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# **Identifying Early Postoperative Serum Parathyroid Hormone Levels as Predictors of Hypocalcaemia After Total Thyroidectomy: A Prospective Non-Randomized Study**

Running Head: Is There Benefit from Early Postoperative PTH Monitoring?

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## **Disclosure Statement**

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

## **Data Availability Statement**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## **Keywords**

parathyroid hormone; thyroidectomy; hypocalcemia; postoperative complications; predictive value of tests; calcium; ROC curve

## Summary

**Objective:** There is no clear cut-off value of serum parathyroid hormone (PTH) or calcium in which patients are at risk for hypocalcemia after total thyroidectomy. We evaluated the usefulness of serum calcium and PTH concentration measurements after total thyroidectomy in predicting late-occurring hypocalcemia.

**Design:** A prospective, single-center, non-randomized longitudinal cohort study of 143 patients undergoing thyroidectomy between August 2019 and December 2019 with serum calcium and PTH levels sampled 1 hour after surgery and on the first and fifth postoperative day. Hypocalcemia was defined as serum calcium levels  $<2.14$  mmol/L regardless of clinical symptoms. Normal PTH range was 1.6 - 6.9 pmol/L.

**Measurements:** The primary outcome measure was presence of hypocalcemia on the first and fifth postoperative day, analyzed by a logistic regression model. The PTH cut-off value for prediction of hypocalcemia was identified using a ROC curve comparing all three time points using the Youden J index.

**Results:** Out of 143 patients, 52 (36.4%) had hypocalcemia on the fifth postoperative day. Advanced age, concomitant neck dissection and serum PTH levels  $<2.9$  pmol/L one hour after surgery and on the first postoperative surgery day were associated with a high risk of hypocalcemia on the first and fifth postoperative day and need for higher doses of calcium supplements ( $P<0.0001$ , AUC 0.748, 95% CI 0.669-0.817, with 76.92% sensitivity and 71.43% specificity).

**Conclusion:** Serum PTH level measured immediately postoperatively and on the first postoperative day is a reliable predictor of postoperative hypocalcemia with important clinical implications.

## **i) Main text**

### **Introduction**

Thyroidectomy is one of the most common surgical procedures performed in modern medicine. Indications for total thyroidectomy include hyperthyroidism, thyroid malignancies and thyroid enlargement causing local compression.<sup>1</sup> It is a safe procedure with few possible complications, the most common being postoperative hypocalcemia caused by hypoparathyroidism, presenting with neuromuscular (positive Chvostek sign or Trousseau sign, numbness or tingling, wheezing, dysphagia and laryngospasm), neurological (irritability, fatigue, choreoathetosis) or cardiovascular symptoms (prolongation of QT interval, syncope, torsade de pointes arrhythmia).<sup>2</sup> Hypoparathyroidism is a condition of parathyroid gland dysfunction leading to low levels of parathyroid hormone (PTH) and hypocalcemia. Risk factors for post-thyroidectomy hypoparathyroidism include total thyroidectomy, autoimmune thyroid disease, central neck dissection, substernal goiter, surgeon inexperience, and malabsorptive conditions.<sup>1</sup> Reports differ, but meta-analyses report that 19%-38% of patients will experience transient postoperative hypocalcemia, while permanent hypocalcemia occurs anywhere from 0% to 3% of cases, leading to prolonged hospitalization and increased long-term patient morbidity.<sup>2</sup> It is mostly mild, but may present with severe symptoms in some patients, requiring rapid diagnosis and treatment. It may develop up to three days postoperatively, and early diagnosis is of great importance, especially in susceptible patients discharged early after surgery and further treated on an outpatient basis.<sup>3</sup> Currently, the most commonly used method of monitoring hypocalcemia, apart from clinical examination and patient history, is measuring the serum calcium concentration. The second most commonly used method is postoperative PTH monitoring.<sup>3,4</sup> Serum PTH levels have a half-life of up to 5 minutes, and have been considered as a potential prognostic factor, but numerous controversies

exist regarding cut-off value identification, hypocalcemia definition criteria, optimal calcium supplementation with few guidelines, if any, in widespread use.<sup>3,4,5</sup>

