**Table 1. Descriptive statistics.**

|  | Total  (N=366) | Cohort 1  (N=62) | Cohort 2  (N=110) | Cohort 3  (N=116) | Cohort 4  (N=78) |
| --- | --- | --- | --- | --- | --- |
| **Hypoparathyroidism** | 44 (12.0%) | 12 (19.4%) | 9 (8.2%) | 15 (12.9%) | 8 (10.3%) |
| **Readmissions related to hypocalcemia** | 27 (7.4%) | 3 (4.8%) | 9 (8.2%) | 5 (4.3%) | 10 (12.8%) |
| **PTH at baseline** |  |  |  |  |  |
| Mean (SD) | 4.4 (2.3) | 4.5 (2.1) | 3.1 (1.9) | 4.7 (1.7) | 5.6 (3.0) |
| Median (Q1, Q3) | 4.0 (2.7, 5.5) | 4.2 (3.2, 5.2) | 2.5 (2.0, 3.7) | 4.6 (3.7, 5.5) | 5.3 (3.6, 7.2) |
| Min - Max | 0.3 - 15.9 | 1.0 - 13.8 | 0.5 - 13.0 | 1.1 - 10.8 | 0.3 - 15.9 |
| Missing | 19 (5.2%) | 0 (0.0%) | 6 (1.6%) | 4 (1.1%) | 9 (2.5%) |
| **PTH at 24 hours** |  |  |  |  |  |
| Mean (SD) | 1.7 (1.3) | 1.8 (1.3) | 1.2 (1.0) | 1.7 (1.2) | 2.2 (1.7) |
| Median (Q1, Q3) | 1.4 (0.5, 2.4) | 1.6 (0.7, 2.7) | 1.1 (0.5, 1.6) | 1.5 (0.6, 2.6) | 2.1 (0.6, 3.3) |
| Min - Max | 0.1 - 8.0 | 0.1 - 5.4 | 0.1 - 4.5 | 0.4 - 4.9 | 0.3 - 8.0 |
| Missing | 28 (7.7%) | 0 (0.0%) | 7 (1.9%) | 11 (3.0%) | 10 (2.7%) |
| **ΔPTH** |  |  |  |  |  |
| Mean (SD) | 55.4 (38.0) | 53.6 (44.0) | 53.4 (45.8) | 59.6 (28.6) | 53.3 (30.9) |
| Median (Q1, Q3) | 60.4 (35.9, 84.7) | 61.8 (30.2, 84.4) | 61.0 (38.9, 86.1) | 64.3 (36.0, 85.2) | 58.1 (38.4, 79.4) |
| Min - Max | -220.0 - 98.4 | -171.4 - 98.0 | -220.0 - 98.4 | -17.4 - 96.3 | -29.2 - 97.0 |
| Missing | 47 (12.8%) | 0 (0.0%) | 13 (3.6%) | 15 (4.1%) | 19 (5.2%) |
| **Calcium at baseline** |  |  |  |  |  |
| Mean (SD) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 2.3 (0.1) |
| Median (Q1, Q3) | 2.4 (2.3, 2.4) | 2.4 (2.3, 2.5) | 2.4 (2.3, 2.4) | 2.4 (2.3, 2.4) | 2.4 (2.2, 2.4) |
| Min - Max | 2.1 - 3.0 | 2.1 - 3.0 | 2.2 - 2.7 | 2.1 - 2.6 | 2.1 - 2.6 |
| Missing | 25 (6.8%) | 0 (0.0%) | 3 (0.8%) | 6 (1.6%) | 16 (4.4%) |
| **Albumin at baseline** |  |  |  |  |  |
| Mean (SD) | 42.8 (4.2) | 43.3 (3.9) | 42.7 (4.5) | 44.3 (3.2) | 39.8 (3.9) |
| Median (Q1, Q3) | 43.0 (40.0, 46.0) | 44.0 (41.0, 46.0) | 44.0 (40.0, 46.0) | 44.0 (42.0, 47.0) | 39.0 (37.5, 43.0) |
| Min - Max | 30.0 - 51.0 | 35.0 - 51.0 | 30.0 - 51.0 | 35.0 - 51.0 | 31.0 - 49.0 |
| Missing | 20 (5.5%) | 0 (0.0%) | 3 (0.8%) | 6 (1.6%) | 11 (3.0%) |
| **Corrected calcium at baseline** |  |  |  |  |  |
| Mean (SD) | 2.2 (0.1) | 2.3 (0.1) | 2.3 (0.1) | 2.2 (0.1) | 2.2 (0.1) |
| Median (Q1, Q3) | 2.2 (2.2, 2.3) | 2.3 (2.2, 2.3) | 2.2 (2.2, 2.3) | 2.2 (2.1, 2.2) | 2.2 (2.2, 2.3) |
| Min - Max | 2.0 - 2.8 | 2.1 - 2.8 | 2.0 - 2.7 | 2.0 - 2.4 | 2.0 - 2.5 |
| Missing | 27 (7.4%) | 0 (0.0%) | 3 (0.8%) | 6 (1.6%) | 18 (4.9%) |
