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

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**Abstract**

**Objective**

To develop and validate a clinical prediction model to predict the occurrence of persistent hypoparathyroidism after total or completion thyroidectomy.

**Design**

Multicenter retrospective cohort study.

**Setting**

Twelve Dutch hospitals.

**Participants**

This study included patients who underwent total or completion thyroidectomy between January 2010 and June 2021, with available preoperative or postoperative (24 hours after surgery) PTH measurements.

**Main outcome**

The occurrence of persistent hypoparathyroidism, 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. Multivariable logistic regression analysis showed that ΔPTH 24 hours after surgery (OR 1.08; 95% CI: 1.05-1.12), corrected calcium 24 hours after surgery (OR 1.44; 95% CI: 1.11-1.87) and not identifying at least one parathyroid during surgery (OR 3.94; 95% CI: 1.63-9.53) were predictors for developing persistent hypoparathyroidism. The discriminative ability of the model was excellent (optimism-corrected C-index 0.88, 95% CI: 0.84-0.92), but calibration assessed through internal-external leave-one-center-out cross-validation was poor due to a low number of events.

**Conclusion**

The model proposed in this study could be used to perform an individual assessment of patients at risk for persistent hypoparathyroidism after total thyroidectomy. External validation of the model is required to determine its usefulness in other patient populations.

**Background**

Hypoparathyroidism is a prevalent complication following total or completion thyroidectomy that can lead to hypocalcemia as a result of unintended surgical damage to the parathyroid glands. While iatrogenic hypoparathyroidism after surgery is mostly temporary and resolves within a few weeks, in some patients hypoparathyroidism becomes a chronic condition known as persistent hypoparathyroidism. The incidence of persistent hypoparathyroidism varies in the literature, partly due to the absence of consensus on its definition, ranging from less than 5% to 15% 1-3. Patients with persistent hypoparathyroidism experience lower health-related quality of life and recent studies suggest an increased mortality risk compared to individuals without this condition 4-6.

Several risk factors for developing persistent hypoparathyroidism are described in literature including extensive surgical procedures (e.g., central lymph node dissection) and post-operatively low parathyroid hormone (PTH) levels 7, 8. It is well established that post-operative PTH levels play a crucial role in predicting persistent hypoparathyroidism after total or completion thyroidectomy 4, 9, 10. 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 11. Although most studies report sensitivity and specificity outcomes of postoperative PTH levels, a comprehensive prognostic model that assesses individual patient risks of developing persistent hypoparathyroidism is currently lacking in the literature.

Identifying patients at high risk of developing persistent hypoparathyroidism can play a crucial role in preventing post-discharge adverse events, including hypocalcemia-related readmissions. Conversely, the recognition of patients with a significantly low risk of persistent hypoparathyroidism 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 persistent 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 was available. Exclusion criteria were: 1) surgery in the central neck compartment within 1 year of the index procedure or 2) external beam radiation therapy of the neck within 1 year of the index procedure. Model development and internal-external validation was performed in four cohorts of adult patients who underwent surgery in twelve Dutch hospitals between January 2010 and June 2021. The cohorts consisted of patients treated in one of the nine general hospitals in the Southwestern region of The Netherlands (cohort 1), an academic hospital in the Southwestern region of The Netherlands before December 31st 2016 (cohort 2), an academic hospital in the Southwestern region of The Netherlands after January 1st 2017 (cohort 3), and patients treated in two Dutch hospitals outside the Southwestern region of The Netherlands (cohort 4). The utilization of these cohorts, encompassing diverse time periods and geographic regions within the Netherlands, was aimed at accomplishing both temporal and geographic validation of the model 12. Prophylactic calcium supplementation after thyroid surgery was not standard of care in any of the hospitals included in this study.