Many recent studies point out that intact PTH preoperatively and low PTH in the early postoperative period are the most predictable indicators of high risk for developing hypocalcemia after thyroidectomy, but few have identified cut-off values and analyzed their predictive potential.<sup>6-13</sup> In this prospective, non-randomized longitudinal cohort study, we aimed to evaluate the predictive potential of early postoperative serum PTH sampling with regard to hypocalcemia occurrence up to five days postoperatively.

## **Patients and Methods**

This study was designed as a prospective non-randomized longitudinal single-center cohort study. It enrolled 143 patients undergoing total thyroidectomy with data collected from August 2019 up to December 2019. The study was approved by the Hospital Board of Ethics (EP-12939/18-17), according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and as amended most recently by the 64th World Medical Assembly, Fontaleza, Brazil, October 2013. It was registered with ClinicalTrials.gov (Identifier: NCT04160637). The patients were eligible if they underwent total thyroidectomy regardless of the surgical indication, if complete serum PTH and calcium data were available through the first five postoperative days and if they signed an informed consent form. Patients with incomplete data, preoperative pathological calcium or PTH levels, or suffering from conditions affecting calcium metabolism and parathyroid function were excluded from the study.

Demographic and clinical data including age, sex, preoperative and postoperative laboratory values (serum calcium and PTH), neck dissection procedures, and postoperative calcium supplement therapy were noted. Primary outcome measures were presence of hypocalcemia on

the first and fifth postoperative day. Secondary outcome measures were the need for calcium supplement therapy during the first five postoperative days and amount of medication given. Preoperative blood samples for serum PTH and calcium measurements were obtained after hospital admission. Postoperative serum PTH was sampled 1 hour after surgery and at 7 am on the first and fifth postoperative day. Serum calcium sampling was performed daily if a patient had hypocalcemia detected on the first postoperative day. PTH was measured using an electrochemiluminescence immunoassay and serum calcium by the o-cresolphthalein complexone method with reference values 1.6 to 6.9 pmol/L and 2.14–2.42 mmol/L (8.0–12.0 mg/dL), respectively. Hypocalcemia was diagnosed if serum calcium was  $<2.14$  mmol/L regardless of clinical symptoms present. The recovery of parathyroid function was defined as the return of serum PTH and serum calcium to normal values, requiring no further calcium or vitamin D supplementation. If the patient did not have laboratory or clinical signs of hypocalcemia, calcium supplement therapy was not administered. Supplement therapy was administered in patients with laboratory findings confirming hypocalcemia. Supplement therapy consisted of peroral elemental calcium (calcium carbonate, 1-gram unit) and/or calcitriol (0.5 microgram unit), with dose adjustments depending on serum calcium values. It was used if serum calcium values were  $<2.00$  mmol/L or clinical symptoms were present. Intravenous calcium gluconate was used only in cases with severe clinical symptoms of hypocalcemia. If postoperative calcium and PTH were normal and there were no symptoms of discomfort, the patient was discharged on the first or second postoperative day and serum PTH and calcium sampling was performed on an outpatient basis. If the patient did not received treatment during hospitalization, no supplements were prescribed after hospital discharge. Tested variables were noted using standard descriptors (arithmetic mean and standard deviation or median). Associations between variables were assessed using Spearman's rho rank correlation coefficient, the Kruskal-Wallis test for independent samples and a logistic

regression model to test statistically significant correlations between PTH and serum calcium values as a primary end point. All tests of statistical significance were performed using a two-sided 5% type I error rate. Every variable that was significantly associated with postoperative complications was further analyzed with a ROC (Receiver Operating Characteristic) analysis and a cut-off value for complication occurrence was identified using the Youden J index (measuring the sensitivity and specificity of a dichotomous tested variable). Area Under the Curve (AUC) > 0.6 was considered statistically significant. P values  $\leq 0.05$  were considered to be statistically significant. Statistical analysis was performed by MedCalc (Version 11.2.1 © 1993-2010. MedCalc Software bvba Software, Broekstraat 52, 9030 Mariakerke, Belgium).