| **Calcium at 24 hours** |  |  |  |  |  |
| Mean (SD) | 2.1 (0.1) | 2.1 (0.2) | 2.1 (0.1) | 2.1 (0.1) | 2.1 (0.2) |
| Median (Q1, Q3) | 2.1 (2.0, 2.2) | 2.1 (2.0, 2.3) | 2.1 (2.0, 2.2) | 2.1 (2.0, 2.2) | 2.1 (2.1, 2.2) |
| Min - Max | 1.7 - 2.6 | 1.8 - 2.4 | 1.7 - 2.6 | 1.7 - 2.5 | 1.7 - 2.4 |
| Missing | 9 (2.5%) | 0 (0.0%) | 0 (0.0%) | 7 (1.9%) | 2 (0.5%) |
| **Albumin at 24 hours** |  |  |  |  |  |
| Mean (SD) | 37.5 (4.8) | 37.2 (3.0) | 37.2 (5.6) | 39.2 (4.7) | 35.8 (4.0) |
| Median (Q1, Q3) | 38.0 (35.0, 40.0) | 37.0 (35.0, 39.0) | 38.0 (35.0, 41.0) | 40.0 (38.0, 41.0) | 36.0 (33.0, 39.0) |
| Min - Max | 0.8 - 48.0 | 31.0 - 48.0 | 0.8 - 46.0 | 2.2 - 47.0 | 27.0 - 45.0 |
| Missing | 14 (3.8%) | 5 (1.4%) | 0 (0.0%) | 7 (1.9%) | 2 (0.5%) |
| **Corrected calcium at 24 hours** |  |  |  |  |  |
| Mean (SD) | 2.1 (0.2) | 2.1 (0.1) | 2.1 (0.2) | 2.0 (0.1) | 2.1 (0.2) |
| Median (Q1, Q3) | 2.1 (2.0, 2.2) | 2.0 (1.9, 2.2) | 2.1 (2.0, 2.2) | 2.0 (1.9, 2.1) | 2.1 (2.0, 2.2) |
| Min - Max | 1.6 - 2.7 | 1.7 - 2.4 | 1.7 - 2.7 | 1.7 - 2.7 | 1.6 - 2.4 |
| Missing | 14 (3.8%) | 5 (1.4%) | 0 (0.0%) | 7 (1.9%) | 2 (0.5%) |
| **ΔCorrected calcium** |  |  |  |  |  |
| Mean (SD) | 7.6 (6.5) | 8.6 (6.6) | 7.9 (6.5) | 7.6 (6.9) | 6.4 (5.7) |
| Median (Q1, Q3) | 7.3 (4.1, 11.7) | 8.3 (4.5, 12.6) | 8.2 (4.7, 11.5) | 7.6 (4.2, 12.1) | 6.1 (3.0, 9.1) |
| Min - Max | -29.8 - 23.1 | -6.0 - 23.1 | -27.7 - 21.0 | -29.8 - 22.5 | -5.5 - 18.0 |
| Missing | 33 (9.0%) | 5 (1.4%) | 3 (0.8%) | 7 (1.9%) | 18 (4.9%) |
| **ΔCalcium** |  |  |  |  |  |
| Mean (SD) | 10.6 (6.2) | 11.7 (7.2) | 11.0 (6.0) | 10.6 (6.1) | 9.1 (5.6) |
| Median (Q1, Q3) | 10.1 (6.7, 14.2) | 11.7 (6.7, 17.0) | 10.8 (8.1, 14.5) | 10.0 (6.7, 13.8) | 8.9 (6.3, 12.4) |
| Min - Max | -8.4 - 27.0 | -8.4 - 27.0 | -3.5 - 25.1 | -3.4 - 25.7 | -6.6 - 22.1 |
| Missing | 26 (7.1%) | 0 (0.0%) | 3 (0.8%) | 7 (1.9%) | 16 (4.4%) |
| **Median age in years**  (Q1, Q3) | 56.0  (42.0, 69.0) | 58.0  (46.2, 72.0) | 56.0  (40.0, 66.8) | 60.0  (48.0, 73.0) | 52.0  (40.0, 61.8) |
| **Males** | 117 (32.0%) | 25 (40.3%) | 52 (47.3%) | 31 (26.7%) | 9 (11.5%) |
| **Surgery type** |  |  |  |  |  |
| Completion | 74 (20.2%) | 11 (17.7%) | 15 (13.6%) | 23 (19.8%) | 25 (32.1%) |
| Total | 292 (79.8%) | 51 (82.3%) | 95 (86.4%) | 93 (80.2%) | 53 (67.9%) |
| **Parathyroid gland not seen  during surgery** | 48 (13.8%) | 3 (4.8%) | 9 (8.5%) | 20 (18.9%) | 16 (21.9%) |
| Missing | 19 (5.2%) | 0 (0.0%) | 4 (3.6%) | 10 (8.6%) | 5 (6.4%) |
| **Central LND = “Yes”** | 112 (31.2%) | 17 (27.4%) | 57 (52.8%) | 33 (29.2%) | 5 (6.6%) |
| Missing | 7 (1.9%) | 0 (0.0%) | 2 (1.8%) | 3 (2.6%) | 2 (2.6%) |

