

Predictive analysis of severe hypocalcemia following total parathyroidectomy for renal secondary hyperparathyroidism

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Abstract. – OBJECTIVE: This study aimed to evaluate the incidence and identify risk factors for severe hypocalcemia following total parathyroidectomy (TPTX) in patients with renal secondary hyperparathyroidism (SHPT).

PATIENTS AND METHODS: We included patients undergoing maintenance hemodialysis or peritoneal dialysis who underwent TPTX from January 1, 2018, to April 30, 2023. Participants were categorized into groups based on postoperative corrected serum calcium levels: severe hypocalcemia (<1.8 mmol/L) and non-severe hypocalcemia (≥1.8 mmol/L). We conducted univariate analyses of demographic and laboratory data to identify potential risk factors, which were further analyzed using a binary logistic regression model.

RESULTS: Significant associations were observed with age, dialysis duration exceeding five years, type of dialysis (peritoneal dialysis), lower preoperative corrected serum calcium, elevated preoperative intact parathyroid hormone (iPTH), and increased preoperative alkaline phosphatase (ALP) levels (all $p < 0.05$). Age, preoperative iPTH, and ALP levels were identified as independent risk factors for severe hypocalcemia post-TPTX.

CONCLUSIONS: Younger patients with renal SHPT who have elevated preoperative iPTH and ALP levels are at an increased risk of experiencing severe hypocalcemia following TPTX. These findings underscore the importance of careful preoperative assessment and monitoring to mitigate the risk of this complication.

Key Words:

Incidence, Risk factors, Hypocalcemia, Renal secondary hyperparathyroidism, Total parathyroidectomy.

Introduction

Chronic kidney disease (CKD) represents a significant global health challenge, contributing

directly to increased morbidity and mortality worldwide¹. Epidemiological data²⁻⁴ reveal that CKD affects approximately 6-10% of populations across various global regions. Specifically, in China, the prevalence among adults was reported⁵ to be around 10.8%, equating to an estimated 120 million individuals affected in 2014. The latest findings⁶ from the Global Burden of Disease study indicate a 41.5% rise in the global mortality rate among CKD patients from 1990 to 2017, culminating in nearly 1.2 million deaths in 2017 alone. In terms of global health impact, CKD ranked 16th among all causes of life loss in 2016 and 7th among non-communicable disease factors⁷. Projections⁸ for 2040 suggest that CKD will ascend to the fifth cause of global life loss and the third due to non-communicable conditions, underscoring its growing threat to public health.

Secondary hyperparathyroidism (SHPT), a frequent complication of CKD, is characterized by the sustained elevation of parathyroid hormone (PTH) levels, which can inflict damage on multiple organ systems. For patients unresponsive to pharmacological interventions, total parathyroidectomy (TPTX) emerges as a necessary surgical recourse. The necessity for TPTX escalates with prolonged dialysis duration, affecting approximately 10-30% of this patient cohort.

Notably, hypocalcemia ranks as a prevalent postoperative complication, carrying the potential for severe consequences, including arrhythmias and mortality. This study aimed to explore the incidence and identify the risk factors associated with severe hypocalcemia following TPTX in individuals suffering from renal SHPT, aiming to enhance clinical outcomes and inform future therapeutic strategies.

Patients and Methods

Studied Subjects

Patients with maintenance hemodialysis or maintenance peritoneal dialysis who underwent TPTX were included as study subjects from January 1, 2018 to April 30, 2023. There were 390 non-severe hypocalcaemia patients and 240 severe hypocalcaemia patients. The inclusion criteria were as follows: (1) TPTX was performed in our hospital; (2) Maintenance hemodialysis or peritoneal dialysis patients, dialysis time is greater than or equal to 3 months; (3) The iPTH was >800 pg/ml in the last 6 months; (4) hypercalcemia or hyperphosphatemia still existed after treatment with calcitriol, paricalciferol, sevilam and lanthanum carbonate; (5) severe clinical symptoms, such as bone pain, unbearable skin itching or muscle weakness affecting daily activities; (6) Imaging examination (neck color ultrasound) showed enlargement of at least one parathyroid gland (>1 cm in diameter) and abundant blood flow signals could be detected. The exclusion criteria were as follows: (1) diagnosis of malignant tumors, such as parathyroid carcinoma; (2) cannot tolerate surgery due to serious heart and lung disease; (3) in a state of severe infection or inflammation; (4) Patients with a history of radiotherapy or surgery in the neck; (5) Patients with recurrence after parathyroidectomy; (6) Unwilling to participate in the study; (7) Incomplete data collection, such as lack of serum alkaline phosphatase. This study was reviewed by the Medical Research Ethics Committee of our hospital, and all patients signed informed consent.