## **Results**

A total of 143 patients were included in the study. (Table 1) The mean age was 55.08 years with a standard deviation of  $\pm 30.5$  years, and 123 were women (86.1%). The serum levels of calcium on the first postoperative day were  $2.09 \pm 0.16$  mmol/L. The clinical and surgical characteristics of patients are displayed in Table 2. Twenty patients (13.98%) underwent selective neck dissection alongside total thyroidectomy if thyroid malignancy was suspected. The patients were grouped according to presence or absence of hypoparathyroidism and hypocalcemia in the first 5 days postoperatively. There were 82 patients (57.3%) with serum calcium levels  $< 2.14$  mmol/L on the first postoperative day, but only 20 patients (13.8%) were symptomatic, and the average serum calcium value on the first postoperative day was  $2.09 \pm 0.16$  mmol/L. On the fifth postoperative day, mean serum calcium levels were  $2.18 \pm 0.17$  mmol/L, 52 (36.4%) patients were hypocalcemic, but only two (1.4%) had clinical symptoms. Serum PTH values 1 hour postoperatively were  $3.12 \pm 1.85$  pmol/L, with 42 patients (29.4%) in the postoperative group with hypoparathyroidism and  $3.31 \pm 1.83$  pmol/L on the first postoperative day, and 40 patients in the group with hypoparathyroidism. There were 44 patients (30.7%) needing calcium



supplement therapy during the first five postoperative days, but only 10 (6.99%) still used peroral calcium supplements until the one-month follow-up exam postoperatively.

Data analysis using a logistic regression model found that older patients were at risk for hypocalcemia on both the first and fifth postoperative day ( $P=0.003$  and  $P=0.025$ , respectively), as well as lower PTH levels one hour after surgery and on the first postoperative day ( $P=0.023$  and  $P=0.018$ ). Patients who had concomitant dissection with total thyroidectomy had lower serum PTH levels ( $P=0.021$ ) one hour after surgery. Patients with lower PTH levels one hour after surgery and on the first postoperative surgery day had a greater chance of developing hypocalcemia on the first and fifth postoperative day ( $P<0.0001$ ), and received larger doses of calcium supplements ( $P<0.0001$ ). The odds ratio between hypoparathyroidism on the first postoperative day and hypocalcemia on the 5th postoperative day is 1.35 with a 95% CI of 0.33 to 5.59.

Cut-off value for PTH levels one hour after surgery predicting hypocalcemia on the fifth postoperative day was  $<2.99$  pmol/L (ROC analysis, AUC 0.746,  $P<0.0001$ , 80.77% sensitivity and 63.74% specificity) (Figure 1). Cut-off value for PTH levels on the first postoperative day predicting hypocalcemia on the fifth postoperative day was  $<2.9$  pmol/L (ROC analysis, AUC 0.748,  $P<0.0001$ , 76.92% sensitivity and 71.43% specificity) (Figure 2). There was no significant difference between the two PTH evaluation points.

Cut-off values for PTH levels one hour after surgery and PTH on the first postoperative day predicting hypocalcemia on the first postoperative day were  $<3.34$  pmol/L (85.37% sensitivity, 77.05% specificity) and  $<3.34$  pmol/L (76.83% sensitivity, 81.97% specificity), respectively (ROC analysis, AUC of 0.835 and 0.804 respectively, both  $P<0.0001$ ) (Figures 3 and 4).

A cut-off value of serum calcium levels on the first postoperative day predicting hypocalcemia on the fifth postoperative day was 2.12 mmol/L (ROC analysis, AUC 0.858,  $P < 0.0001$ , 94.23% sensitivity and 68.13% specificity) (Figure 5).