Abbreviations: PTH, parathyroid hormone; ΔPTH, (PTH at baseline - postoperative PTH after 24 hours) / (PTH at baseline) x 100%; Corrected calcium, measured calcium (mmol/L) + 0.016 x (34 - albumin (g/L)); ΔCorrected calcium, (corrected calcium at baseline – postoperative corrected calcium after 24 hours) / (corrected calcium at baseline) x 100%; ΔCalcium, (calcium at baseline – postoperative calcium after 24 hours) / (calcium at baseline) x 100%; LND, lymph node dissection.

**Table 2. Full, final, and simple model predicting hypoparathyroidism with a uniform shrinkage factor of 0.868**. Table displays odds ratios and the 95% confidence intervals of the logistic regression model predicting the probability of hypoparathyroidism. The final model is selected using backward selection with p-values < 0.05. The coefficients are averaged over the ten imputed data sets.

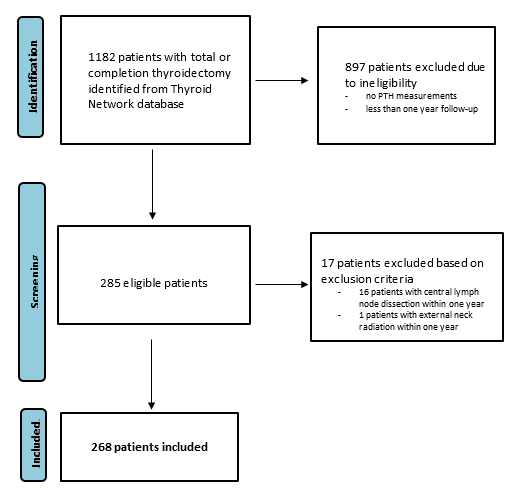
|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Full model | | |  | Final model | | |  | Simple model | | |
|  | OR | 95% CI | Imp. |  | OR | 95% CI | Imp. |  | OR | 95% CI | Imp. |
| Intercept | 2.48 | [1.80; 3.42] |  |  | 1.84 | [1.35; 2.51] |  |  | 0.00 | [0.00; 0.00] |  |
| ΔPTH  (1% increase) | 1.08 | [1.04; 1.12] | 20.6 |  | 1.08 | [1.05; 1.12] | 22.5 |  | 1.08 | [1.05; 1.12] | 28.3 |
| Corrected calcium at 24 hours  (0.2 versus 0.1) | 1.47 | [1.13; 1.91] | 8.1 |  | 1.44 | [1.11; 1.86] | 7.8 |  |  |  |  |
| Parathyroid gland not seen | 3.64 | [1.46; 9.09] | 7.7 |  | 3.90 | [1.62; 9.37] | 9.3 |  |  |  |  |
| Age in years  (i.q.r. 69 versus 42 years) | 1.14 | [0.62; 2.10] | 0.2 |  |  |  |  |  |  |  |  |
| Males versus females | 0.95 | [0.45; 2.01] | 0.0 |  |  |  |  |  |  |  |  |
| Completion surgery versus total | 1.47 | [0.44; 4.85] | 0.4 |  |  |  |  |  |  |  |  |
| Central LND = Yes versus No | 1.33 | [0.62; 2.85] | 0.5 |  |  |  |  |  |  |  |  |
| *C-index\** | 0.88 | [0.85; 0.92] |  |  | 0.88 | [0.84; 0.92] |  |  | 0.85 | [0.81; 0.89] |  |

