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Factors Predicting Post-thyroidectomy Hypoparathyroidism Recovery

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Abstract
Background Hypoparathyroidism is the most common complication after thyroidectomy and the main reason for frequent outpatient visits; however, there is a poor understanding of its outcomes and no clear follow-up strategies are available. We aimed to predict post-thyroidectomy hypoparathyroidism outcomes and identify relevant factors.
Methods A multicenter, standardized prospective study was conducted. The parathyroid hormone level (PTH) was measured preoperatively and at the first hour after surgery, then at each outpatient follow-up visit after 1 week, 3 weeks, and 1 month, and then every 2 months, until it either reached normal values or up to 6 months. Cox proportional hazard modeling was used to determine the factors that affect PTH recovery. A Weibull distribution model was used to predict time to recovery. Both models were evaluated by goodness of fit.
Results A total of 186 patients were enrolled in the study; 53 (28.5 %) developed hypoparathyroidism, 47 of them (88.6 %) females. Their mean age was 41.2 years, and 11.4 % were diabetic. Of these women, 33 (62.3 %) recovered within 1 month, 10 (18.9 %) recovered after 1 month but within 6 months, 7 (13.2 %) did not recover within 6 months, and 3 (5.6 %) missed follow-up. Factors that are found to affect and predict the speed of recovery were the preoperative PTH level, perioperative percent drop in PTH level, diabetes mellitus, and gender.
Conclusions This study provides potentially useful information for early prediction of PTH recovery, and it highlights the factors that affect the course of hypoparathyroidism recovery, which in turn should be reflected in better patient management, improved patient satisfaction, and overall cost-effectiveness.

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Introduction

Hypocalcemia is the most common significant complication after thyroidectomy [1]. It is mostly caused by hypoparathyroidism, which usually occurs as a result of inadvertent gland injury, removal, or devascularization [2]. Because of its complexity, it represents the main reason for prolonged postoperative follow-up. Post-thyroidectomy hypocalcemia requires frequent calcium and vitamin D blood monitoring and dose management, which adds to patient discomfort and increases the cost of care.

There is controversy regarding the exact definition of transient and permanent (persistent) post-thyroidectomy hypocalcemia and hypoparathyroidism, as well as the appropriate duration of resulting follow-up [3]. While most of the literature considers 6 months postoperatively as a cut-off time to differentiate between transient and permanent [3, 4], other authors recommend 1 year [5]. Recovery within the first postoperative month can be expected in the majority of patients [6, 7].

Parathyroid hormone (PTH) level is an excellent early predictor of post-thyroidectomy hypocalcemia [2], but it is not known if it can be used as a prognostic factor for the eventual outcome of post-thyroidectomy hypocalcemia.

The aim of the present study was to determine, among post-thyroidectomy patients with hypoparathyroidism, the factors that significantly affect the likelihood for PTH recovery and simultaneously to determine the distribution of the time-to-recovery. We hypothesized that the severity of parathyroid gland injury, reflected by the magnitude of the postoperative PTH level decline, can be used in conjunction with other patient characteristics to predict the outcome of post-thyroidectomy hypocalcemia.

Materials and methods

To achieve the goals of this study, a prospective, multicenter standardized protocol was applied over three years (November 2009 to November 2012). The study was conducted in two tertiary care centers: King Fahad Medical City and King Abdulazeez University Hospital in Riyadh, Saudi Arabia. The authors obtained Institutional Review Board approval before implementing the protocol and data collection.

