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Disclosure: The authors signed a disclosure that there are no financial or other (including personal) relationship, intellectual passion, political or religious beliefs, and institutional affiliations that might lead to a conflict of interest.

Presented at the Philippine Society of Otolaryngology-Head and Neck Surgery Analytical Research Contest, SV More Group of Companies, 16 Sgt. Tuazon cor. Don A. Roces Ave., Quezon City, September 19, 2025; and the Philippine General Hospital Department of Otolaryngology - Head and Neck Surgery Analytical Research Presentation, 2025, PGH Ward 10 Conference Room, June 25, 2025.

Data Availability and Sharing Statement: Datasets generated and analyzed in this study are included in the published article.



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# Clinical Factors Associated with Immediate Postoperative Hypocalcemia After Total Thyroidectomy at the Philippine General Hospital: A Case Series with Planned Data Collection

## ABSTRACT

**Objective:** To identify clinical factors associated with immediate hypocalcemia post-thyroidectomy.

### Methods:

**Design:** Case Series with Planned Data Collection

**Setting:** Tertiary National University Hospital

**Participants:** Total enumeration reviewed records of 664 patients aged 19 years old and above, previously admitted under the Philippine General Hospital Department of Otolaryngology – Head and Neck Surgery from 2019 to 2023 who underwent total thyroidectomy (including completion thyroidectomy and those with neck dissection) and had serum calcium determination done both 6 and 24 hours post-operation. Cumulative incidence of hypocalcemia was determined, and patient-related, procedure-related, and tumor-related factors were investigated, with multivariable logistic regression analysis performed to identify the association between clinical factors and postoperative hypocalcemia.

**Results:** The cumulative incidence of hypocalcemia at 6 hours and 24 hours post-operation was 28.92% (95%CI: 25.49%–32.53%) and 19.49% (95%CI: 16.01%–23.36%), respectively. The clinical factors with notable increased odds for postoperative hypocalcemia were female sex (adjusted OR: 3.5; 95%CI: 1.2623–9.6362), total thyroidectomy as type of surgery (adjusted OR: 0.7; 95%CI: 0.2905–1.6805; adjusted OR: 0.8; 95%CI: 0.2616–2.6670), histopathologic type of papillary thyroid carcinoma (adjusted OR: 1.4; 95%CI: 0.8949–2.0719; adjusted OR: 1.6, 95%CI: 0.8985–2.7771), and the presence of parathyroid tissue in the excised specimen (adjusted OR: 1.2; 95%CI: 0.7436–1.9002; adjusted OR: 1.6; 95%CI: 0.8406–2.9496). The only statistically significant factor out of all those investigated was female sex.

**Conclusion:** The only statistically significant clinical factor associated with hypocalcemia in our study was female sex, with total thyroidectomy as type of surgery, histopathologic type of papillary thyroid carcinoma, and presence of parathyroid tissue in the excised specimen as other factors noted with increased odds for hypocalcemia.

**Keywords:** hypocalcemia; thyroidectomy; clinical factors; incidence; postoperative complications; case series; tertiary hospital; female sex



**The standard of care** in the management of different thyroid diseases including thyroid malignancies is thyroidectomy, a procedure with minimal morbidity but that is not without risk for complications.<sup>1</sup> The two most commonly seen are hypocalcemia and recurrent laryngeal nerve injury.<sup>2</sup> Hypocalcemia or a decrease in the serum calcium levels is brought about in post-thyroidectomy patients by injury, ischemia, or inadvertent excision of the parathyroid gland.<sup>3</sup> The incidence of both transient and permanent hypocalcemia varies between studies, from 0.3 to 49% for transient and 2 to 12% for permanent, with a wide range of symptoms.<sup>4</sup> Patients may be asymptomatic if calcium levels are only mildly reduced, but can also have severe symptoms requiring hospitalization. Patients may present with paresthesia, circumoral numbness, muscle spasms, cramps, involuntary contractions, seizures, laryngospasm, neuromuscular irritability, cognitive impairment, personality disturbances, prolonged QT intervals as well as other electrocardiographic changes mimicking myocardial infarction or heart failure.<sup>5</sup>