\*The C-index is corrected for optimism by bootstrapping. Abbreviations: OR, odds ratio; CI, confidence interval, Imp., importance defined by the Chi-square of the Wald-statistic; PTH, parathyroid hormone; ΔPTH, (PTH at baseline - postoperative PTH after 24 hours) /(PTH at baseline) x 100%; Corrected calcium, measured calcium (mmol/L) + 0.016 x (34 - albumin (g/L)); LND, lymph node dissection.

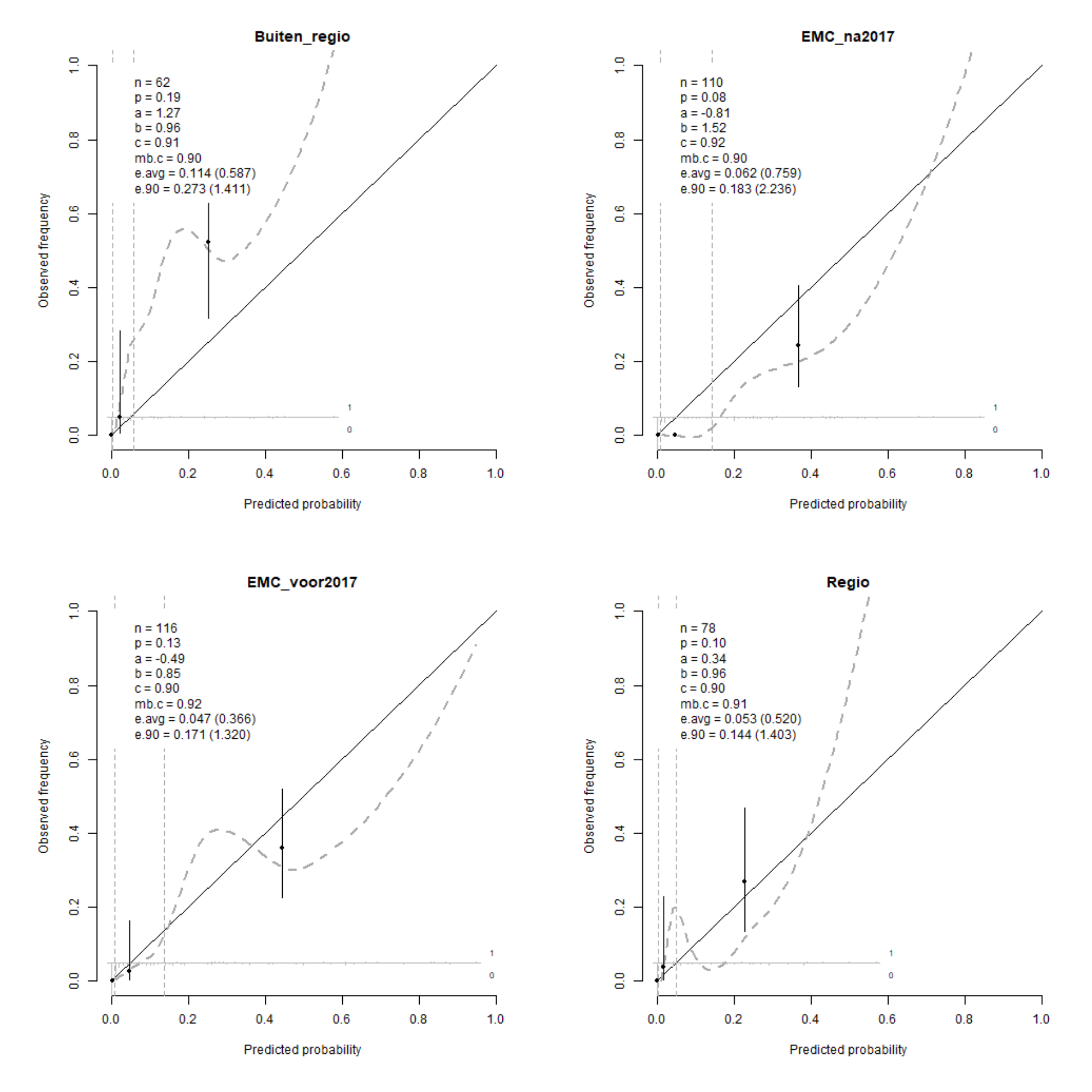
**Table 3. Predictions of hypothyroidism and readmission for all patients**. The predictions are averaged over the ten imputed data sets.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Predicted probability of hypoparathyroidism | | | | |
|  | p < 10% |  | 10% ≤ p ≤ 30% |  | p > 30% |
| N | 228 (62.6%) |  | 75 (20.2%) |  | 63 (17.2%) |
| No readmission | 226 (99.1%) |  | 68 (90.7%) |  | 45 (71.4%) |
| Readmission | 2 (0.9%) |  | 7 (9.3%) |  | 18 (28.6%) |