## **Discussion**

Symptoms of postoperative hypocalcemia vary from asymptomatic patients with no symptoms to fatal outcomes due to laryngeal and diaphragmatic spasm.<sup>3,4,5</sup> Early identification of patients at risk for postoperative hypocalcemia is important due to optimization of postoperative management, reducing unnecessary testing on one hand and avoiding overtreatment of the majority of asymptomatic patients on the other.<sup>2,14</sup> Prophylactic oral administration of calcium and calcitriol decreases the risk of transient postoperative hypocalcemia but prolongs hospitalization time due to close monitoring of calcium levels.<sup>4,12-18</sup> Our study asserts that postoperative PTH monitoring either on the day of surgery or during the first postoperative day enables accurate prediction of postoperative hypocalcemia. The identification of PTH cut-off points (2.9 pmol/L) as predictors of hypocalcemia still present on the fifth postoperative day is especially clinically relevant. Either time point for measurement may be chosen as a valid prediction interval. This prospective study did not use PTH as a criterion for medical intervention, adding to the argument that it is an independent and highly time-sensitive predictor, in contrast with serum calcium values that change as soon as calcium supplements are introduced into therapy.<sup>15</sup> Some surgeons administer calcium and calcitriol supplements regardless of calcium levels immediately after surgery which reduces hypocalcemia but also gives unnecessary medication to patients who might not have developed hypocalcemia.<sup>13,14</sup>

Currently, there is no consensus on how to predict the occurrence of postoperative hypocalcemia by measuring PTH or serum calcium levels. The role of serum PTH in predicting postoperative hypocalcemia has been analyzed extensively.<sup>2,3,7-18</sup> Studies differ in their

selection criteria, follow-up period, definitions of hypocalcemia and hypoparathyroidism and types of data analysis. Major drawbacks of many of these are retrospective design, using PTH levels as treatment criteria, and lack of cut-off points identification. Several earlier attempts to define cut-off points for PTH levels as predictors of hypocalcemia have listed PTH levels of 10 pg/mL (1.06 pmol/L) or calcium levels of 8 mg/dL (2.00 mmol/L) as accurate predictors.<sup>2,1-17</sup> One prospective observational study found that the AUCs of both postoperative PTH and decrease of iPTH values were extremely high, close to 1, demonstrating that a strong correlation between PTH levels and the onset of clinical hypocalcemia after total or completion thyroidectomy exist. They found that those with a decrease of PTH < 80% can be safely discharged home without treatment, as the risk of developing clinical hypocalcemia was essentially zero, and that calcium supplements can be prescribed to those with a postoperative PTH level of <3 pg/mL, similar to the results in our study.<sup>14,16,17,19</sup> Other studies found that patients with PTH >19.55 pg/ml (2.07 pmol/L) 4h after surgery or 14.35 pg/ml (1.52 pmol/L) on the first morning after surgery can be safely discharged from hospital without supplemental calcium and/or vitamin D.<sup>2,20</sup> However, there is also data suggesting that up to 18% of patients above these proposed cut-off points still present with postoperative hypocalcemia.<sup>18</sup>

The ROC curve analysis is an ideal method in determining the performance of a continuous variable and classifying patients into dichotomous categories. Even though both of our measured time points showed to be accurate predictors of hypocalcemia, our follow-up time was too short to evaluate patients with permanent hypoparathyroidism, but other studies have shown that the majority of patients with PTH <1.06 pmol/L recover well within several months of follow-up.<sup>6</sup>

The sample was relatively large, and avoidance of using PTH levels as a therapeutic criterion helped with reducing bias, but a relatively large proportion of patients were labeled as being hypocalcemic due to a relatively high diagnostic threshold of 2.14 mmol/L for hypocalcemia.