At present, some factors which could have an effect on postoperative calcium levels have yet to be fully investigated, including specific procedure-related and tumor-related characteristics, as well as pre-operative interventions such as calcium supplementation. Despite the many studies that have already been done in different countries such as India,<sup>6</sup> Lithuania,<sup>7</sup> and Saudi Arabia<sup>8</sup> with regards to factors associated with hypocalcemia, they all yield different results for each population, with only one study done locally.<sup>1</sup> It is important that further studies are done in different populations, especially in our local setting, as determining specific characteristics of patients who have a higher chance of having postoperative hypocalcemia not only help in consolidating our general understanding of their effect in post-thyroidectomy patients, but could also help in directing studies towards interventions that could decrease its incidence.

Our study aimed to identify clinical factors associated with postoperative hypocalcemia at 6 hours and 24 hours after undergoing thyroidectomy in our institution. Specifically, we wanted to determine the association between patient-related factors (age, sex, pre-operative calcium supplementation, duration of thyroid disease prior to surgery, comorbidities), procedure-related factors (type of surgery, including whether the patient had a concomitant neck dissection or already underwent previous surgery of the thyroid; duration of surgery), and tumor-related factors (thyroid gland weight, histopathologic type, extrathyroidal extension, perineural or vascular invasion, presence of parathyroid tissue in the excised specimen) with 6-hour and 24-hour postoperative hypocalcemia.

## METHODS

With University of the Philippines Manila Research Ethics Board (REB) approval (UPMREB 2024-0222-01) this case series with planned data collection considered for inclusion adult thyroid patients (aged 19 years and above) admitted under the Department of Otolaryngology-Head and Neck Surgery (ORL-HNS) of the Philippine General Hospital (PGH) who underwent total thyroidectomy (including those who underwent completion thyroidectomy and those who had a concomitant neck dissection) within a 5-year period from 2019 to 2023, and had serum calcium determination done 6 and 24 hours post-operation. Total enumeration was performed, and records of all patients who met the above inclusion criteria were included. Those with concomitant parathyroid disease, or had renal problems, active malignancy aside from the thyroid, or metabolic bone diseases were excluded.

Based on the annual census of the department of ORL-HNS for the period of 2019-2023, inpatient charts were obtained from the PGH Medical Records Division. Records were reviewed and data was extracted by the first author and a research assistant, and encoded using Microsoft Excel version 16.77.1 (Microsoft Corp., Redmond, WA, USA).

The data collected were the independent variables: age (measured in years), sex (male or female), duration of thyroid disease prior to surgery (measured in months), comorbidities (defined as presence or absence of any other chronic diseases aside from the primary thyroid disease), preoperative calcium supplementation (whether or not calcium supplements were initiated prior to the scheduled procedure), type of surgery (defined as either total thyroidectomy or completion thyroidectomy and whether a concomitant neck dissection was done), duration of surgery (measured in hours), thyroid gland weight (measured in grams), histopathologic type (defined as the histopathologic diagnosis of the specimen from the procedure, whether benign, papillary or other types of carcinoma), extrathyroidal extension (defined as the presence or absence of extrathyroidal extension in the final histopathology report), perineural or vascular invasion (defined as either invasion of the nerves or vessels based on the final histopathology report), as well as the presence of parathyroid tissue (note of parathyroid tissue in the excised specimen based on the final histopathology report).

