**Title: Development and internal-external validation of a prognostic model for long-term hypoparathyroidism after total or completion thyroidectomy.**

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**Abstract**

**Objective**

To develop and internal-externally validate a clinical prediction model to predict the occurrence of long-term hypoparathyroidism after total or completion thyroidectomy.

**Design**

Multicenter retrospective cohort study.

**Setting**

Eleven hospitals Dutch hospitals.

**Participants**

Patients were included if they underwent a total or completion thyroidectomy between January 2010 and June 2021.

**Main outcome**

The occurrence of long-term hypoparathyroidism. Long-term hypoparathyroidism was defined as the need for active vitamin D supplementation 1 year after surgery, and inability to be tapered of vitamin D supplementation. The prediction model was developed using multivariable logistic regression analysis and was internal-externally validated using leave-one-center-out cross-validation.

**Results**

Of the 366 included patients, 44 (12.0%) patients developed hypoparathyroidism in the first year follow-up after surgery. No patients had long-term hypoparathyroidism when PTH levels decreased less than 70 percent 24 hours after surgery. Multivariable logistic regression analysis showed that delta PTH 24 hours after surgery (OR 1.08; 95% CI: 1.05-1.12), corrected calcium 24 hours after surgery (OR 1.43; 95% CI: 1.12-1.82) and not identifying at least one parathyroid during surgery (OR 3.78; 95% CI: 1.58-9.04) were predictors for developing long-term hypoparathyroidism. The discriminative ability of the model was excellent (optimism-corrected C-index 0.89, 95% CI: 0.85-0.92), but calibration assessed through internal-external leave-one-center-out cross-validation was poor due to low number of events.

**Conclusion**

The model proposed in this study showed satisfactory performance and could be used to perform an individual assessment of patients at risk for long-term hypoparathyroidism after total thyroidectomy.

**Background**

Hypoparathyroidism is a prevalent complication following total or completion thyroidectomy that can lead to hypocalcemia as a result of unintended damage to the parathyroid glands. While iatrogenic hypoparathyroidism is often temporary and resolves within a few weeks 1, in some patients hypoparathyroidism becomes a chronic condition known as long-term hypoparathyroidism. The incidence of long-term hypoparathyroidism varies in the literature, partly due to the absence of consensus on its definition, ranging from less than 5% to 15% 2-4. Patients with long-term hypoparathyroidism experience lower health-related quality of life and recent studies suggest an increased mortality risk compared to individuals without this condition 5-7.

Several risk factors for developing long-term hypoparathyroidism are described in literature including extensive surgical procedures (e.g., central lymph node dissection) and low post-operative parathyroid hormone (PTH) levels 8, 9. Post-operative PTH levels play a crucial role in predicting long-term hypoparathyroidism after total or completion thyroidectomy 5, 10, 11. A recent meta-analysis demonstrated the existence of multiple PTH-based methods for predicting hypoparathyroidism, varying in terms of the timing of PTH measurements and the threshold levels employed 12. Although most studies report sensitivity and specificity outcomes of postoperative PTH levels, a comprehensive prognostic model that assesses individual patient risks of developing long-term hypoparathyroidism is currently lacking in the literature.

Identifying patients at high risk of developing long-term hypoparathyroidism can play a crucial role in preventing post-discharge adverse events, including readmissions caused by hypocalcemia. Conversely, the recognition of patients with a significantly low risk can de-escalate the intensity of follow-up care. In this study, we aimed to address this critical gap by developing and validating a comprehensive clinical prognostic model predicting the occurrence of long-term hypoparathyroidism following total or completion thyroidectomy.

**Methods**

**Study design**

This was a multicenter retrospective cohort study.

**Patients and data collection**

Patients were included in this study if 1) they underwent a total or completion thyroidectomy, 2) PTH has been determined preoperatively (up to one year preoperatively) or postoperatively on day 1 and if 3) follow-up data up to 1 year is available. Exclusion criteria were: surgery in the central neck compartment or external beam radiation therapy of the neck within 1 year of the index procedure. Model development and internal-external validation was performed in a cohort of adult patients who underwent surgery between January 2010 and June 2021 in one of the ten hospitals in the South-Western region of the Netherlands participating in a collaborative organization called the Thyroid Network and one academic hospital outside the region (Supplement X).

Baseline characteristics such as age, sex, preoperative diagnosis, medical history, blood values (calcium, albumin, PTH and vitamin D serum levels), surgical procedure, pathological specimen and follow-up data were obtained. Serum calcium levels were corrected for albumin levels according to the formula: corrected calcium (mmol/L) = measured calcium (mmol/L) + 0.016 x (34-albumin (g/L)). The reference value for calcium is 2.20-2.65 mmol/L. The change in PTH levels (delta PTH) was calculated by (PTH at baseline - postoperative PTH after 24 hours) / (PTH at baseline) ⋅ 100%. The change in corrected calcium levels (delta corrected calcium) was calculated by (corrected calcium at baseline - postoperative corrected calcium after 24 hours) / (corrected calcium at baseline) ⋅ 100%. The TRIPOD (transparent reporting of a multivariable model for individual prognosis or diagnosis) guidance for development and reporting of multivariable prediction models was followed (Supplement X) 13.

