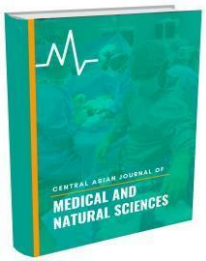

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Article

Development and Pilot Internal Validation of a Digital Clinico-Biochemical Model for Predicting Hungry Bone Syndrome after Parathyroidectomy

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Abstract: Background. Hungry Bone Syndrome (HBS) remains one of the most clinically significant forms of severe postoperative hypocalcemia after parathyroidectomy. The absence of standardized preoperative risk stratification limits early prevention and individualized postoperative monitoring. Objective. To develop and perform pilot internal validation of a digital clinico-biochemical model for predicting HBS based on preoperative variables. Materials and methods. A training cohort of 200 observations was analyzed; HBS was registered in 20 patients (10.0%). Predictors included the type of hyperparathyroidism, intact parathyroid hormone level, alkaline phosphatase activity expressed as a multiple of the upper limit of normal, corrected calcium, and an integrated digital score. Discriminative ability was assessed by ROC analysis; time-dependent prognostic significance was evaluated using Kaplan-Meier analysis and Cox regression. Results. The median score was higher in patients with HBS than in those without HBS: 14.75 [13.70-15.62] versus 8.10 [5.88-10.50] points ($p<0.001$). The area under the ROC curve was 0.961 (bootstrap 95% CI 0.927-0.986). The operational high-risk group included 30 patients; HBS developed in 17 of them (56.7%) versus 3 of 170 (1.8%) outside the high-risk group. Sensitivity of the high-risk flag was 85.0%, specificity was 92.8%, and negative predictive value was 98.2%. Kaplan-Meier analysis demonstrated significant separation between risk groups (log-rank chi-square=100.284; $p<0.001$). In the Cox model, each additional score point was associated with a 59.4% increase in event hazard (HR=1.594; $p=0.001$). Conclusion. The proposed digital model demonstrated strong internal discrimination and a marked ability to identify patients with clinically meaningful HBS risk. These results should be considered pilot findings and require external prospective validation.

Keywords: Hungry Bone Syndrome, hyperparathyroidism, parathyroidectomy, hypocalcemia, PTH, ALP, corrected calcium, ROC analysis, Cox regression, digital model.

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1. Introduction

Hungry Bone Syndrome is a pathophysiologically distinct form of postoperative hypocalcemia that occurs after abrupt elimination of chronic parathyroid hormone hypersecretion. Against the background of long-standing hyperparathyroidism, bone tissue remains in a state of accelerated remodeling; after removal of the source of excessive PTH, calcium and phosphorus intensively shift from the extracellular compartment into the bone matrix. Clinically, this may manifest as persistent hypocalcemia, the need for substantial replacement therapy with calcium and active vitamin D metabolites, prolonged hospitalization, and an increased risk of symptomatic complications [1].

Classic predictors of HBS include markedly elevated PTH, high alkaline phosphatase activity as a marker of bone turnover, low or low-normal preoperative calcium, chronic kidney disease, dialysis dependence, and skeletal manifestations of hyperparathyroidism. In routine clinical practice, however, these signs are often interpreted separately. This creates a practical problem: surgeons and endocrinologists recognize the presence of risk but lack a simple and interpretable system that converts preoperative parameters into a reproducible risk category [2].

In this context, the development of a digital clinico-biochemical risk score has dual value. First, it standardizes preoperative assessment. Second, it enables advance planning of calcium monitoring frequency, preventive therapy intensity, and the level of postoperative surveillance [3].

Objective

To develop and perform pilot internal validation of a digital clinico-biochemical model for predicting Hungry Bone Syndrome after parathyroidectomy based on preoperative variables and an integrated risk score [4].

2. Materials and Methods

Study design and data source

The study was designed as the development and pilot internal validation of a prognostic model in a training cohort of 200 observations. The dataset included the patient identifier, type of hyperparathyroidism, preoperative PTH level, ALP/ULN, corrected calcium, integrated score, binary high-risk flag (risk_high), occurrence of HBS, and a time variable for event analysis. HBS was coded as a binary event (hbs=1), corresponding to the development of the syndrome after surgery.

It is important to emphasize that this stage represents an internal pilot assessment of the digital algorithm rather than definitive external clinical validation. Therefore, the results should be interpreted as proof of concept and as a basis for subsequent prospective testing.