The dependent variables collected were the 6- and 24-hour post-operation corrected calcium levels of the patient measured in mmol/L, computed using the formula:  $Corrected\ Ca = Serum\ Ca + 0.02 (40 - Serum\ Alb)$ . Hypocalcemia was defined as a corrected serum calcium level of less than 2 mmol/L.<sup>2</sup>

All eligible patients were grouped based on whether they were normocalcemic or hypocalcemic, with the hypocalcemia group divided into corresponding subgroups of 6 hours and 24 hours post-operation as per the standard practice of serum calcium determination at the study population's institution. This is based on a study where these two specific points were noted to be useful in predicting whether a patient will develop post-thyroidectomy hypocalcemia, as well as the trend established from both values possibly indicating whether the hypocalcemia will be temporary or permanent.<sup>9</sup> Patients who were hypocalcemic after the 6-hour determination point were no longer included in the population of patients with 24-hour post-operative calcium measurement because they would have received calcium infusions and their second measurement would reflect post-correction values.

**Data Analysis**

Data analysis was performed using Stata version 16.1 (2020, StataCorp LLC, College Station, TX, USA). For all factors, missing values were neither replaced nor imputed. Descriptive statistics utilized for normally distributed continuous numerical variables were means and standard deviations, and medians and interquartile ranges for non-normally distributed continuous numerical as well as discrete numerical variables. Categorical variables were described using frequencies and percentages. Trends in the data were then identified based on the distributions per clinical factor.

The cumulative incidences were presented as point estimates and 95% confidence intervals (95%CI). The association between the clinical factor variables of interest and post-operative hypocalcemia were determined using multivariable logistic regression analysis. The degree of association of each variable of interest in the multivariable model was presented as odds ratios (OR) and 95% confidence intervals (95%CI), both unadjusted (from simple direct logistic regression between the independent and dependent variable) and adjusted (from multiple logistic regression between the same independent variable and dependent variable but holding all other variables in the model constant), the latter being mainly used to establish the association with the outcome of interest.

**RESULTS**

A total of 664 records of patients who met the inclusion criteria were reviewed. Complete records were available for all clinical factors investigated except for thyroid weight, which was not routinely included in the histopathology reports for all patients. The missing values were no longer replaced and the total numbers for each group for this specific factor were adjusted accordingly. *Table 1* shows the

**Table 1.** Patient characteristics according to outcome status

Clinical Factors <sup>a</sup>	Normocalcemic n=380	Hypocalcemic at 6th hour n=192	Hypocalcemic at 24th hour n=92	Total n=664
Patient-related factors				
Age (years) <sup>b</sup>	49 (36.5–59.5)	47 (38–55.5)	52 (41–60)	48.5 (37.5–58.0)
Sex				
Male	67 (17.63%)	25 (13.02%)	5 (5.43%)	97 (14.61%)
Female	313 (82.37%)	167 (86.98%)	87 (94.57%)	567 (85.39%)
Duration of thyroid disease prior to surgery (months) <sup>b</sup>	36 (12–96)	60 (24–132)	42 (22–120)	48 (16–108)
Comorbidities				
Absent	215 (56.58%)	118 (61.46%)	54 (58.70%)	387 (58.28%)
Present	165 (43.42%)	74 (38.54%)	38 (41.30%)	277 (41.72%)
Pre-operative calcium supplementation				
No	113 (29.74%)	47 (24.48%)	27 (29.35%)	187 (28.16%)
Yes	267 (70.26%)	145 (75.52%)	65 (70.65%)	477 (71.84%)
Procedure-related factors				
Type of surgery				
Total thyroidectomy	351 (92.37%)	180 (93.75%)	88 (95.65%)	619 (93.22%)
Completion thyroidectomy	29 (7.63%)	12 (6.25%)	4 (4.35%)	45 (6.78%)
Concomitant neck dissection				
No	294 (77.37%)	147 (76.56%)	66 (71.74%)	507 (76.36%)
Yes	86 (22.63%)	45 (23.44%)	26 (28.26%)	157 (23.64%)
Duration of surgery (hours) <sup>b</sup>	3.42 (2.63–4.50)	3.83 (2.885–5.225)	3.79 (2.800–4.875)	3.67 (2.75–4.83)
Tumor-related factors				
Thyroid gland weight (grams) <sup>b</sup>	41 (23–84) <sup>c</sup>	50 (25–105) <sup>d</sup>	36 (25–81) <sup>e</sup>	44 (23.7–90.0) <sup>f</sup>
Histopathologic type				
Benign	160 (42.11%)	73 (38.02%)	37 (40.22%)	270 (40.66%)
Papillary CA	201 (52.89%)	111 (57.81%)	52 (56.52%)	364 (54.82%)
Follicular CA	6 (1.58%)	3 (1.56%)	1 (1.09%)	10 (1.51%)
Other CA	13 (3.42%)	5 (2.60%)	2 (2.17%)	20 (3.01%)
Extrathyroidal extension				
No	343 (90.26%)	172 (89.58%)	91 (98.91%)	606 (91.27%)
Yes	37 (9.74%)	20 (10.42%)	1 (1.09%)	58 (8.73%)
Perineural or vascular invasion				
No	285 (75.00%)	154 (80.21%)	73 (79.35%)	512 (77.11%)
Yes	95 (25.00%)	38 (19.79%)	19 (20.65%)	152 (22.89%)
Presence of parathyroid tissue in the excised specimen				
No	319 (83.95%)	157 (81.77%)	73 (79.35%)	549 (82.68%)
Yes	61 (16.05%)	35 (18.23%)	19 (20.65%)	115 (17.32%)