**Outcome measures**

The primary outcome of this study was long-term hypoparathyroidism. Long-term hypoparathyroidism was defined as the need for active vitamin D supplementation 1 year after surgery, and inability to be tapered of vitamin D supplementation 14. Secondary outcome was the incidence of readmissions after initial discharge.

**Statistical analysis for model development**

Missing values were imputed using Multivariate Imputations by Chained Equations (MICE) 15. Variables used in the multiple imputation model included the candidate predictors, auxiliary variables and the outcome 16. The multiple imputation procedure generated 10 imputed datasets with identical known values, but with varying imputed values to account for the uncertainty of the missing values. Identification of possible predictors of the outcome was based on clinical expertise and the existing literature. Univariate and multivariable logistic regression analysis with 95% confidence intervals was used to estimate the effect of the covariates on the occurrence of long-term hypoparathyroidism. Selection of variables for the final model was conducted using backwards selection 17, 18 (ref). To prevent overfitting of the model and to avoid optimism in the final prediction, we utilized a bootstrap validation approach with 1000 resamples and a uniform shrinkage method to derive an adjustment factor 19, 20. This adjustment factor was then multiplied by the final regression coefficient of each selected predictor. Interaction terms were not taken into consideration in this prediction model. Performance measures of the prediction model were determined by evaluating measures of discrimination and calibration. Calibration of the model was assessed by plotting observed frequencies versus predicted probabilities and by calculating the calibration intercept (calibration-in-the-large) and slope. Perfect predictions should lie on the 45-degree line for agreement with the outcome in the calibration plot. Discrimination of the model was assessed by providing the receiver operating characteristic curve (ROC). An area under the ROC curve (AUC) of 1.0 indicates perfect discrimination, whereas an AUC of 0.5 indicates no discrimination. Pooled estimates of the performance measures obtained from the imputed datasets were computed using Rubin’s Rule 21. We divided the patients into risk groups: patients with a PTH decrease of less than 70% were classified as ‘no risk’ (REF LONCAR). Patients with a PTH decrease of more than 70% were divided in risk groups based on predicted probabilities of the model (%); low risk (0-10%), intermediate risk (10%-40%) and high risk (>40%) patients. Internal-external validation was used in order to maximize the power of the limited number of included patients (ref). In order to assess whether the model’s discriminatory ability is superior to individual prognostic factors, we also compared the AUC of the model with the AUC of the PTH and corrected calcium decreases. All statistical tests were performed using the R Project for Statistical Computing version 4.1.2 (<https://www.r-project.org/>).

**Results**

The flow diagram of patient inclusion is shown in Supplemental Figure 1, and the patients characteristics are summarized in Table 1. The cohort included 366 patients after exclusion of 16 patients due to surgery in the central neck compartment 1 patient due to external beam radiation therapy in the head and neck region within one year after initial surgery. The median age of the derivation cohort was 56.0 [IQR, 42.0-69.0] and 32% was male (n=117). Total thyroidectomy was performed in 292 (80%) patients and 74 (20%) patients underwent a completion thyroidectomy. Long-term hypoparathyroidism occurred in 44 (12.0 %) patients one year after surgery. We observed low percentages of missing values for PTH measurements in the derivation cohort (n=19, 5.2% baseline PTH; n=28, 7.7% 24-hour PTH). All eligible patients were included in the model development and validation after imputing missing values.

After backwards selection methods, multivariable logistic regression analysis of all 366 patients showed that delta PTH 24 hours after surgery (OR 1.10; 95% CI 1.06-1.11), not identifying at least one parathyroid during surgery (OR 5.3; 95% CI 2.0-14.6) and corrected calcium 24 hours after surgery (OR 1.07; 95% CI 1.01-1.14) were all significantly associated with long-term hypoparathyroidism (Table 2). The model demonstrated a strong discriminatory capacity with an optimism-corrected AUC of 0.89 (CI 0.85-0.92) (Figure X). Internal-external validation of the model showed an overall high c-index, but poor calibrationX (Figure X). The addition of 24-hour corrected calcium and the identification of one parathyroid gland during surgery to the 24-hour PTH decrease significantly improved the discriminatory capacity of the model (Table 2).