Baseline characteristics such as age, sex, preoperative diagnosis, blood values (calcium, albumin, PTH), surgical procedure, 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 (ΔPTH) was calculated by (PTH at baseline - postoperative PTH after 24 hours) / (PTH at baseline) x 100%. The change in corrected calcium levels (Δ corrected calcium) was calculated by (corrected calcium at baseline - postoperative corrected calcium after 24 hours) / (corrected calcium at baseline) x 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 (Supplementary File 1) 13.

**Outcome measure**The primary outcome of this study was persistent hypoparathyroidism, defined as the need for active vitamin D supplementation 1 year after surgery, and inability to be tapered of vitamin D supplementation 14.

**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. Estimates of the imputed datasets were pooled using Rubin’s Rule 17. We predicted the probability of persistent hypoparathyroidism based on the available patient characteristics using multivariable logistic regression analysis 18. Identification of candidate predictors of the outcome was based on clinical expertise and the existing literature. Selection of variables for the final model was conducted using backward selection with a p<0.05. We calculated the importance of each predictor in the model using Wald tests. To compare the fit of nested models, we used likelihood ratio tests. Interaction terms were not taken into consideration for this prediction model. To prevent overfitting of the model, we utilized a bootstrap approach with 1000 resamples to derive a uniform shrinkage factor 19, 20. This shrinkage factor was then multiplied by the final regression coefficient of each selected predictor and the intercept was adjusted appropriately. Predictions of the final model were made easily accessible through a web application 21. To assess the relationship between the risk of persistent hypoparathyroidism and hypocalcemia-related readmissions, we divided patients into risk groups based on predicted probabilities of the model (%); low risk (<10%), intermediate risk (10%-30%) and high risk (>30%) patients.

The performance of the model was assessed using the concepts of calibration and discrimination 22. Calibration of the model was assessed by calibration plots, i.e., plotting observed frequencies versus predicted probabilities in groups. Perfect predictions should lie on the 45-degree line for agreement with the outcome in the calibration plot. We used leave-one-center-out cross-validation to assess the validity of the model, i.e., models were fit using data leaving one cohort out of the development set and making predictions for the left out cohort. Discrimination of the model was assessed by providing the C-index 22. A C-index of 1.0 indicates perfect discrimination, i.e., the model perfectly distinguishes between high and low risk patients, whereas a C-index of 0.5 indicates that the model is no better than chance. All statistical analyses were performed with R (version 4.1.0) 23.

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

The model with all candidate predictors that fitted the data best and was most clinically applicable included ΔPTH, postoperative corrected calcium after 24 hours, parathyroid glands not seen during surgery, age, sex, type of surgery, and central lymph node dissection (Supplemental Table 1). Although it seemed that ΔPTH might need to be modelled non-linearly (Supplemental Figure 1), there was no statistical evidence that the more flexible model was a better fit than the rigid model (LR test ; Supplemental Table 2). From bootstrapping with backward selection we observed a uniform shrinkage factor of 0.868. After backwards selection methods, multivariable logistic regression analysis of all 366 patients showed that ΔPTH (OR 1.08; 95% CI 1.05-1.12), corrected calcium 24 hours after surgery (OR 1.44; 95% CI 1.11-1.87), and not identifying at least one parathyroid during surgery (OR 3.94; 95% CI 1.63-9.53) were all significantly associated with persistent hypoparathyroidism (Table 2). The final model demonstrated a strong discriminatory capacity with an optimism-corrected C-index of 0.88 (CI 0.84-0.92). Internal-external validation of the model showed an overall high c-index, but poor calibration (Figure 2). Although ΔPTH is the most important predictive factor, 24-hour corrected calcium and the identification of one parathyroid gland during surgery were found improve the model significantly (LR-test see Supplemental Figure 2; C-index 0.85 versus 0.88 see Table 2).