<sup>a</sup>Described as frequencies (percentages in parenthesis) unless otherwise stated  
<sup>b</sup>Median (25th–75th percentile in parenthesis)

<sup>c</sup>n = 351

<sup>d</sup>n = 173

<sup>e</sup>n = 86

<sup>f</sup>n = 610



**Table 2.** Cumulative incidence of patients with normocalcemia and hypocalcemia

Calcium Status	Frequency	Cumulative Incidence	
		Point Estimate	95% Confidence Interval
Normocalcemic <sup>a</sup>	380	57.23%	53.37%–61.03%
Hypocalcemic at 6 <sup>th</sup> hour <sup>a</sup>	192	28.92%	25.49%–32.53%
Hypocalcemic at 24 <sup>th</sup> hour <sup>b</sup>	92	19.49%	16.01%–23.36%

<sup>a</sup>Denominator: 664

<sup>b</sup>Denominator: 472 (minus patients noted to be hypocalcemic at 6 hours post-operation)

**Table 3.** Association of clinical factors with hypocalcemia at 6 hours and 24 hours post-operation

Clinical Factors	Hypocalcemia at 6 <sup>th</sup> hour		Hypocalcemia at 24 <sup>th</sup> hour	
	Unadjusted OR <sup>a</sup>	Adjusted OR <sup>b</sup>	Unadjusted OR <sup>c</sup>	Adjusted OR <sup>d</sup>
Patient-related factors				
Age (years)	0.9870 (0.9751–0.9991)	0.9829 (0.9683–0.9978)	1.0132 (0.9971–1.0296)	1.0245 (1.0044–1.0450)
Sex				
Male	Ref.	Ref.	Ref.	Ref.
Female	1.2024 (0.7370–1.9617)	0.9961 (0.5753–1.7245)	3.7246 (1.4561–9.5271)	3.4877 (1.2623–9.6362)
Duration of thyroid disease prior to surgery (months)	1.0020 (1.0005–1.0036)	1.0017 (0.9998–1.0035)	1.0010 (0.9988–1.0032)	0.9989 (0.9962–1.0015)
Comorbidities				
Absent	Ref.	Ref.	Ref.	Ref.
Present	0.8310 (0.5897–1.1711)	0.9824 (0.6498–1.4854)	0.9169 (0.5777–1.4553)	0.8281 (0.4693–1.4612)
Pre-operative calcium supplementation				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.3009 (0.8864–1.9094)	1.3415 (0.8735–2.0603)	1.0189 (0.6181–1.6794)	0.9487 (0.5364–1.6779)
Procedure-related factors				
Type of surgery				
Total thyroidectomy	Ref.	Ref.	Ref.	Ref.
Completion thyroidectomy	0.8869 (0.4479–1.7560)	0.6987 (0.2905–1.6805)	0.5502 (0.1885–1.6058)	0.8352 (0.2616–2.6670)
Concomitant neck dissection				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.9840 (0.6625–1.4614)	0.7555 (0.4632–1.2324)	1.3467 (0.8059–2.2506)	1.2726 (0.6857–2.3616)
Duration of surgery (hours)	1.0383 (0.9843–1.0952)	1.0294 (0.9639–1.0993)	1.0712 (1.0026–1.1445)	1.1216 (1.0301–1.2211)
Tumor-related factors				
Thyroid gland weight (grams)	1.0021 (1.0002–1.0041) <sup>b</sup>	1.0017 (0.9995–1.0039)	1.0009 (0.9980–1.0037) <sup>d</sup>	1.0012 (0.9979–1.0044)
Histopathologic type				
Benign	Ref.	Ref.	Ref.	Ref.
Papillary CA	1.1840 (0.8350–1.6787)	1.3616 (0.8949–2.0719)	1.1187 (0.6993–1.7898)	1.5796 (0.8985–2.7771)
Follicular CA	1.1566 (0.2913–4.5922)	1.8348 (0.4380–7.6866)	0.7207 (0.0842–6.1686)	0.6888 (0.0737–6.4353)