Demographic and clinical data were determined as follows:

- The following baseline tests were obtained on admission to the hospital: PTH, vitamin D3 (1,25 dihydroxyvitamin D), corrected calcium (cCa), electrolytes, renal and thyroid function.
- During the first postoperative hour measurement of the PTH level was repeated in the recovery room, and a 6 h PTH level was obtained in the ward.
- Patients with a 6 h PTH $\leq$1.7 pmol/L (approximately 15.5 pg/mL, conversion factor is 0.11) were defined as hypoparathyroid, and those patients were considered to be at high risk of hypocalcemia. This definition is based on our previous published data, from a similar patient cohort [2].
- Hypocalcemic patients were those who had symptoms (e.g., circumoral and finger numbness) with or without signs (e.g., carpopedal spasm and Chvostek's sign), with an associated cCa level $\leq$2 mmol/L (8 mg/dL, conversion factor is 0.25) and a normal magnesium level.
- Low-risk patients (PTH >1.7 pmol/L) were discharged on the first postoperative day with a follow-up appointment scheduled for one week postoperatively. No further testing was done for those patients unless they exhibited symptoms or signs of hypocalcemia at the time of the follow-up visit.
- Hypoparathyroid patients were followed up to 6 months or until PTH levels returned to normal, according to the following protocol:
    - Patients were instructed to come to the clinic at 1 week, 3 weeks, 1 month, and 2 months from the time of hospital discharge
    - During every clinic visit PTH and cCa levels were measured, and patients were assessed for symptoms and signs of hypocalcemia; calcium and vitamin D doses were managed accordingly
    - After 6 months follow-up, if the patient's PTH level rose above 1.7 pmol/L with no further hypocalcemic manifestations, the patient's condition was labeled as (transient hypoparathyroidism), but if the PTH level remained $\leq$1.7 pmol/L, it was labeled as (prolonged hypoparathyroidism).

Patients with less than total thyroidectomy (unless completion) or with concomitant parathyroidectomy were excluded. Serum intact PTH levels were measured by electrochemiluminescence immunoassay (Roche Elecsys System 2010, Roche Diagnostics, Mannheim, Germany), with normal reference (1.6–6.9 pmol/L).

Statistical methods

Sample size

The outcome measure for this study was time to reach a PTH level of at least 1.7 pmol/L. According to the Cox model with at most two dichotomous covariates indicating a 1.75–2.25 likelihood ratio for PTH recovery, a sample size of 50 hypoparathyroidism patients was deemed adequate to produce a statistical power of at least 0.88 with a 0.05 significance level.

Outcome measures The main outcome measure for this study is the first time to reach a PTH level of at least 1.7 pmol/L; for that, Kaplan-Meier (KM) analysis [8] was used univariately to determine time-to-recovery distributions and associated distributional cut-points. In addition, KM was used to guide the analysis and inclusion of potential covariates into the multivariate model. Modeling was pursued to accomplish three goals: (1) estimation of likelihood of PTH recovery with group-wise comparisons of hazard (i.e., likelihood) functions through hazard ratios (HR); (2) model-based prediction of time to PTH recovery; and (3) modeling methodology and selection of model predictors.

Modeling methodology and selection of model predictors Goals one and two were accomplished via Cox proportional hazard modeling [9]. This also included testing for the constant proportionality assumption. Goal three was accomplished by seeking a parametric lifetime regression model (accelerated failure-time model) that explored several known time-to-recovery distributions including the Weibull [10], exponential, gamma, lognormal, and log-logistic. Accordingly, a suitable parametric model was selected to portray the time to PTH recovery as a function of clinical and demographic covariates.

The covariates sought for modeling included preoperative PTH, percent of drop at perioperative PTH testing, type of surgery, pathology, thyroid function status, surgeon, body mass index (BMI), age, gender, renal disease, and diabetes mellitus.

Models were evaluated and validated with Akaike's information criteria (AIC), (AICC) which is AIC with a correction for finite sample sizes, and a −2 log likelihood test.

Selection of cut-points for the two covariates of perioperative PTH percent drop and preoperative PTH was accomplished using receiver operating characteristic (ROC) logistic regression analysis that pursued cut-points with the most optimal sensitivity and specificity. Accordingly, a cut-point of 88 % or more for the perioperative PTH percent drop and the value 5 for preoperative PTH were selected. Statistical analysis and figures were performed using SAS 9.3 software.