Data Collection

Comprehensive demographic and clinical data were meticulously gathered for each patient through the hospital's electronic medical records system. This included age, gender, the underlying cause of chronic renal failure, dialysis modality (hemodialysis or peritoneal dialysis), details of the surgical procedure performed (total parathyroidectomy), and the quantity of parathyroid tissue removed during surgery. Additionally, a detailed medication profile was compiled for each patient, documenting the use of calcium supplements, phosphate binders, and active forms of vitamin D and their analogs administered perioperatively. In cases where specific details were not readily available or missing from the medical records, proactive steps were taken to complete the dataset. This involved direct outreach to the patients, their family members, or the healthcare professionals

overseeing their dialysis treatment at local facilities. Various communication methods were employed, including telephone calls, text messaging, and digital platforms such as WeChat, to ensure the thoroughness and accuracy of data collection. This holistic approach enabled the collection of a robust dataset, facilitating a comprehensive analysis of the factors influencing postoperative outcomes in patients undergoing total parathyroidectomy for renal secondary hyperparathyroidism.

Laboratory Index

Laboratory assessments were conducted to evaluate key biochemical markers before and after surgery. Preoperative and 24-hour postoperative serum calcium and phosphorus levels were recorded, along with serum intact parathyroid hormone (iPTH) levels measured preoperatively and 1 to 3 days following surgery. Baseline data collection also included serum hemoglobin, albumin (ALB), and alkaline phosphatase (ALP) levels, obtained before the surgical intervention. Hemoglobin concentrations were analyzed using a blood cell analyzer (Kobe, Hyogo Prefecture, Japan), while serum ALB, calcium, phosphorus, and ALP levels were quantified via an automatic biochemical analyzer (Chicago, Illinois, USA). iPTH concentrations were determined through chemiluminescence immunoassay, ensuring high sensitivity and specificity. To maintain consistency and minimize redundancy in testing, preoperative iPTH measurements conducted within 72 hours prior to admission were accepted if performed at an accredited external laboratory, with results directly integrated into our analysis. This approach streamlined the preoperative evaluation process, focusing on essential and relevant laboratory investigations to guide clinical decision-making.

Statistical Analysis

Data analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA), a robust statistical software package. A significance threshold of $p < 0.05$ was established for all tests, indicating statistical relevance. Initial data handling involved inserting all collected information into a structured database, followed by a normality assessment of the measured variables. Comparative analyses between groups were conducted using either the *t*-test or appropriate non-parametric tests, depending on data distribution. Furthermore, a binary logistic regression model facilitated multivariate analysis, allowing for the identification of independent predictors of severe hypocalcemia

post-total parathyroidectomy. This comprehensive statistical approach provided a solid foundation for evaluating the relationships between various preoperative factors and postoperative outcomes.

Results

Incidence and Preliminary Analysis of Postoperative Severe Hypocalcemia

In this cohort of 784 patients who underwent total parathyroidectomy, individuals were categorized based on post-surgical serum-corrected calcium levels into two groups: those with severe hypocalcemia (serum-corrected calcium <1.8 mmol/L) and those without (serum-corrected calcium ≥1.8 mmol/L). Of these, 27.3% (214 patients) experienced severe hypocalcemia within 24 hours following surgery. Notably, significant differences emerged among the groups concerning age, duration of dialysis exceeding five years, and the utilization of peritoneal dialysis as the mode of renal replacement therapy (all $p < 0.05$), as detailed in Table I.

Univariate Analysis of Preoperative Laboratory Indices and Severe Hypocalcemia

Upon examining preoperative laboratory markers, statistically significant associations were identified with lower serum corrected calcium, elevated preoperative iPTH, and increased preoperative ALP levels (all $p < 0.05$), underscoring their potential as predictors of severe hypocalcemia postoperatively. The specific data supporting these findings are presented in Table II.

