**Mortality prediction in intensive care units including premorbid functional status
improved performance and internal validity**

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Highlights

- We developed and validated an in-hospital mortality prediction model using 61,224 admissions (6,463 non-survivors) from an international multicenter cohort study. Among the clinically relevant predictors were age, severity of acute illness and admission type, along with premorbid functional status and diagnoses as modeling variables.
- We found excellent internal discrimination and calibration properties of the developed prediction model.
- We used a proposed framework for interpreting validation and transportability properties of prediction models and concluded that while our model showed good geographic discrimination transportability, other performance measures revealed a moderate to high heterogeneity between hospitals.

Abstract

Objective: Prognostic models are key for benchmarking intensive care units (ICUs). They require up-to-date predictors and should report transportability properties for reliable predictions. We developed and validated an in-hospital mortality risk prediction model to facilitate benchmarking, quality assurance, and health economics evaluation.

Study Design and Setting: We retrieved data from the database of an international (Finland, Estonia, Switzerland) multicenter ICU cohort study from 2015-2017. We used a hierarchical logistic regression model that included age, a modified Simplified Acute Physiology Score-II, admission type, premonitory functional status, and diagnosis as grouping variable. We used pooled and meta-analytic cross-validation approaches to assess temporal and geographical transportability.

Results: We included 61,224 patients treated in the ICU (hospital mortality 10.6%). The developed prediction model had an area under the receiver operating characteristic curve 0.886, 95% confidence interval (CI) 0.882-0.890; a calibration slope 1.01, 95% CI (0.99-1.03); a mean calibration -0.004, 95% CI (-0.035-0.027). While the model showed very good internal validity and geographic discrimination transportability, we found substantial heterogeneity of performance measures between ICUs (I-squared: 53.4% to 84.7%).

Conclusion: A novel framework evaluating the performance of our prediction model provided key information to judge the validity of our model and its adaptation for future use.

63 **Keywords**

64 Case mix, in-hospital mortality, intensive care, prediction model, transportability, validation

What is new?

Key findings:

Our mortality prediction model—which combined established clinically relevant predictors with premorbid functional status and diagnoses as modeling variables—showed very good internal validity, geographic discrimination and temporal transportability, with a substantial heterogeneity of performance measures between ICUs.

What does this add to what is known?

Premorbid functional status and diagnosis are known predictors of ICU-relevant study outcomes, but are not regularly implemented in established scoring systems. The inclusion of this information showed increased predictive model performance compared to predictions from established risk scoring systems, while showing good internal validation and geographic discrimination transportability.

What is the implication and what should change now?

To the best of our knowledge, this is one of the first development and validation studies to investigate geographical and temporal transportability properties of an ICU mortality prediction model. Transportability properties are key in the reliable monitoring and benchmarking of ICUs and for their planning. They provide an important piece of information about the model validity in other study populations and settings, and should be quantified in future validation studies of ICU prediction models.

87	Abbreviations
88	
89	APACHE: Acute Physiology and Chronic Health Evaluation
90	AUC: area under the curve
91	CI: confidence interval
92	ECOG: Eastern Cooperative Oncology Group
93	FICC: Finnish Intensive Care Consortium
94	ICI: Integrated Calibration Index
95	ICU: intensive care unit
96	LASSO: Least absolute shrinkage and selection operator
97	LOESS: Locally estimated scatterplot smoother
98	PI: Prediction interval
99	ROC: receiver operating characteristic
100	SAPS: Simplified Acute Physiology Score
101	OR: odds ratio
102	WHO: World Health Organization

1. Introduction

Scoring systems for prediction of mortality risk are widely used to characterize severity of illness in intensive care unit (ICU) patients in clinical trials, benchmarking, quality assurance, and health economics evaluations [1]. The two most widely used scoring systems—APACHE (acute physiology and chronic health evaluation) [2] and SAPS (simplified acute physiology score) [3]—were introduced in the 1980's and repeatedly updated to preserve and improve their predictive value in response to advances in patient care, therapeutic options with prognostic relevance, and changes in demographics. Despite the updates (the most recent generations are APACHE-IV and SAPS-3 [4–8]) and recalibration, these models may lose their validity over time, and have poor external validity when applied in different health care systems. This may interfere with benchmarking of ICUs, and ultimately impact the decision-making of clinicians, health care providers and regulatory bodies. ICU prediction models developed in study populations from the United Kingdom (ICNARC), Australia and New Zealand (ANZIC) and the Netherlands have been updated to address poor validity and were extended with new clinical predictors like functional status which were strongly associated with the study outcome [9–12].

