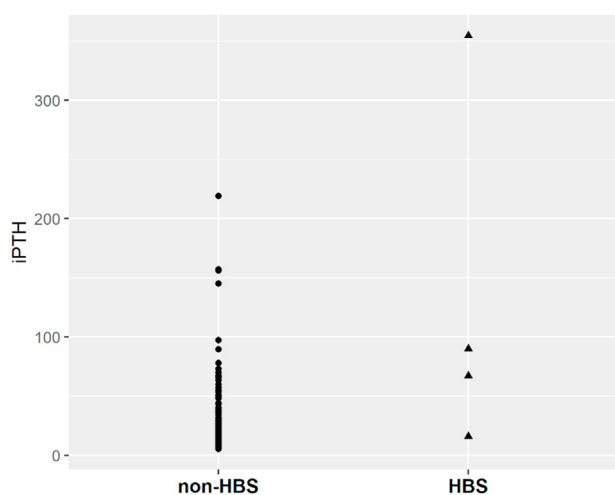


Fig. 2. Distribution of intact parathyroid hormone (iPTH) levels (pmol/L) in hungry bone syndrome (HBS) and non-HBS groups.

Figs. 1 and 2, respectively. Of the 4 patients who developed HBS, 3 had adenomas on histological examination. One had histological evidence of parathyroid carcinoma. The characteristics of the 4 patients with HBS are described (Table 3).

#### 4. Discussion

In this very first dual-center study of a well characterized, multi-ethnic population of PHPT patients from a developed country in the Asia Pacific region, a low incidence of HBS was seen following PTX. This is lower than that has been reported elsewhere. The rate of HBS thus is likely to be dependent upon the severity of PHPT in the population and how well-defined and rigorous the study is. The 2 hospitals included in this study see the majority of PHPT patients and have the largest parathyroidectomy volumes in Singapore. Therefore, the study cohort is quite representative of our PHPT population. The results of the study confirm our earlier anecdotal observations that the incidence of HBS post-parathyroidectomy for PHPT in Singapore appears to be decreasing in tandem with the decrease in the incidence of symptomatic PHPT here and in the rest of the developed world.

Table 3  
Characteristics of the four patients who developed hungry bone syndrome (HBS).

Hospital	Age (yr)	Gender	Nephrocalcinosis 25 (OH)D level (ng/mL)	Pre-op ALP Level (IU/L) (Normal range)	Pre-op iPTH level (pmol/L)	Volume Of Adenoma (cm <sup>3</sup> )	Exposure to bisphosphonate/denosumab within 6 months pre-operatively	Histology of parathyroid lesion	Nadir of serum corrected calcium (mmol/L) (Normal range) in post-operative period	Serum magnesium (mmol/L) (Normal range) at time of nadir serum calcium	Serum iPTH (pmol/L) (Normal range) at time of nadir serum calcium	Serum phosphate (mmol/L) (Normal range) at time of nadir serum calcium	Length of hospital stay (days)
NUH	24	Female	Yes	10.8 (257–40–130)	67	1.5	No	Adenoma	2.02 (2.15–2.55)	0.76 (0.75–0.97)	5.6 (1.3–9.3)	0.6 (0.85–1.45)	4
NUH	41	Female	No	21.8 (302–40–130)	354.6	12	No	Adenoma	2.01 (2.15–2.55)	0.84 (0.75–0.97)	3.8 (1.3–9.3)	0.76 (0.85–1.45)	18
NUH	76	Male	No	9.6 (139–40–130)	89.9	5.32	No	Carcinoma	2.07 (2.15–2.55)	0.83 (0.75–0.97)	1.3 (1.3–9.3)	Not available	24
SGH	71	Female	No	32.6 (167–32–103)	16	2.88	Yes	Adenoma	2.01 (2.10–2.60)	0.78 (0.75–0.97)	2.3 (0.9–6.2)	0.66 (0.77–1.38)	21

NUH: National University Hospital; SGH: Singapore General Hospital; iPTH: intact parathyroid hormone, ALP: alkaline phosphatase; 25(OH)D: 25 hydroxyvitamin D.