Model architecture

The model was constructed according to the following logic: patient preoperative data -> clinico-biochemical features -> integrated score -> risk category. The core of the model includes the type of hyperparathyroidism, intact parathyroid hormone level, alkaline phosphatase activity expressed as a multiple of the upper limit of normal, and corrected calcium. The clinical concept of the model also allows expansion by adding chronic kidney disease, dialysis dependence, and the severity of skeletal changes.

In the analyzed training cohort, the final score ranged from 0.6 to 18.0 points. The operational high-risk flag corresponded to score >13.0; in practice, this group included patients with scores from 13.1 to 18.0.

Statistical analysis

Quantitative variables are presented as median [interquartile range] and additionally as mean +/- standard deviation. The HBS and non-HBS groups were compared using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher's exact test. The discriminative ability of the score was assessed by ROC analysis with calculation of AUC; the 95% confidence interval for AUC was additionally estimated using a bootstrap approach. The optimal threshold was determined by the Youden index. Time-to-event analysis included Kaplan-Meier curves, the log-rank test, and Cox regression. A p value <0.05 was considered statistically significant.

3. Results

Cohort characteristics and HBS incidence

The training cohort included 200 observations. HBS was registered in 20 patients, corresponding to an incidence of 10.0%; 180 patients (90.0%) were censored or had no event. The distribution by type of hyperparathyroidism was relatively balanced: type_hpt=1 in 72 patients, type_hpt=2 in 68 patients, and type_hpt=3 in 60 patients. The incidence of HBS was 9.7%, 13.2%, and 6.7%, respectively; differences between hyperparathyroidism types did not reach statistical significance (p=0.464). Therefore, the type of hyperparathyroidism alone did not provide sufficient risk stratification, confirming the need for a multifactorial model [5].

Table 1. Preoperative variables in the HBS and non-HBS groups

Variable	HBS=0 (n=180)	HBS=1 (n=20)	p
PTH, pg/mL, median [IQR]	791.0 [596.5-976.1]	1417.2 [1215.2-1616.9]	<0.001
ALP/ULN, median [IQR]	1.62 [1.34-1.85]	2.92 [2.56-3.14]	<0.001
Corrected Ca, mmol/L, median [IQR]	2.24 [2.18-2.31]	2.01 [1.98-2.08]	<0.001
Integrated score, median [IQR]	8.10 [5.88-10.50]	14.75 [13.70-15.62]	<0.001
Integrated score, mean +/- SD	8.18 +/- 3.18	14.63 +/- 1.72	<0.001

Patients with HBS were characterized by markedly higher PTH and ALP/ULN values, lower corrected calcium, and a substantially higher integrated score. The most pronounced separation between groups was observed for the score, supporting the advantage of integrating several clinico-biochemical parameters into a single scale [6].

Discriminative ability of the score

ROC analysis demonstrated high ability of the score to distinguish patients who subsequently developed HBS from those who did not. The AUC was 0.961; bootstrap 95% CI was 0.927-0.986. According to the Youden index, the optimal statistical threshold was located at approximately 12.20 points and provided sensitivity of 95.0% with specificity of 88.9% (Youden=0.839). At the same time, a stricter operational high-risk threshold of score >13.0 provided higher specificity and a clinically convenient identification of the maximum-risk group [7].

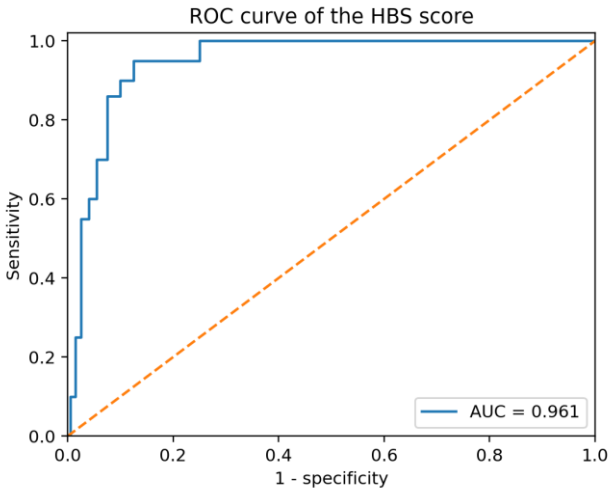

Figure 1. ROC curve of the integrated HBS score. The area under the curve was 0.961, corresponding to high internal discrimination of the model.