Other CA	0.8995 (0.3157–2.5633)	1.2162 (0.3994–3.7030)	0.6653 (0.1439–3.0756)	0.8111 (0.1580–4.1647)
Extrathyroidal extension				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.3280 (0.7514–2.3472)	1.7357 (0.8368–3.6001)	0.1019 (0.0138–0.7525)	0.0700 (0.0086–0.5684)
Perineural or vascular invasion				
No	Ref.	Ref.	Ref.	Ref.
Yes	0.7749 (0.5128–1.1710)	0.6098 (0.3538–1.0509)	0.7808 (0.4480–1.3610)	0.7787 (0.3783–1.6030)
Presence of parathyroid tissue in the excised specimen				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.0924 (0.7048–1.6931)	1.1887 (0.7436–1.9002)	1.3611 (0.7664–2.4172)	1.5746 (0.8406–2.9496)

<sup>a</sup>n = 664 unless otherwise stated

<sup>b</sup>n = 610

<sup>c</sup>n = 472 unless otherwise stated

<sup>d</sup>n = 437

various patient characteristics as well as their distribution based on the patient's postoperative serum calcium level.

The median age of patients was 48.5, with the majority being females (85.4%), with no comorbidities (58.3%). Median duration of thyroid disease was 48 months (ranging from 16 to 108 months) and a majority of the patients were given preoperative calcium supplementation (71.8%). Most (93.22%) underwent total thyroidectomy as their main surgical procedure, with only 6.78% having undergone completion thyroidectomy. Concomitant neck dissection of varying types were performed in 23.64% of patients alongside their primary thyroid surgery. Median duration of surgery was 3.67 hours (ranging from 2.75 to 4.83 hours). The median tumor weight was 44 g (ranging from 23.7 g to 90 g). Majority of the final histopathologic reports revealed papillary thyroid carcinoma (54.82%), with extrathyroidal extension (8.73%), perineural or vascular invasion (22.89%), and presence of parathyroid tissue (17.32%).

Table 2 shows the cumulative incidence of hypocalcemia at the two time points, with the incidence at 6 hours post-operation being 28.92% (95%CI: 25.49%–32.53%) and the hypocalcemic patients based on the second serum calcium determination at 24 hours post-operation having a cumulative incidence of 19.49% (95%CI: 16.01%–23.36%).

For patient-related factors, in terms of duration of disease, it was noted that the hypocalcemic group at 6 hours and 24 hours had a longer median duration of disease prior to surgery (at 60 months and 42 months respectively) compared to the normocalcemic group. For procedure related factors, it was observed that for both hypocalcemic groups at 6 and 24 hours post-operation, the median durations of surgery were slightly increased (3.83 hours and 3.79 hours, respectively)

compared to the median for the normocalcemic group of 3.42 hours. For tumor-related factors, in terms of the average thyroid gland weight (with the population adjusted accordingly due to the missing data), it was noted that the median was higher for those with hypocalcemia at 6 hours post-operation (50 grams) compared to those in the normocalcemic group (41 grams).