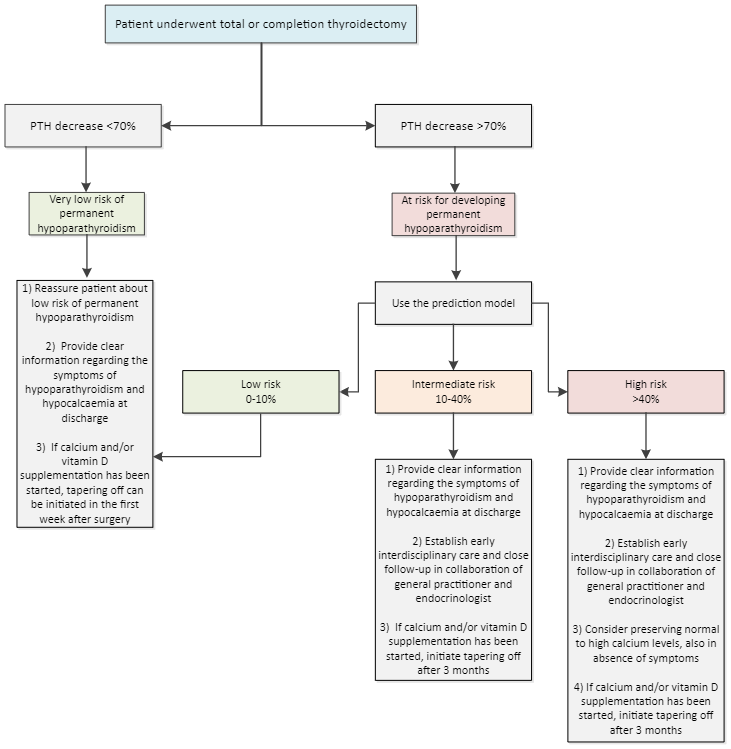
**Figure 1. Patient enrollment process flowchart**



**Figure 2. Internal-external model performance of the final model without shrinkage on one single imputed data set**.



**Figure 3. Proposed use of prediction model in clinical practice**



**Supplemental table 1. Comparison of functional form of PTH and calcium in the full model without shrinkage in one single imputed data set.**

|  |  |  |
| --- | --- | --- |
| Functional form of PTH | Functional form of Calcium | AIC |
| PTH24u | Ca24u | 205.9 |
| PTH24u | CorrCa24u | 200.7 |
| PTH24u | ΔCa | 211.1 |
| PTH24u | ΔCorrCa | 207.9 |
| ΔPTH | Ca24u | 186.7 |
| **ΔPTH** | **CorrCa24u** | **182.7** |
| ΔPTH | ΔCa | 190.4 |
| ΔPTH | ΔCorrCa | 188.3 |