Table 2. Clinical interpretation of the main score thresholds

Score threshold	Sensitivity	Specificity	Youden index	Clinical meaning
>=10.55	100.0%	76.7%	0.767	Maximum sensitivity; more false positives
>=12.15	95.0%	88.9%	0.839	Optimum by the Youden index
>=13.10	85.0%	92.8%	0.778	Operational high-risk group

Clinical performance of the high-risk flag

The operational high-risk group included 30 patients (15.0% of the entire cohort). In this group, HBS developed in 17 of 30 patients (56.7%), whereas outside the high-risk group it occurred in only 3 of 170 patients (1.8%). The relative risk of HBS in the presence of the high-risk flag was 32.1 (95% CI 10.0-102.9), and the odds ratio was 72.8 (95% CI 18.9-281.1; p<0.001) [8].

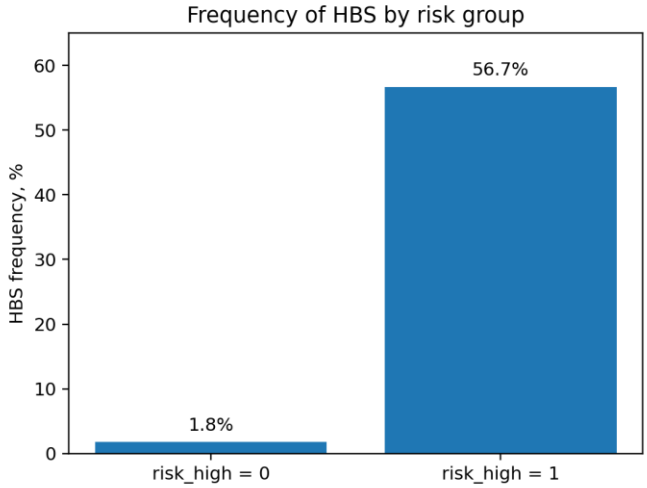

Figure 2. Frequency of HBS in the risk_high=0 and risk_high=1 groups. The high-risk group demonstrated an approximately 32-fold increase in the relative risk of the event.

Table 3. Diagnostic characteristics of the high-risk flag

Parameter	Value	95% CI
Sensitivity	85.0%	64.0-94.8%
Specificity	92.8%	88.0-95.7%
PPV	56.7%	39.2-72.6%
NPV	98.2%	94.9-99.4%
Accuracy	92.0%	-
F1-score	0.68	-

Time-to-event analysis

Kaplan-Meier analysis showed pronounced divergence of HBS-free survival curves between patients with and without the high-risk flag. In the risk_high=0 group, there were 170 observations and 3 events; the censored proportion was 98.2%. In the risk_high=1 group, there were 30 observations and 17 events; the censored proportion was 43.3% [9]. Mean event-free time was 10.865 in the risk_high=0 group versus 6.300 in the risk_high=1 group. The median time to event in the high-risk group was 5.000, whereas the median was not reached in the risk_high=0 group. The log-rank test confirmed a statistically significant difference between distributions: chi-square=100.284; p<0.001 [10].

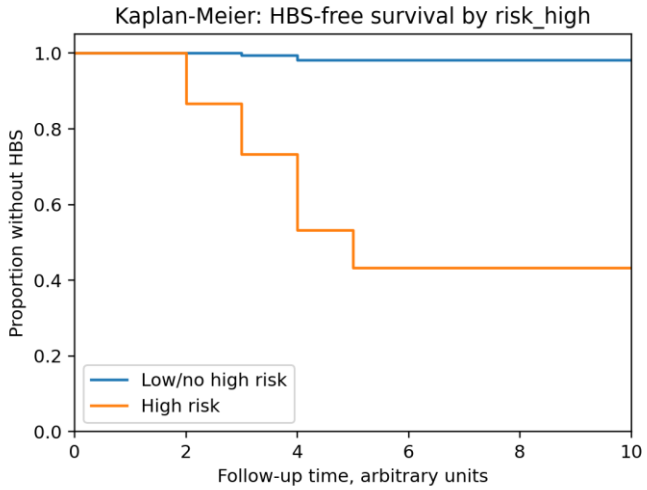

Figure 3. Kaplan-Meier curves showing the proportion of patients without HBS according to the high-risk flag.