Table 3 shows that among patient-related factors, female sex was associated with the highest odds ratio (OR) for developing hypocalcemia. The odds of having hypocalcemia at 24 hours post-operation was 3.5x higher for females than males while holding all other variables constant (95%CI: 1.2623–9.6362). Interestingly, the odds of hypocalcemia at 24 hours post-operation was 1.3x higher for those who had preoperative calcium supplementation compared to those who did not receive calcium supplementation (95%CI: 0.8735–2.0603), and 1.2x higher in patients without comorbidities (adjusted OR: 0.83; 95%CI: 0.4693–1.4612). Meanwhile, the age of patients and duration of thyroid disease prior to surgery did not seem to be associated with hypocalcemia.

In terms of procedure-related factors, the odds of developing hypocalcemia at 6 hours and 24 hours post-thyroidectomy for total thyroidectomy cases were 1.4 (adjusted OR: 0.70; 95%CI: 0.2905–1.6805) and 1.2x (adjusted OR: 0.84; 95%CI: 0.2616–2.6670) higher compared to completion thyroidectomy cases, respectively. Concomitant neck dissection had differing results at the two time points: 1.4x higher odds of hypocalcemia at 6 hours post-operation for those without concomitant neck dissection (adjusted OR: 0.76; 95%CI: 0.4632–1.2324), while having a 1.3x higher odds at 24 hours post-operation for those who underwent neck dissection (95%CI: 0.6857–2.3616), with all other variables held constant. Finally, duration of the surgery was associated with a minimal increase in the odds for hypocalcemia at 24 hours post-operation (adjusted OR: 1.12; 95%CI: 1.0301–1.2211).

Finally, most tumor-related factors included in our study showed some association with the development of hypocalcemia at 6 hours and 24 hours post-thyroidectomy except for thyroid weight. Compared to having benign histopathologic findings, the adjusted odds of developing hypocalcemia at 6 hours post-thyroidectomy were increased with malignant histopathologic types, with follicular carcinoma at 6 hours post-operation being the highest (adjusted OR: 1.83; 95%CI: 0.4380–7.6866), followed by papillary thyroid carcinoma (adjusted OR: 1.36; 95%CI: 0.8949–2.0719), and finally, all other histopathologic subtypes of carcinoma (adjusted OR: 1.22; 95%CI: 0.3994–3.7030). Interestingly, at 24 hours post-thyroidectomy, the odds of hypocalcemia were only higher with the papillary subtype (adjusted OR: 1.58; 95%CI: 0.8985–2.7771), while it became lower for those with findings of follicular (adjusted OR: 0.69; 95%CI: 0.0737–6.4353)

and other carcinomas (adjusted OR: 0.81; 95%CI: 0.1580–4.1647), compared to benign findings. The presence of parathyroid tissue in the final histopathology report was also noted to have higher odds for hypocalcemia, 1.2x at 6 hours post-operation (95%CI: 0.7436–1.9002) and 1.6x at 24 hours post-operation (95%CI: 0.8406–2.9496), while holding all other variables constant. On the other hand, the absence of perineural or vascular invasion had higher odds of hypocalcemia at both 6 hours (adjusted OR: 0.61; 95%CI: 0.3538–1.0509) and 24 hours (adjusted OR: 0.78; 95%CI: 0.3783–1.6030) post-operation. Lastly, the odds of hypocalcemia at 6 hours post-thyroidectomy were 1.7x higher for those with documented extrathyroidal extension (adjusted OR: 0.1; 95%CI: 0.0138–0.7525), but the adjusted odds were 14.29x higher for the absence of extrathyroidal extension (adjusted OR: 0.07; 95%CI: 0.0086–0.5684) at 24 hours post-thyroidectomy. It is important to note however that only a single patient was included under the extrathyroidal extension variable at this time point, and thus interpretation of the result should take this into account.