This surely contributed to a higher number of patients in the hypocalcemia group, but also reduced the possibility of omitting patients that were just under that value, since the mean value of serum calcium on the fifth postoperative day was  $2.18 \pm 0.17$  mmol/L. Other limitations which should be noted include the fact that patients were prescribed various calcium supplementation regimens and that documentation of hypocalcemic symptoms was subjective, based on patients' complaints. Performing neck dissections may have also been a source of bias, increasing the number of patients at risk for postoperative hypocalcemia. Although selective neck dissections reduce the risk of locoregional recurrence, this procedure has also been shown to significantly increase the rate of postoperative temporary hypocalcemia, as was the case in our study.<sup>21</sup> Although our sample size was rather small and our follow-up time was short for evaluation of permanent hypocalcemia, the fact that patients were hospitalized, operated and treated within a single medical facility by a trained team with similar follow-ups and choices of treatment enhances the validity of our findings.

## **Conclusions**

This prospective study established that early postoperative PTH is an accurate predictor of postoperative hypocalcemia. Both immediate postoperative PTH values and those sampled on the first postoperative day may be used, adding to the importance of evaluating patients at risk for hypocalcemia and reporting clinically relevant cut-off points that might impact the follow-up protocol. The protocol of early PTH measurement could be incorporated into present hospital follow-up, with minimal impact on additional expenses and logistics management. Hence, patients with a serum PTH level  $>2.99$  pmol/L on after surgery may be safely discharged from the hospital without the need for additional treatment.

## **ii) References**

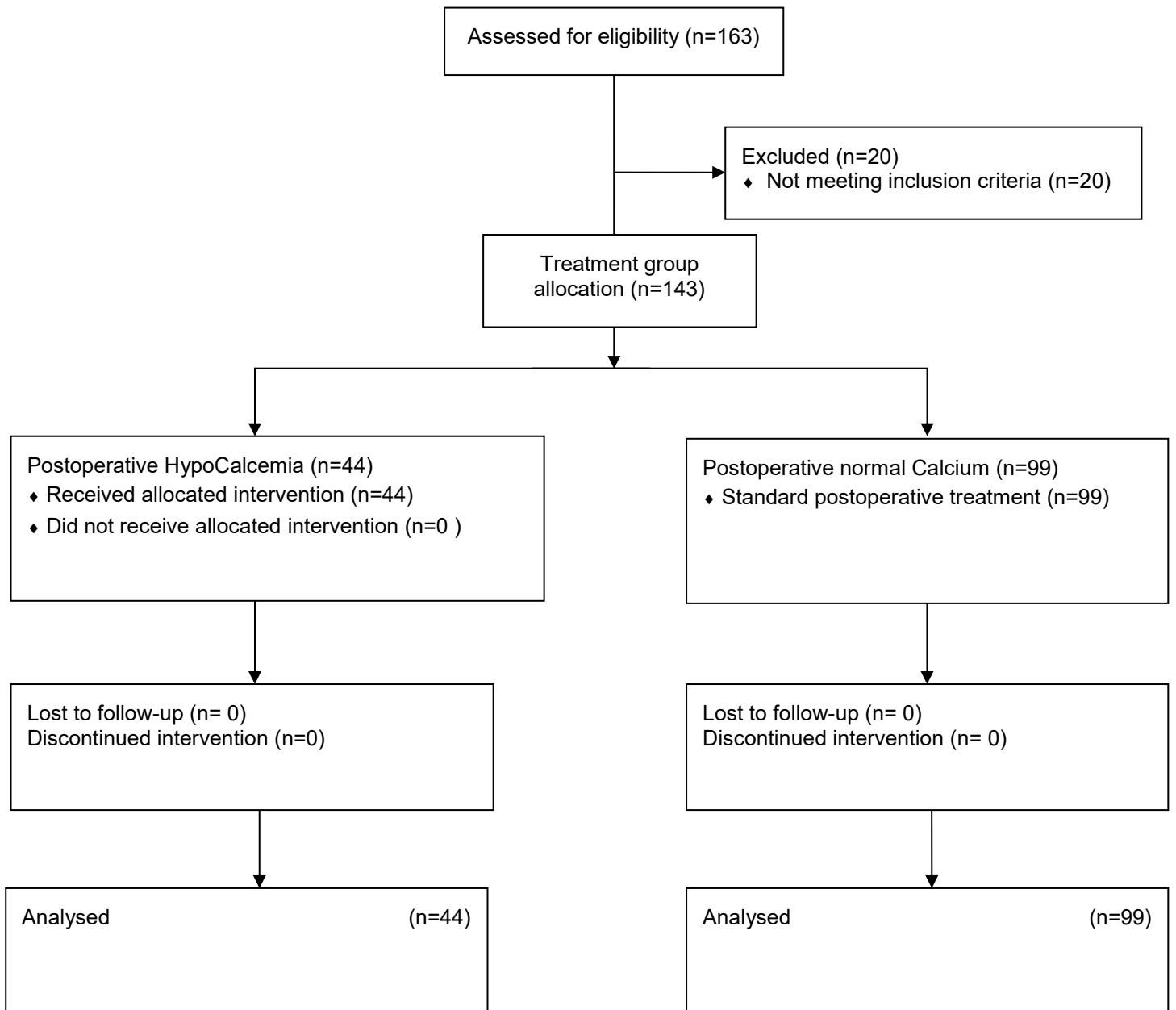
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iii) Tables