Table 3 shows the subdivision of patients into the different risk groups. No patients with a PTH decrease of less than 70% in this cohort developed long-term hypoparathyroidism. In the derivation cohort, X (X%) were classified as low risk, X patients (X%) were classified as intermediate risk and X patients (X%) were located in the high-risk group. X (X%) patients in the low-risk group developed long-term hypoparathyroidism, whereas X (X%) patients in the intermediate-risk group and X (X%) patients in the high risk group developed long-term hypoparathyroidism. Readmission rates related to symptoms of hypocalcemia after discharge were concordant with the risk groups (Table 4).

**Discussion**

This study identified predictors for long-term hypoparathyroidism in patients who underwent total or completion thyroidectomy and developed a prognostic model for this population. The prediction model proposed in this study showed high discriminating power (AUC X) and is the first model for prediction long-term hypoparathyroidism that has been internally or externally validated. Larger multicenter studies are necessary to confirm the existing findings, enhance accuracy, and extend the validity of the current model.

There has been one other study that proposed a prediction tool for developing long-term hypoparathyroidism after total thyroidectomy 22. That prediction tool was not validated and contained two parameters which could only be measured after one month: PTH and calcium levels at 1 month after surgery. The current study considered the selection of variables who are available just one day after surgery. This facilitates a quick individual assessment of patients at risk for long-term hypoparathyroidism after total thyroidectomy and could aid in personalized discharge instructions and supplementation regimens. By identifying patients at higher risk, healthcare providers can further allocate appropriate follow-up care, calcium and vitamin D supplementation, and potentially reduce the burden on healthcare resources by targeting interventions to those who need them most.

The incidence of long-term hypoparathyroidism in our cohort was X%, which seems to be in line with incidences reported in other nation-wide multicenter studies 4, 23. Furthermore, we substantiated findings of Loncar *et al*., who found that patients with a delta PTH of less than 70% 24-hour after surgery had no risk of long-term hypoparathyroidism 24. In the current study, no patient developed long-term hypoparathyroidism who had a delta PTH of less than 70%. This observation suggests that evaluating the 24-hour PTH decrease can serve as an initial assessment tool to determine if a patient is at risk for long-term hypoparathyroidism. Moreover, our study highlights the significance of incorporating additional variables other than PTH into the prognostic model. Although a decrease in PTH levels emerged as the most significant predictor accounting for X% of the models’ predictive ability, we observed that parathyroid gland identification and 24-hour calcium measurements significantly enhanced the discriminatory ability of the model. Consequently, this comprehensive approach provides clinicians with a more robust tool for prognostication and aids in optimizing patient care strategies following thyroidectomy procedures.

During the early postoperative phase following thyroidectomy, the main objectives are to ensure that patients remain free of symptoms and can be discharged without any risks. However, unnecessary calcium supplementation comes with important health risks such as cardiovascular events and kidney stones 25 and should be prescribed purposefully, accounting for individual patients' risks and benefits. While the primary focus of the model developed in this study was to predict the occurrence of long-term hypoparathyroidism, we also observed a notable correlation between a higher risk of long-term hypoparathyroidism and an increased likelihood of readmissions due to symptoms related to hypocalcemia. We observed no readmissions in patients with a PTH decrease <70% and patients with a low predicted probability of developing long-term hypoparathyroidism (<10%). This suggests that providing clear information regarding the symptoms of hypoparathyroidism and hypocalcaemia at discharge may be sufficient for patients in low-risk patients. Patients with an intermediate to high risk of long-term hypoparathyroidism should receive early interdisciplinary care and close follow-up in collaboration of general practitioner and endocrinologist 14. Future research endeavors should establish distinct prediction models that can accurately assess the risk of symptoms and readmissions during the initial postoperative period. These efforts should aim to enhance and tailor the management strategies implemented after surgery to each individual patient.

Future studies should aim to overcome certain limitations observed in this study. We had a relatively small sample of patients with long-term hypoparathyroidism (X cases) which makes the model more prone to overfitting. Therefore, we revised the prediction model by adjusting the coefficients of the original logistic regression model with a shrinkage factor which was estimated using bootstrapping 26. Bootstrapping facilitates obtaining optimal estimates of internal validity of logistic regression models developed in smaller samples (e.g., events per variable ≤10) 27. Larger-scale studies are warranted to update the model and perform external validation, ensuring its reliability and generalizability. Furthermore, it is a retrospective cohort study. We tried to carefully extract the data but some information bias cannot be ruled out. Lastly, we used a reference change value of 70% for the initial PTH decrease assessment. We assumed that there was no substantial difference in in-laboratory measurement variation between the different hospitals.

**Conclusion**

The model proposed in this study showed excellent performance measures and could be used to perform an individual assessment of patients at risk for long-term hypoparathyroidism after total thyroidectomy. External validation of the model proposed in this study is required to determine its usefulness in other patient populations.

**Ethical approval**

The Medical Ethics committee of the Erasmus Medical Center approved this study ( (MEC-2018-1195, MEC-2013-233, MEC-2017-1041).

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