## DISCUSSION

The cumulative incidences of hypocalcemia in the study are 28.92% and 19.49% at 6 hours and 24 hours post-thyroidectomy, respectively. In terms of the clinical factors, only female sex was statistically significant. The rest of the factors were associated with higher odds for post-operative hypocalcemia but were not considered statistically significant, which include presence of pre-operative calcium supplementation and absence of comorbidities for patient-related factors; total thyroidectomy, duration of surgery, both the presence and absence of neck dissection for procedure-related factors; and histopathologic type, presence of parathyroid tissue, presence of extrathyroidal extension, as well as the absence of perineural or vascular invasion for tumor-related factors.

The postoperative hypocalcemia incidences for this population are consistent with or are slightly higher than previously reported incidences of hypocalcemia, from 6.9% to 23% in centers abroad such as in the studies of Torabi *et al.*<sup>10</sup> and Sharifi *et al.*,<sup>11</sup> to 11.98% in a local study by Tongol and Mirasol.<sup>2</sup> These differences may be attributed to the different factors present in each patient population, with the study population's institution being a tertiary hospital of a different region compared to the first two studies cited, and a local government hospital compared with the local private hospital in the latter cited study.

For the clinical factors noted, female sex had the highest odds ratio at 24 hours post-operation and the only one that was statistically significant. This is consistent with the findings of Sands *et al.* that female patients (24.7%) had a significantly higher incidence of transient postoperative hypocalcemia compared to men (11.8%;  $p < .05$ ) with a



relative risk ratio of 2.1 (95%CI: 1.0-4.6).<sup>12</sup> Although specific mechanisms are still not well understood, this may be attributed to physiologic and anatomic differences between males and females. Examples of these include the effect of having female sex steroid and cortisol receptors in parathyroid tissue,<sup>13</sup> males possessing polymorphisms of regulatory genes providing an advantage in terms of proliferation and mitosis of parathyroid tissue,<sup>14</sup> and the morphologic differences between the parathyroid glands of males and females.<sup>15</sup>

In terms of pre-operative calcium supplementation, it was surprising to note that at the 6-hour postoperative time point, there were higher odds of hypocalcemia for those with calcium intake prior to surgery. This is contrary to its previously reported protective effects by increasing pre-operative serum calcium levels in the randomized control trial of Sittitrai *et al.*<sup>16</sup> and the study of Arer *et al.*<sup>17</sup> However, this may be one of the limitations of our study, as preoperative calcium intake was only presented as a dichotomous variable, given that the specifics regarding onset and duration of intake especially prior to admission were not often uniformly noted in the medical records. Therefore, it would be prudent in future studies to establish a proper temporal relationship between pre-operative supplementation and the odds of having postoperative hypocalcemia.

It was also noted that the absence of comorbidities had a higher odds for hypocalcemia based on the results of the study. There is no broad conclusion made with regards to having comorbidities in general and its association with hypocalcemia in the literature, given the wide range of possible comorbidities a patient might have. Another study noted that those who had postoperative hypocalcemia were less likely to have medication-requiring hypertension, which correlates the outcome with one specific individual comorbidity.<sup>7</sup> There is an option for future studies to look into each of the many comorbidities and their individual association with postoperative hypocalcemia.

For procedure-related factors, one clinical factor associated with hypocalcemia was a concomitant neck dissection. This is consistent with the findings of Torabi *et al.* that a central neck dissection was significantly associated with increased rates of hypocalcemia, as this type of procedure is done in more advanced stages of thyroid carcinoma with higher risk for parathyroid injury given the more involved surgical procedure done.<sup>10</sup> However, in our study the odds ratios differed between the two time points as well, and at 6-hours post-operation it was the absence of neck dissection that was associated with hypocalcemia. Further studies may establish a more definite explanation for this specific clinical factor.