Table 1 Clinical characteristics of studied patients

Characteristics	Number (%) All cases ($n = 186$)	Number (%) Hypoparathyroid cases ($n = 53$)
Type of surgery		
Total thyroidectomy (TT)	133 (72.6)	35 (66.0)
TT + unilateral neck dissection	5 (2.7)	2 (3.8)
TT + bilateral neck dissection	4 (2.2)	4 (7.5)
TT + central neck dissection	5 (2.7)	2 (3.8)
Completion thyroidectomy	34 (18.5)	9 (17.0)
Completion + bilateral neck dissection	2 (1)	1 (1.9)
Thyroid pathology		
Multinodular goiter	57 (31.5)	18 (34.0)
Papillary thyroid carcinoma	70 (38.6)	23 (43.4)
Follicular thyroid carcinoma	3 (1.6)	1 (1.9)
Hurthle cell adenoma	7 (3.8)	2 (3.7)
Follicular adenoma	6 (3.3)	2 (3.7)
Hashimoto's thyroiditis	19 (10.5)	3 (5.6)
Graves' disease	7 (3.8)	1 (1.9)
Lymphocytic thyroiditis	9 (5)	3 (5.6)
Medullary thyroid carcinoma	1 (0.5)	0
Large B-cell lymphoma	2 (1)	0
Clinically classified thyroid function		
Normal	131 (70.4)	39 (73.6)
Hypothyroidism	43 (23.1)	12 (22.6)
Hyperthyroidism	12 (6.4)	2 (3.7)

Results

Fifty-three patients (28.5 %) of the 186 patients originally enrolled in the study developed post-thyroidectomy hypoparathyroidsim (i.e., PTH was $\leq$1.7 pmol/L). Of those 53 patients, 47 (88.6 %) were females; their mean age was 41.2 years (17–79 years), 6 (11.4 %) were diabetics, their mean (median) BMI was 31.1 (30.7) kg/m^2, and 17 % had thyroidectomy with neck dissection. Other clinical characteristics are summarized in Table 1. Of the 53 hypoparathyroid patients studied, 41 (77.4 %) patients were recruited from King Fahad Medical City (KFMC) and 12 (22.6 %) came from King Abdulazeez University Hospitals (KAUH).

Forty-three of the 53 (81.1 %) patients had their PTH level return to normal within 6 months of follow-up (hypoparathyroidism traditionally defined as transient). In 33 of these 43 patients (76.7 %) the PTH level reverted to normal within 1 month, which represents 62.3 % of the total 53 with hypoparathyroidism. Of the 53 hypoparathyroid patients, 7 (13.2 %) had not recovered after 6 months of follow-up, and the remaining three patients (5.6 %) were lost to follow-up. Follow-up beyond 6 months showed that of the seven patients who did not recover, the PTH level reverted to normal in one patient before the end of the first year, two patients did not recover, and four patients were lost to follow-up after 6 months (as our initial end point was 6 months in the study protocol). Of these seven patients, three had total thyroidectomy alone, two had completion thyroidectomy, and two had total thyroidectomy with neck dissection.

Overall, KM estimates of median time to PTH recovery was 13 days; the mean ± SE was 32.7 days ± 6.67 (min, max) were (5 and 150) days.

Main effects hazard (likelihood) of PTH recovery (reversion to PTH >1.7 pmol/L)

Adjusting for age, gender, BMI, and type of surgery, Cox proportional hazard modeling indicated that preoperative PTH and perioperative PTH percent drop significantly influenced the likelihood of PTH recovery (Table 2). Compared to patients with <88 % perioperative PTH drop, those with $\geq$88 % PTH drop had only about a 10 % chance of PTH recovery within 6 months (0.096 HR, $p = 0.0003$).

At the same time, those with preoperative PTH ≥5 pmol/L, as compared to those with preoperative PTH <5, had a 5.8-fold increase in the likelihood of PTH recovery ($p = 0.001$). Lastly, although diabetes mellitus HR was borderline significant, perhaps because of sample size limitations, diabetics in this sample had about one third (relative to nondiabetics) the likelihood that PTH will revert to normal within 6 months of follow-up. Figure 1a–d depicts the pronounced differences in the likelihood distributions (survival curves) for stratified levels at each of preoperative PTH, perioperative PTH percent drop, DM, and gender, respectively.