Two (0.9%) patients with a PTH decrease of less than 70% in this cohort developed persistent hypoparathyroidism, and none was readmitted due to hypocalcemia (Supplemental Table 3). These two patients had a PTH decrease of 67.3% and 68.6%, respectively. In the entirety of the study cohort, a total of 229 patients (62.6%) were categorized as low risk, 74 patients (20.2%) as intermediate risk, and 63 patients (17.2%) as high risk (Table 3). Persistent hypoparathyroidism was observed in 1.7% (n=4/229) of low-risk patients, 16.2% (n=12/74) of intermediate-risk patients, and a 44.4% (n=28/63) of high-risk patients. Two (0.9%) low risk patients were readmitted, whereas seven (9.5%) patients in the intermediate risk group and 18 (28.6%) patients in the high risk group were readmitted.

**Discussion**

This study developed a prognostic model for persistent hypoparathyroidism in patients who underwent total or completion thyroidectomy. The model showed high discriminating power (C-index 0.88) and is the first model for prediction persistent hypoparathyroidism that has been internally or externally validated. There has been one other study that proposed a prediction tool for developing persistent hypoparathyroidism after total thyroidectomy 24. 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 a selection of variables available just one day after surgery. This facilitates a quick individual assessment of patients at risk for persistent 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 persistent hypoparathyroidism in our cohort was 12.0%, which seems to be in line with incidences reported in other nation-wide multicenter studies 3, 25. Furthermore, we substantiated findings of Loncar *et al*., who found that patients with a ΔPTH of less than 70% 24-hour after surgery had very low risks of persistent hypoparathyroidism 26. In the current study, only two patients (0.9%) developed persistent hypoparathyroidism with a ΔPTH of less than 70%. This suggests that evaluating the 24-hour PTH decrease can serve as an initial assessment tool to determine if a patient is at risk for persistent hypoparathyroidism. Our study further highlights the significance of incorporating additional variables other than PTH into the prognostic model. Although the decrease in PTH levels emerged as the most significant predictor, we observed that 24-hour calcium measurements and parathyroid gland identification during surgery significantly enhanced the discriminatory ability of the model. Future research endeavors should explore the integration of these variables in larger patient cohorts to validate their utility in predicting persistent hypoparathyroidism.

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 27 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 persistent hypoparathyroidism, we also observed a notable correlation between a higher risk of persistent hypoparathyroidism and an increased likelihood of hypocalcemia-related readmissions. We documented 2 (1%) readmissions in patients with a low predicted probability of developing persistent hypoparathyroidism (Table 3). Providing clear information regarding the symptoms of hypoparathyroidism and expectations in weaning off supplementation within one year may be sufficient for low risk patients. Patients with a higher risk of persistent hypoparathyroidism may benefit from early interdisciplinary care and closer follow-up in collaboration of general practitioner and endocrinologist 14. The developed model, which is available online 21, offers clinicians a more robust tool for prognostication, thereby assisting in optimizing patient care strategies following total thyroidectomy. Further research endeavors should establish distinct prediction models that can accurately assess the risk of symptoms of hypocalcemia 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 further aim to overcome certain limitations observed in this study. We had a relatively small sample of patients with few events, i.e., only 44 patients had long-term hypoparathyroidism. This complicates the development of a well-calibrating model that can generalize to other patient populations. Moreover, a small sample with few events make the model more prone to incidental findings. Therefore, we used uniform shrinkage obtained by bootstrapping and validated the model using leave-one-center-out cross-validation 28, 29. However, larger-scale studies are warranted to update the model and perform external validation, ensuring its reliability and generalizability. Moreover, this is a retrospective cohort study. We carefully extracted the data but possibly some information bias remains. Lastly, we assumed that there was no substantial difference in in-laboratory measurement variation between the different hospitals.

**Conclusion**

The model proposed in this study could be used to perform an individual assessment of patients at risk for persistent hypoparathyroidism after total thyroidectomy. External validation of the model proposed in this study is required to determine its usefulness in other patient populations.

**Funding**

No funding.

**Availability**

The statistical code was made available at <https://github.com/CHMMaas/PredictionHypoparathyroidism>

The web-application of the model is available at

<https://erasmusmcpublichealth.shinyapps.io/Hypoparathyroidism/>

**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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