Use of bisphosphonates preoperatively has been proposed to prevent HBS in PHPT [12]. Bisphosphonates inhibit osteoclastic bone resorption and decrease activation frequency of remodelling sites and thereby help to refill remodelling spaces. In the context of PHPT, pre-operative bisphosphonate use could theoretically decrease the severity and duration of HBS by significantly decreasing or even normalizing bone turnover before surgery [12]. However, despite the low preoperative use of bisphosphonates in our study population, our incidence of HBS was low. We also did not find a significant difference in the pre-operative use of bisphosphonates between patients who developed HBS and those who did not.

Low levels of serum vitamin D have been proposed to be a potential risk factor for HBS development in some studies [9,20,21] but not in others [22]. Though it has not been conclusively shown in any study, populations with extremely low levels of vitamin D may have higher incidence rates of HBS post-operatively. Vitamin D supplementation, especially in those who have deficient vitamin D levels, may theoretically shorten the duration of symptomatic hypocalcaemia associated with classic hypoparathyroidism post-operatively. However, no difference was noted in vitamin D levels or pre-operative use of vitamin D supplementation between patients who developed HBS and those who did not in our study.

Although 65.7% of our patient population had a densitometric diagnosis of osteoporosis, only 1 patient had overt evidence of OFC on radiographs and histologically proven skeletal brown tumors. This again reflects the early recognition of the disease. Radiographic skeletal abnormalities are usually found in patients presenting late in the disease course [3,10] and OFC is seen in less than 2% of cases of PHPT in the Western world [23]. Of note, the patient with OFC in our cohort did not develop HBS post-operatively.

Some, but not all previous studies have reported higher pre-operative levels of serum iPTH [9] and/or ALP [9,10] as predictive of HBS after PTX. Higher PTH and ALP levels may reflect a higher degree of bone turnover pre-operatively. It has been shown that 24 h after PTX, bone resorption markers fall significantly while bone formation markers remain unchanged [24], and in fact may even increase [25], suggesting that a decoupling occurs between osteoclast and osteoblast activity in the immediate post-operative period. With higher pre-operative bone turnover, continued osteoblastic activity that persists after removal of the adenomatous parathyroid gland could subsequently lead to HBS. In our cohort, median levels of PTH (78.4 pmol/L) as well as ALP (211 IU/L) were significantly higher for those who developed HBS than for those who did not (18.7 pmol/L and 111 IU/L, respectively). On univariate logistic regression, pre-operative iPTH and ALP levels were significantly associated with a risk of developing HBS. However, given that the occurrence of HBS in our population is low, the impact of this finding is unlikely to be robust and thus its interpretation should be made with caution. Delineating cut off values for iPTH and ALP levels that predict post-operative HBS on such small sample sizes would not be statistically appropriate or scientifically sound and therefore, though we identified pre-operative iPTH and ALP threshold values of  $\geq 66.5$  pmol/L, and  $\geq 138$  IU/L respectively as predictive of post-operative HBS on a preliminary Receiver Operating Curve (ROC) analysis, we did not attempt to proceed further with the analysis. It must be noted that all the studies that were performed earlier and are often cited in the world literature regarding risk factors predictive of HBS after PHPT, had only small sample sizes of HBS patients, and the complicated statistical methodologies that they used to find associations and predictive capabilities deserve closer retrospective scrutiny [9,10,12].

Adenoma size estimated on high-resolution real-time USS has been shown to correlate well with its volume anatomically [9], and a larger adenoma volume also has been noted to be predictive of

HBS after PTX [9]. It can be postulated that larger adenomas secrete more PTH leading to a more profound bone-turnover state pre-operatively. However, although we did find a significant correlation between adenoma volume and iPTH levels in our study population, and adenoma volume differed between patients who did and did not develop HBS, we did not find a significant effect between this and the risk of developing HBS (Table 2). Given its pathophysiology, histology type (hyperplasia versus adenoma) and type of PTX (bilateral exploration versus minimally invasive PTX) are not expected to impact HBS rates though hyperplasia and bilateral exploration are more likely to be associated with hypoparathyroidism and hypocalcaemia [7].