Time to PTH Recovery

The parametric Weibull distribution was found to fit the data, which postulated log of time to PTH recovery as a function of several potential predictors. Consequently, adjusting for age and gender, perioperative PTH percent

Table 2 Cox proportional hazard model maximum likelihood estimates of hazard of PTH recovery (α = 0.05 for CI)

Parameter	Reference	Estimate	SE	*p* value	Hazard ratio	95 % confidence limits
Gender	Females	−0.52974	0.82427	0.5204	0.589	0.11 to 2.96
BMI	Unit increase	0.09748	0.03919	0.0129	1.102	1.02 to 1.19
Age	Unit increase	0.00517	0.01631	0.7512	1.005	0.97 to 1.03
Type of surgery	Without neck dissection	−0.13942	0.63536	0.8263	0.870	0.25 to 3.02
PTH percent drop	<88 % vs ≥88 %	−2.34273	0.64665	0.0003	0.096	0.02 to 0.34
Preoperative PTH	<5 vs ≥5 pmol/L	1.74950	0.53034	0.0010	5.752	2.03 to 16.26
Diabetes mellitus	Nondiabetic vs diabetic	−1.12593	0.65732	0.0867	0.324	0.08 to 1.17

SE standard error, *BMI* body mass index, *PTH* parathyroid hormone

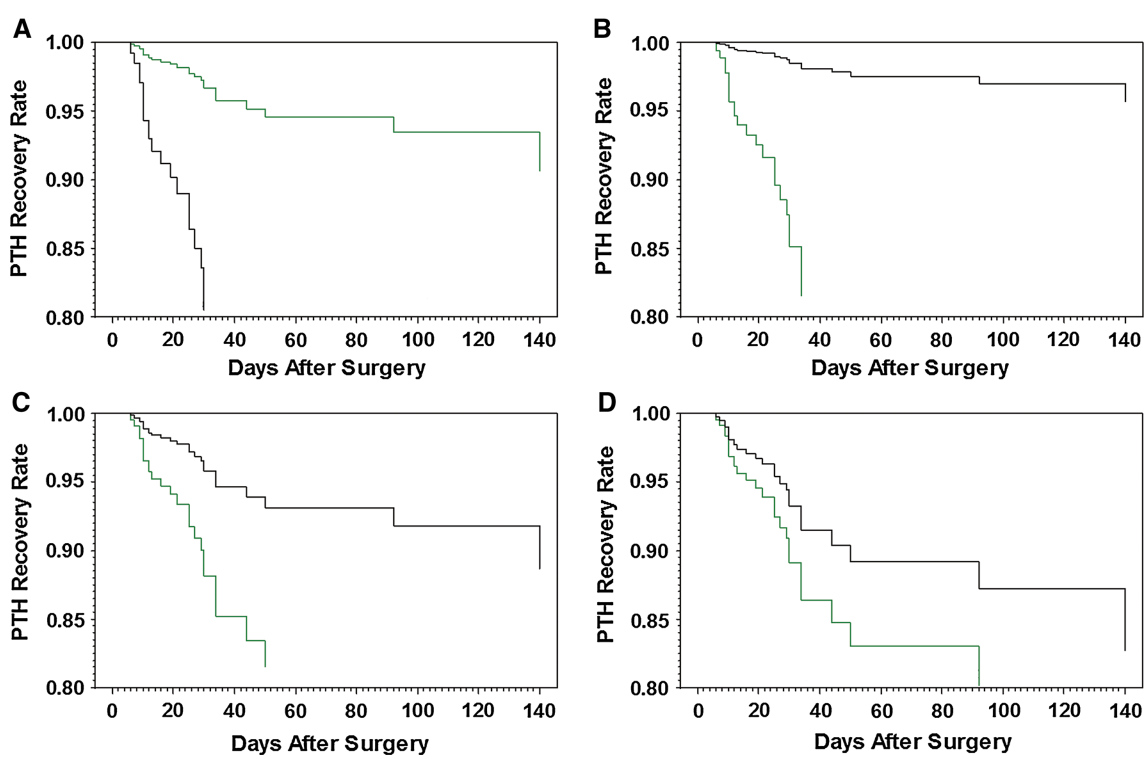

Fig. 1 Cox proportional hazard model adjusted parathyroid hormone (PTH) recovery (PTH >1.7) rate by influential covariates. **a** Preoperative PTH <5 (*green line*) versus ≥5 pmol/L (*black line*), **b** perioperative PTH percent of drop <88 % (*green line*) versus ≥88 % (*black line*), **c** diabetic patients (*black line*) versus nondiabetic patients (*green line*), **d** Male (*green line*) versus female (*black line*) (Color figure online)

Table 3 Estimates of postoperative time to reaching PTH level of 1.7 based on parametric Weibull survival distribution modeling of patients who recovered within 6 months

Covariate	Distributional cut-points for time to recovery by days			
	Mean ± SE	25th	50th	75th
Perioperative PTH % drop				
≥88 %[a]	34.6 ± 11.3	10	21	34
<88 %	26.9 ± 6.5	7	12	30
Preoperative PTH				
≥5[a] pmol/L	20.8 ± 5.6	7	10	21
<5 pmol/L	38.2 ± 10.1	10	25	44
Diabetes mellitus				