Table 1. CONSORT 2010 Flow Diagram





**Table 2.**

Clinical and surgical characteristics of 143 patients who underwent total thyroidectomy

Age (years)	55.08 ± 30.5
Women (N)	123 (86.1%)
Selective neck dissection (region VI)	20 (13.98%)
PTH 1 hour postoperatively (pmol/L)	3.12 (1.85)
PTH 1 <sup>st</sup> postoperative day (pmol/L)	3.31 (1.83)
Calcium 1 <sup>st</sup> postoperative day (mmol/L)	2.09 (0.16)
Calcium 5 <sup>th</sup> postoperative day (mmol/L)	2.18 (0.17)
Hypoparathyroidism 1 hour postoperatively (N)	42 (29.4%)
Hypoparathyroidism 1 <sup>st</sup> postoperative day (N)	40 (27.9%)
Hypocalcemia 1 <sup>st</sup> postoperative day (N)	82 (57.3%)
Hypocalcemia 5 <sup>th</sup> postoperative day (N)	52 (36.4%)
Patients needing calcium supplement therapy (N)	44 (30.7%)

Data are expressed as N (number), mean ± SD, or frequency (%).

### Figure Labels

**Figure 1.** PTH levels one hour after surgery predicting hypocalcemia on the fifth postoperative day with a cut-off of <2.99 pmol/L, ROC analysis, AUC 0.746, P<0.0001, 80.77% sensitivity and 63.74% specificity.

**Figure 2.** PTH levels on the first postoperative day predicting hypocalcemia on the fifth postoperative day with a cut-off of <2.9 pmol/L, ROC analysis, AUC 0.748, P<0.0001, 76.92% sensitivity and 71.43% specificity.

**Figure 3.** PTH levels one hour after surgery predicting hypocalcemia on the first postoperative day with a cut-off of  $<3.34$  pmol/L, ROC analysis, AUC 0.835,  $P<0.0001$ , 85.37% sensitivity, 77.05% specificity.

**Figure 4.** PTH on the first postoperative day predicting hypocalcemia on the fifth postoperative day with a cut-off of  $<3.34$  pmol/L, ROC analysis, AUC 0.804,  $P<0.0001$ , 76.83% sensitivity, 81.97% specificity.

**Figure 5.** Serum calcium levels on the first postoperative day predicting hypocalcemia on the fifth postoperative day with a cut-off of  $<2.12$  mmol/L, ROC analysis, AUC 0.858,  $P<0.0001$ , 94.23% sensitivity and 68.13% specificity.