Table 4. Cox regression model for time to HBS

Covariate	B	SE	Wald	HR (Exp(B))	p
score	0.466	0.144	10.453	1.594	0.001
risk_high	1.131	0.927	1.490	3.100	0.222

The overall Cox model was statistically significant (chi-square=65.810; df=2; p<0.001; -2 Log Likelihood=144.629). In the multivariable model, the continuous score retained independent prognostic significance: each additional point was associated with a 59.4% increase in the hazard of HBS. When the score and its derived binary risk_high flag were entered simultaneously, the latter did not reach statistical significance, which expectedly reflects partial collinearity between the continuous scale and its binary categorization [11].

4. Discussion

The principal finding of this study is that the integrated digital score was substantially more informative than the categorical characteristic of hyperparathyroidism type alone. Although secondary hyperparathyroidism is traditionally regarded as a higher-risk clinical context for HBS, differences by type_hpt were not statistically significant in this training cohort. In contrast, integration of biochemical markers of disease severity and bone turnover produced clear separation between groups [12].

A practically important finding is not only the high AUC value but also the structure of model errors. The high-risk flag had a moderate positive predictive value but a very high negative predictive value. This means that the model is particularly useful as a tool for excluding high risk: a patient outside the high-risk group is very unlikely to develop HBS. At the same time, a patient with the high-risk flag will not necessarily develop the complication but requires more aggressive monitoring and a preventive plan.

The high AUC in the training cohort indicates strong internal discrimination, but it should not be interpreted as proof that the model is ready for broad clinical implementation. Prognostic models commonly demonstrate degradation of performance metrics when transferred from internal to external validation. Therefore, the next stage should include an independent clinical cohort, prospectively registered HBS criteria, standardized time points for measuring calcium, phosphorus, magnesium, and PTH, and assessment of model calibration [13].

Clinical implications

The proposed model may be used as a digital preoperative triage instrument. For patients with a high score, it is reasonable to plan more frequent calcium, phosphorus, and

magnesium measurements in the early postoperative period, readiness for intravenous calcium correction, early administration of active vitamin D metabolites, and longer follow-up. For patients outside the high-risk group, the model may help avoid excessive surveillance intensity while maintaining standard safety. Thus, the value of the model lies not in replacing clinical decision-making but in standardizing the degree of alertness and the preventive care pathway [14].

Study limitations

- The analysis was performed in a training cohort rather than an independent external cohort; therefore, the results represent pilot internal validation.
- The number of HBS events was limited (20 cases), increasing the risk of unstable estimates and wide confidence intervals for individual parameters.
- The score has a discrete-continuous structure and includes repeated values; this may affect ROC estimates, as also noted in the statistical output.
- Clinical implementation requires external validation, calibration analysis, decision-curve analysis, and assessment of the algorithm in a real postoperative management pathway [15].

5. Conclusion

In a pilot training cohort of 200 observations, HBS was registered in 20 patients (10.0%). The integrated HBS score demonstrated high internal discrimination: AUC=0.961 (bootstrap 95% CI 0.927-0.986). Patients with HBS had a significantly higher score: 14.75 [13.70-15.62] versus 8.10 [5.88-10.50] points ($p<0.001$), higher PTH and ALP/ULN, and lower corrected calcium. The high-risk flag identified 30 patients, among whom the incidence of HBS reached 56.7% versus 1.8% outside the high-risk group; the relative risk was 32.1 and OR=72.8. The diagnostic characteristics of the high-risk flag were: sensitivity 85.0%, specificity 92.8%, PPV 56.7%, NPV 98.2%, and accuracy 92.0%. Kaplan-Meier analysis confirmed a pronounced difference between risk groups (log-rank chi-square=100.284; $p<0.001$), and Cox regression demonstrated independent time-dependent prognostic significance of the score (HR=1.594; $p=0.001$). These data support the potential of the digital clinico-biochemical model for preoperative risk stratification of HBS; however, clinical implementation requires external prospective validation.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Kamulzhanova Zh.A. - concept, data collection and systematization, manuscript preparation; Rozibaev B.A. - statistical analysis, digital model architecture, interpretation of results; Kudratova N.A. - scientific supervision and critical revision of the clinical section.

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