Yes	60.2 ± 29.3	9	22	150
No	27.2 ± 5.6	9	13	30
Gender				
Male	47.0 ± 3.0	44	47	50
Female	31.7 ± 7.0	9	12	30

[a] Based on logistic regression receiver operating characteristic (ROC) analysis

drop, preoperative PTH level, BMI, and diabetes mellitus were identified as the main influential covariates (Table 3). The model that predicts time to PTH recovery is determined by the specific attributes (levels) for the patients in terms of these identified factors. The model coefficients of these identified covariates, as shown in Table 4, are for a female nondiabetic patient with preoperative PTH of <5 pmol/L and a PTH percent drop ≥88 %. The intercept then corresponds to patients in the reference categories of these factors; namely a male diabetic patient with a preoperative PTH of ≥5 pmol/L and a PTH percent drop <88 %. Table 4 also relies on the acceleration factor by which median PTH recovery (or any other distributional cut-point like percentiles or the mean) is multiplied to reflect the effect of that level. The prediction of the Weibull model produces, for any set of covariate values, a distribution of times to PTH recovery. Furthermore, Table 4 shows that the scale parameter of the fitted Weibull model is 0.7539 ± 0.096, which indicates an increasing likelihood for PTH recovery as time goes on.

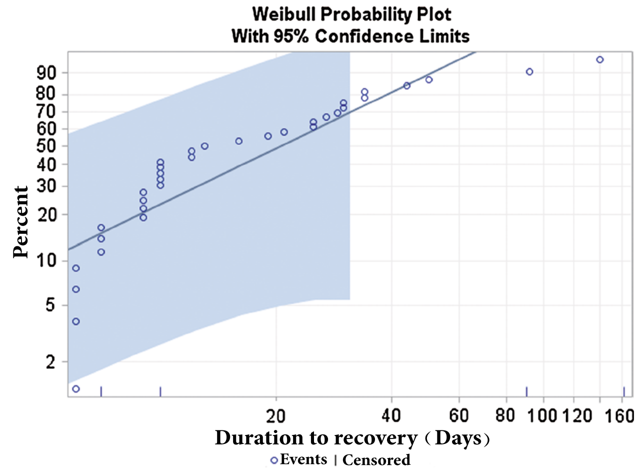

Fig. 2 Goodness of fit of the Weibull time to recovery prediction model. Almost all of the recovered patients were within the 95 % confidence interval (*blue shaded area*) of the model prediction. *Events* patients in whom PTH recovered; *Censored* patients in whom PTH did not recover (Color figure online)

Model validations

Figure 2 indicates that the Weibull distribution fits the data very well, as most of the data points fall within the 95 % confidence limits. Similarly, the −2 log likelihood, AIC, and AICC fit statistics all indicate an adequate fit for the Weibull distribution (Table 4).