In terms of the type of surgery, the data shows that total thyroidectomy cases had higher odds for hypocalcemia compared to cases that involved completion thyroidectomy. In most patients

completion thyroidectomy only entailed manipulation of a remaining lobe and its adjacent structures, with less parathyroid glands at risk of injury. Moreover, the time between procedures may also have allowed any potentially affected parathyroid glands to have recovered function that may have been lost after the first surgery.<sup>1</sup> However, the cited study was not able to establish any significant association between type of surgery and hypocalcemia.

For tumor-related factors, histopathologic diagnosis of carcinomas in general as well as extrathyroidal extension were noted clinical factors associated with hypocalcemia. Both factors can be markers of the aggressive nature of a given thyroid mass, leading to a more difficult surgery due to invasion of adjacent structures and often difficult planes of dissection, which could increase the likelihood of parathyroid gland injury or removal.<sup>11</sup> However, at 24 hours post-operation the odds ratio shifted to where there were now higher odds for a benign lesion to have hypocalcemia compared to a follicular carcinoma or other type of carcinoma, as well as higher odds for hypocalcemia with the absence of extrathyroidal extension. This may be due to the small number of patients for each of these groups at this time point, and interpretation of this specific set of odds ratios should take this limitation into account. This reasoning may be applied as well to the odds ratios for those with perineural or vascular invasion, where it was their absence that had higher odds for hypocalcemia.

One of the more straightforward clinical factors in terms of mechanisms for hypocalcemia was the presence of parathyroid tissue in the final histopathology report. This would imply that portions of the parathyroid glands were removed intraoperatively, causing a decrease in parathyroid hormone secretion and subsequently in the post-operative serum calcium levels. A previous study found that the most significant predictor of hypocalcemia on bivariate analysis was intraoperative injury of the parathyroid glands (adjusted OR: 2.5; 95%CI: 1.11-5.59).<sup>18</sup> These results highlight the importance of surgeons being careful with manipulation and preservation of the parathyroid glands during thyroid surgery, and that training institutions should ensure that proper surgical techniques are taught in dissecting along the thyroid and preserving all four glands.

Other limitations of our study include data collection being done only by a review of medical records which did not provide any means to validate variables, such as details on exact onset and duration of pre-operative calcium supplementation. Our results are also limited by the size of the population, with some groups having only a small number of patients. Our study also only considered transient hypocalcemia as its outcome, with the option for future studies to further investigate clinical factors influencing cases of permanent hypocalcemia. Moreover, pre-operative serum calcium determination was not always done, and

there may be patients that were already hypocalcemic even prior to the surgery that may affect the outcomes of our results. It is suggested that a prospective study be done in the future to assure a more complete set of independent variables. Finally, the study population was limited to a single tertiary hospital in the country, and it may be difficult to generalize the results of our study to a broader range of patients who undergo thyroidectomy in other institutions.

In conclusion, the identified clinical factors associated with hypocalcemia from our study population were female sex for patient-related factors, total thyroidectomy as the type of surgery for procedure-

related factors, and the papillary thyroid carcinoma histopathologic type as well as the presence of parathyroid tissue in the excised specimen for tumor-related factors, with female sex being the only one that was statistically significant. As of the time of our study, we are not aware of any definite guidelines for pre-operative serum calcium determination as well as pre-operative calcium supplementation in our institution. Identifying patient groups with higher odds for postoperative hypocalcemia can help serve as a guide for further studies to determine possible interventions for these cases.

**ACKNOWLEDGEMENTS**

We thank Dr. Nathaniel W. Yang, Dr. Agnes N. Tirona-Remulla, Dr. Christine Joy S. Arquiza, and Dr. Kimberly Mae C. Ong-Nelson for their valuable inputs in helping amend and clarify certain points of our study. We also thank our research assistant Ms. Joan Pepito for her hard work in helping facilitate the data collection for our study, Ms. Micah Dolores Dispo (MSPH Biostatistics) for her valuable inputs for the statistical analysis of our study, and Dr. Leslie Faye T. Cando for her very insightful comments and suggestions with regards to the structure and presentation of this written manuscript.

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