**Supplemental table 2. Flexibility of ΔPTH, calcium, and age in the full model without shrinkage in one single imputed data set.**

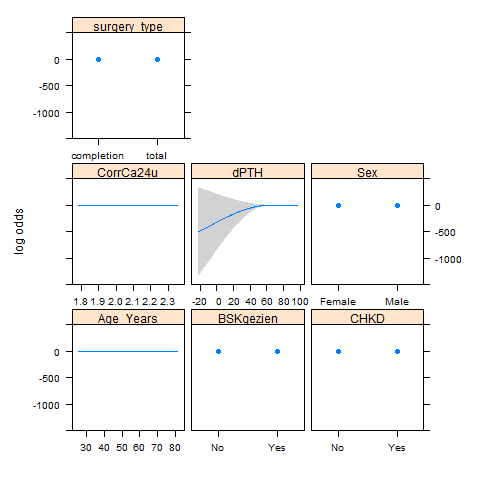
|  |  |  |  |
| --- | --- | --- | --- |
| ΔPTH | Corrected calcium | Age | AIC |
| ΔPTH | CorrCa24u | Age | 182.7 |
| rcs(ΔPTH, 3) | CorrCa24u | Age | 183.9 |
| **rcs(ΔPTH, 4)** | **CorrCa24u** | **Age** | **182.4** |
| rcs(ΔPTH, 5) | CorrCa24u | Age | 184.9 |
| ΔPTH | rcs(CorrCa24u, 3) | Age | 184.1 |
| ΔPTH | rcs(CorrCa24u, 4) | Age | 185.9 |
| ΔPTH | rcs(CorrCa24u, 5) | Age | 187.6 |
| ΔPTH | CorrCa24u | rcs(Age\_Years, 3) | 183.8 |
| ΔPTH | CorrCa24u | rcs(Age\_Years, 4) | 185.8 |
| ΔPTH | CorrCa24u | rcs(Age\_Years, 5) | 185.0 |
| rcs(ΔPTH, 4) | rcs(CorrCa24u, 3) | Age | 184.1 |
| rcs(ΔPTH, 4) | CorrCa24u | rcs(Age\_Years, 3) | 183.7 |
| ΔPTH | rcs(CorrCa24u, 3) | rcs(Age\_Years, 3) | 185.1 |
| rcs(ΔPTH, 4) | rcs(CorrCa24u, 3) | rcs(Age\_Years, 3) | 185.3 |

Likelihood ratio test of best flexible model versus rigid model .

**Supplemental table 3. PTH and readmission**. ΔPTH is averaged over the ten imputed data sets.

|  |  |  |
| --- | --- | --- |
|  | PTH 70% | PTH > 70% |
| No readmission | 23 | 316 |
| Readmission | 0 | 27 |

**Supplemental figure 1. Plot predict of flexible model without shrinkage, i.e., PTH, calcium, and age modelled with restricted cubic splines with three degrees of freedom of one single imputed data set.**

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**Supplemental Figure 1. Model performance of models uncorrected for optimism**. The predicted probabilities were averaged over the ten imputed data sets. No shrinkage was applied to the models. There is statistical evidence that the final model is better than the simple model (Likelihood ratio test ). There is no statistical evidence that the full model is better than the final model, therefore we choose the sparse model (Likelihood ratio test ).

|  |  |
| --- | --- |
| Full model | Final model |
| Z:\Project Predict Hypoparathyroidism\Development\Results\model.performance.full.model.png | Z:\Project Predict Hypoparathyroidism\Development\Results\model.performance.final.model.png |
| Simple model |  |
| Z:\Project Predict Hypoparathyroidism\Development\Results\model.performance.simple.model.png |  |

**Functional form of full model**

Abbreviations: ΔPTH, (PTH at baseline - postoperative PTH after 24 hours) /(PTH at baseline) x 100%; Corrected calcium, measured calcium (mmol/L) + 0.016 x (34 - albumin (g/L)); LND, lymph node dissection.

**Functional form of final model without shrinkage**

Abbreviations: ΔPTH, (PTH at baseline - postoperative PTH after 24 hours) /(PTH at baseline) x 100%; Corrected calcium, measured calcium (mmol/L) + 0.016 x (34 - albumin (g/L)); LND, lymph node dissection.