Discussion

Post-thyroidectomy hypoparathyroidism is a major cause of prolonged outpatient follow-up and hospital care cost; however, there is a poor understanding of its prognosis, outcomes, and follow-up strategies. To our knowledge, a prospective attempt to enhance the understanding of this question was never made.

Sitges-Serra et al. [6], in a retrospective review of patients who had post-thyroidectomy hypoparathyroidism, found that parathyroid function recovered in 59 % of

Table 4 Analysis of maximum likelihood parameter estimates

Parameter	Reference	Estimate	SE	Acceleration factor	*p* value
Preoperative PTH	<5 pmol/L	1.4408	0.3318	3.22	<0.0001
Gender	Female	−0.2348	0.6010	−0.209	0.6960
Diabetes mellitus	Nondiabetic	−1.0105	0.4817	−0.636	0.0359
BMI	Unit increase	−0.0652	0.0240	−6.312	0.0066
Age	Unit increase	−0.0120	0.0122	−1.193	0.3249
PTH % of drop	≥88 %	1.8961	0.4012	5.66	<0.0001
Scale		0.7539	0.0960		
Weibull shape		1.3264	0.1690		

Model goodness of fit: −2 log likelihood (90.896), AIC (106.896), and AICC (111.696) patients within 1 month, whereas 80 patients (36 %) developed protracted hypoparathyroidism, with 78 % reaching normal parathyroid function within 1 year. Protracted hypoparathyroidism was defined as an intact parathyroid hormone (iPTH) level below 13 pg/mL with a need for calcium supplementation at 1 month after thyroidectomy. Factors associated with late recovery of parathyroid function were higher serum calcium and low but detectable iPTH levels 1 month after surgery, while parathyroid autotransplantation did not protect against permanent hypoparathyroidism.

Youngwirth et al. [7] retrospectively reviewed patients who had total or completion thyroidectomy. Thirty-three (12 %) of them had PTH deficiency (PTH levels <10 pg/mL), 24 patients (73 %) had recovery of their PTH levels to ≥10 pg/mL at their 1-week follow-up appointment, and (27 %) patients still had PTH levels <10 pg/mL. With long-term follow-up (up to 1 year), (82 %) patients had recovered, with a PTH level of ≥10 pg/mL, while (18 %) patients had a serum PTH level <10 pg/mL.

This study attempted to enhance the understanding of the course of post-thyroidectomy hypoparathyroidism by providing early determination of expected time to PTH recovery (reaching ≥1.7 pmol/L). The clinical factors that were found to be statistically significant in affecting PTH recovery were: perioperative PTH percent drop, preoperative PTH level, diabetes mellitus status, gender, BMI, and age. Cut-off values used for perioperative PTH percent drop and preoperative PTH level were based on ROC analysis that predicted PTH recovery with high level of accuracy. This, in turn, potentially adds to the clinical knowledge of a patient's prognosis to better manage that patient's course of calcium and vitamin D treatment and follow-up, therefore potentially resulting in patient satisfaction and health care cost efficiency.

Factors affecting the rate of parathyroid gland function Recovery

Preoperative PTH level represents the baseline function of the parathyroid glands while the percentage of drop in the perioperative PTH level represents how severely the glands were injured. Our findings show that patients with either preoperative PTH ≥5 pmol/L or a PTH drop <88 % will need less time to recovery than those with preoperative PTH <5 pmol/L or a PTH drop ≥88 %. Based on the acceleration factor (Table 4) and keeping the value of other covariates fixed, the median time for reaching normal PTH for those with <5 pmol/L preoperative PTH is expected to be 3.2-fold longer than the time taken by those with ≥5 pmol, which might be explained by the fact that these patients had better baseline parathyroid gland function. Similarly, the median time for patients with at least an 88 % PTH drop is expected to be 5.7-fold longer than the time to recovery of those with a <88 % PTH drop. It is of interest to note that patients with diabetes mellitus tend to have a more prolonged time to recovery than nondiabetic patients (2.7-fold the time for nondiabetics). This finding can probably be explained by the fact that diabetes mellitus affects angiogenesis and delays the wound healing process [11].