Multivariate Logistic Regression Analysis

Further analysis using a multivariate binary logistic regression model pinpointed age, preoperative iPTH, and ALP levels as independent risk factors for the development of severe hypocalcemia following surgical intervention (all $p < 0.05$). These results, presented in Table III, highlight the complex interplay of demographic and biochemical variables in influencing postoperative outcomes, offering valuable insights for risk stratification and management strategies in

Table I. General conditions of severe hypocalcaemia group and non-severe hypocalcaemia group.

Basic information	Non-severe hypocalcaemia (N=390)	Severe hypocalcaemia (N=240)	p
Age	50.7±7.7	43.8±9.8	<0.001
Gender		0.44	
Male	264	91	
Female	126	179	
Peritoneal dialysis			0.03
Yes	39	12	
No	351	228	
Dialysis period			<0.001
>5 year	136	48	
≤5 year	254	192	
Primary disease classification			0.54
Chronic glomerulonephritis	310	190	
Polycystic kidney or solitary kidney	14	5	
Diabetic nephropathy	12	2	
Hypertensive nephropathy	4	20	
Obstructive nephropathy	11	5	
Others	39	18	
Calcium			0.53
Yes	30	15	
No	360	225	
Non-calcium-phosphorus binding agent			0.76
Yes	42	24	
No	348	216	
Activated vitamin D			0.72
Yes	230	145	
No	160	95	
Calcimimetics			0.19
Yes	71	54	
No	319	186	

Table II. Laboratory parameters of the severe hypocalcemia group and non-severe hypocalcemia group.

Basic information	Non-severe hypocalcaemia (N=390)	Severe hypocalcaemia (N=240)	<i>p</i>
Low preoperative serum correction calcium			0.12
Yes	31	28	
No	359	212	
Preoperative hypercalcemia			0.80
Yes	152	96	
No	238	144	
Preoperative hyperphosphatemia			0.53
Yes	364	227	
No	26	13	
Preoperative calcium-phosphorus product <35			0.38
Yes	39	19	
No	351	221	
Preoperative calcium-phosphorus product >40			0.76
Yes	348	216	
No	42	24	
Preoperative iPTH	1,674.5 (1,230.2, 2,286.8)	2,210.6 (1,790, 2,573.5)	<0.001
Preoperative ALP	260.9 (120.2, 513.2)	560.9 (390, 884.5)	<0.001
Postoperative iPTH	10.9 (10.1, 23.8)	11.5 (10.8, 24.5)	0.76
Cr	945.8±158.4	948.1±157.4	0.86
Ca	2.58±0.36	2.56±0.34	0.48

iPTH, Intact parathyroid hormone; ALP, alkaline phosphatase.

Table III. Multivariate Logistic regression analysis of postoperative severe hypocalcemia in SHPT patients.

Factors	OR	95% CI	<i>p</i>
Age	0.950	0.912-0.994	0.023
Peritoneal dialysis	0.658	0.351-1.212	0.188
Dialysis period	1.395	0.926-2.098	0.114
Low preoperative serum correction for calcium	1.114	0.788-1.577	0.537
Preoperative iPTH	1.002	1.000-1.004	0.002
ALP	1.002	1.000-1.003	0.030

SHPT, Secondary hyperparathyroidism; ALP, alkaline phosphatase; PTH, parathyroid hormone.

patients undergoing total parathyroidectomy for secondary hyperparathyroidism.

Discussion

SHPT, a complication arising from diminished renal function, typically manifests in the advanced stages of chronic kidney disease. It is characterized by elevated PTH synthesis and secretion, leading to parathyroid cell proliferation. The exact pathogenesis of SHPT remains incompletely understood, though classical CKD-associated factors such as hypocalcemia, hyperphosphatemia, and decreased levels of 1,25-dihydroxyvitamin D are acknowledged contributors. Additionally, the role of fibroblast growth factor

23 (FGF-23) in the pathophysiology of SHPT has gained recognition, indicating its significance in the development of SHPT among CKD patients⁹⁻¹². As SHPT progresses, parathyroid gland growth transitions from diffuse to nodular, reducing the gland's responsiveness to regulatory feedback¹³. This unchecked secretion of iPTH can exacerbate disturbances in calcium and phosphorus metabolism, potentially leading to vascular and soft tissue calcification, alongside other complications like bone pain, deformities, and cardiovascular issues, significantly impairing patient quality of life and increasing mortality risk^{14,15}.