Hypomagnesaemia can induce a state of PTH resistance resulting in hypocalcaemia and elevated PTH levels [26]. It is not clear if the hypocalcaemia and raised PTH levels that were diagnosed as HBS in some of the earlier studies were merely due to low magnesium levels which were either unrecognized or untreated, and thus resulted in an overdiagnosis of HBS. Magnesium levels may not have been measured upon detection of hypocalcaemia in those patients. Hypocalcaemia that reversed after hypomagnesaemia (if any) was corrected was therefore not considered as indicative of HBS in our study.

Our study has some limitations associated with its retrospective nature. It is probable that the unavailability of skeletal X-rays in all patients may have led to an inadvertent underestimation of OFC. However, given the asymptomatic nature of presentation of most of our patients and their incidental diagnosis of PHPT, this is unlikely. It is also unlikely to have implications on the incidence rates of HBS in our population. The median length of hospitalization stay in most patients was only 2 days. There is a small possibility that this could have underestimated the occurrence of HBS in our study population. However, this is unlikely since on long term follow-up (for up to 3 months post-operatively), no patient was readmitted with evidence of HBS. We did not have bone turnover marker data in our patients and hence we were unable to elucidate the pathophysiological process underscoring the development of HBS in the 4 patients who did develop it. The low rates of HBS noted in our population precluded the clear statistical delineation of possible predictive biochemical factors and their cut-off levels.

Despite these limitations, our study has several advantages. It was conducted in consecutive, multi-ethnic patients undergoing PTX for PHPT at the 2 largest public hospitals in Singapore that see the majority of PHPT patients here making the findings applicable to our population. The results we obtained were without any specific interventions or protocolized regimens aimed at reducing the incidence of HBS post-operatively. Parathyroidectomies were performed by multiple surgeons over a seven-year period. The low rate of HBS we noted is thus unlikely to be due to specialty or interventional bias. Our findings, thus, are likely to be truly reflective of routine clinical practice and indicative of the real occurrence of HBS in a developed country such as Singapore where PHPT is diagnosed early in its course. It is not likely that the low rate we noted was due to post-operative calcium supplementation since, none of our patients were routinely started on such a supplementation regimen.

## 5. Conclusions

It is reassuring that the incidence of HBS following PTX for PHPT is low in Singapore. The low rates of HBS following PTX for PHPT is likely due to the milder form of presentation of PHPT in our population. It is possible that if such robust and most importantly well-characterized studies that accurately define both PHPT and HBS are conducted in other developed countries in the Asia Pacific and the rest of the world, a similar pattern of much lower rates of the latter condition than has been previously reported is likely to be seen.

This does not negate the fact that HBS, if it does develop, is a serious condition and results in significant morbidity and prolonged hospitalization as was seen in our patients also. Predicting the few cases that may still occur and instituting appropriate peri-operative protocols may help to lower the incidence even further. This may also help to facilitate early discharge and promote more efficient utilization of resources since in low-risk patients, serum calcium monitoring may be needed less frequently.

### CRedit author statement

**Manju Chandran:** Conceptualization, Data Curation, Formal Analysis, Writing - Original Draft, Writing - Review and Editing. **John P. Bilezikian:** Supervision, Writing - Review and Editing. **Nurshazwani Mat Salleh:** Data Curation. **Hao Ying:** Formal Analysis. **Joel Lau:** Data Curation. **James Lee:** Data Curation. **Mechteld C De Jong:** Data Curation. **Aye Chan Maung:** Data Curation, Writing - Original Draft. **Rajeev Parameswaran:** Supervision, Data Curation.

### Conflicts of interest

The authors declare no competing interests.

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