Transient and permanent hypoparathyroidism

Post-thyroidectomy hypocalcemia/hypoparathyroidism outcomes are traditionally classified as either transient and permanent, with existing controversy surrounding the cutoff duration that is used for those definitions (either 6 months [3, 4] or 1 year [5, 12]. Results from the present study, along with sparse published data on these thresholds [6, 7], do not support these definitions. A suggested redefinition of these cut-points based on our results is to define post-thyroidectomy hypoparathyroidism as *transient* if PTH recovers within one month, as *protracted* if recovery occurs between 1 month and 1 year, and as *permanent* if recovery does not occur within one year of post-thyroidectomy.

We found that patients who needed a longer time to PTH recovery usually had higher calcium and vitamin D doses at discharge (Fig. 3). Long-term calcium and vitamin D supplementation has its own complications, especially with high doses: these include hypercalciuria, nephrocalcinosis, renal impairment, and soft tissue calcification [13]. Thus, new treatment modalities have been suggested, such as recombinant parathormone, although it is not yet approved for the treatment of hypoparathyroidism [14, 15]. The model from our study can be used as a guideline for early selection of patients who are likely to have permanent hypoparathyroidism or a longer time to recovery from

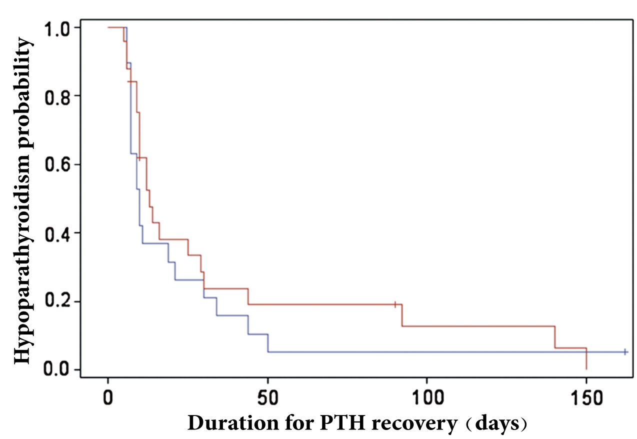

Fig. 3 Kaplan-Meier curve showing that patients who were discharged with calcium supplementation more than 3,000 mg/day (*red line*) tended to have longer time to recovery than those discharged on calcium supplementation less than 3,000 mg/day (*blue line*) (Color figure online)

transient/protracted hypoparathyroidism. It is also worth noting that these patients can be good candidates for newly emerging targeting alternatives, like the new synthetic human parathyroid hormone, instead of subjecting them to the hazards of long-term or lifelong high doses of calcium and vitamin D supplementations.

This study protocol was executed with some challenges and difficulties. For instance, the study protocol called for postoperative follow-up at 1 week, 3 weeks, 1 month, and then every two months up to 6 months. Patient's adherence to this follow-up schedule was extremely high at the 1 week visit, but it diminished for subsequent visits, for various socioeconomic reasons. The lack of strict follow-up may have led to overestimation of time to PTH recovery. Another related point is that the underlying model for this analysis only considered main effects, meaning that interaction among factors like perioperative PTH percent drop, preoperative PTH, and diabetes mellitus were not considered in these analyses because of sample size. These interacting factors will be taken into consideration in the next study protocol, with provision for sample size to carry out such analysis. Another obvious point is that follow-up for this study protocol was capped at six months, which essentially precluded inclusion of those who recovered after six months. The next study protocol will expand follow-up to one year. It is also worth mentioning that clinical validation and improvement of precision for the expected time of PTH recovery models are underway in a prospective multicenter study protocol.

In conclusion, this study provides potentially useful information for early prediction of PTH recovery, and it highlights the factors that can affect the course of this recovery. Preoperative PTH level, perioperative PTH percent drop, and diabetes mellitus are factors that were determined by both likelihood and time to affect recovery.

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