TPTX offers a surgical remedy for SHPT unresponsive to medical management. Despite advancements improving the accessibility of TPTX, postoperative hypocalcemia remains a prevalent

complication, with incidences reported between 26-47%¹⁶. Some studies in the literature have suggested that hypocalcaemia after TPTX can be used as a marker of successful surgery. The abrupt decline in circulating PTH post-TPTX pivots the balance towards bone formation, sequestering calcium within the bone matrix and precipitating hypocalcemia. While typically transient and manageable with calcium and active vitamin D supplementation, severe cases pose significant risks, including life-threatening arrhythmias and neuromuscular irritability.

Contemporary studies in the literature have explored predictors of post-TPTX hypocalcemia, albeit with mixed outcomes. Our investigation aligns with previous findings¹⁷ indicating younger SHPT patients as being more susceptible to severe hypocalcemia post-TPTX. This correlation may be attributed to peak bone formation rates observed in the 20-45-year age group, which, coupled with a post-surgical drop in PTH, enhances osteogenic activity. Consequently, the younger demographic shows a heightened risk for postoperative hypocalcemia, consistent with our observations¹⁸.

The present study found that renal SHPT patients at a younger age were more likely to develop severe hypocalcaemia after TPTX, which is consistent with previous literatures¹⁹⁻²¹. Kritmetapak et al²² found that younger age (<45 years old) is significantly correlated with hypocalcaemia, and even Erbil et al²³ believe that age is significantly correlated with hypocalcaemia and was the only predictor of postoperative hypocalcaemia. This may be related to the characteristics of human growth and development. The population is at the peak of bone formation in the age group of 20 to 45 years old. With the increase of age, testosterone or estrogen generally shows a downward trend, so the activity of osteoblastic cells decreases with the increase in age. After TPTX, the level of circulating parathyroid hormone decreases sharply and osteogenic activity increases. The observation results of most studies found in the literature tend to be that the younger the age, the higher the risk of postoperative hypocalcaemia, and the results of this study are also consistent with it.

With the rapid development of medical science and technology and the continuous improvement of medical and health conditions, the life quality of dialysis patients has been significantly improved, and the duration of dialysis has been continuously extended. The process of dialysis is a process in which metabolic waste is continuously

exchanged with the filter membrane, which replaces the filtration and reabsorption functions of the decompensated kidney and improves the accumulation of metabolic waste²⁴. However, even after hemodialysis or peritoneal dialysis treatment, the function of the kidney cannot be completely replaced. Various complications caused by dialysis will increase with the increase of dialysis age, such as calcium and phosphorus metabolism disorders, secondary hyperparathyroidism, and vascular calcification. However, there are few clinical reports on the effects of different dialysis ages on calcium and phosphorus metabolism in maintenance dialysis patients, and mostly no exact correlation is found. In this study, the single-factor analysis showed that dialysis age was an influential factor for postoperative severe hypocalcaemia, but the multi-factor analysis showed that dialysis age was not an independent risk factor for postoperative severe hypocalcaemia. However, the sample size of the current study is still small, and further increasing the sample size is needed in the future.

Conclusions

In conclusion, renal SHPT patients with younger age, higher preoperative parathyroid hormone levels, and higher preoperative alkaline phosphatase levels were more likely to develop severe hypocalcemia after total parathyroidectomy.

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Ethics Approval

This study is approved by Ethics Committee of General Hospital of Northern Theater Command. Ethical Approval's number is Y(2020)075.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Data Availability

All data generated or analyzed during this study are included in this published article.

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Authors' Contributions

Wei Zhang conceived study design and content concept; Ting Bi and Sijia Bai performed the data collection, extraction and analyzed the data; Guangming Cheng and Xiaodong Feng were responsible for literature search; Wei Zhang interpreted and reviewed the data and drafts.

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Conflict of Interest

The authors declare that they have no competing interests.

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