The performance of prediction models depends on their validity and transportability, and can be classified into different frameworks [13–15]. Geographical and temporal transportability indicate performance outside the study population used for the development of the prediction model, e.g., in other hospitals or time periods [14,15]. Lack of transportability, case mix differences, changes in mortality between ICUs and over time, drive the need to recalibrate existing prediction models or to develop new ones [14,16]. Reporting their validation and transportability is important to avoid biased outcome predictions and to support the planning of ICU benchmarking programs where new ICUs might be included or a comparison with ICUs outside an existing benchmark system might evolve.

The aim of this study is to develop and validate an in-hospital mortality risk prediction model by adding simple indicators of premorbid functional status to established outcome predictors

(age, severity of illness, diagnosis, admission type) in order to quantify the validity and transportability properties of the prediction model and to interpret their impact using a proposed framework for validation [14,15].

2. Methods

The manuscript has been written in accordance with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [17]. The TRIPOD checklist is provided in Supplemental Table 1.

2.1 Study design and population

We conducted a retrospective multicenter study, with prospectively collected data from the international Finnish Intensive Care Consortium benchmarking database (FICC) that includes ICUs from Finland, Estonia and Switzerland. We used all intensive care admissions of the years 2015-2017. We excluded readmissions, admissions after cardiac surgery, and admissions with care restricted to evaluation for potential organ donation. Cardiac surgery admissions were excluded due to their specific pre- and perioperative risk profiles.

2.2 Data source

We used data from 2015-2017 in the FICC database. The FICC consists of 22 ICUs in Finland, and the ICUs of one university hospital in Estonia (100% of university ICU admissions and 16% all ICU admissions in Estonia) and one in Switzerland (33 % of all university hospital ICU admissions and 11 % of all ICU admissions in Switzerland). All except two ICUs were multidisciplinary.

Data related to clinical diagnosis, severity of illness scoring systems, care interventions, physiologic, administrative, and in-hospital mortality are prospectively collected during the ICU and hospital stay into local patient health care records (electronic in Finland and Switzerland, paper in Estonia) [18]. Each admission is validated by trained ICU nurse data

managers or intensivists using logical rules, median filtering and graphic displays to ensure data quality, before transfer to the FICC database.

2.3 Ethical approval

The model was developed in conjunction with a health economic analysis, whose study protocol, database contents and data management process were approved by the National Institute of Health and Welfare, Finland (Decision numbers THL/1524/5.05.00/2017 and THL/1173/05.00/2018). According to the regulations in Finland, Estonia, and Switzerland, no ethics committee approval was needed for retrospective use of anonymized data.

2.4 Study outcomes

Prediction of in-hospital mortality. Data on in-hospital mortality was prospectively collected for each admission from the hospital record.

2.5 Predictors

Based on the literature and discussions among clinical experts we used the following predictors: age, a modified SAPS-II score which excludes age and admission type (see [Supplemental Text 1](#)), surgical vs. non-surgical admission, emergency versus elective admission, diagnosis (APACHE-III diagnoses [19,20], [Supplemental Table 2](#)) and functional status based on the WHO ECOG classification [21], with the two best categories combined into one (category 0: Normal functional status or able to perform light work, 1: Light limitations: Unable to work but capable of all selfcare, 2: Moderate limitations: Need for some help in selfcare, 3: Severe limitations: Fully dependent on help).

2.6 Statistical methods

We describe the study population using frequencies (n), percentages (%), median and interquartile range (IQR). For the prediction model development we followed the recommendations by Steyerberg and Harrell [22,23]. In brief, Steyerberg and Harrell recommend not to use data-splitting approaches for validation and that heterogeneity of

performance measures should be assessed. We used hierarchical multivariable logistic regression models accounting for nested admissions within APACHE-III diagnostic groups to develop the prediction model ($M_{developed}$). A second prediction model excluded premorbid functional status as predictor ($M_{developed2}$). We modeled the continuous variables age and modified SAPS-II score as restricted cubic splines with 3 knots chosen at the 10th, 50th and 90th percentiles [13,24]. A priori we included an interaction effect between age and the modified SAPS-II score. We report predictor effects as odds ratios (OR) with 95% confidence intervals (CI). We assessed the overall association of variables and model fit using $\chi^2(k)$ statistics with k degrees of freedom from a deviance test. For parsimony of the risk score, we set varying intercept estimates for APACHE-III diagnoses to zero if the 95% CI overlapped by an OR of 1. We calculated the probability of hospital death from the original SAPS-II score to compare predictions from derived models [4]. We assessed discrimination ability with the area under the receiver operating characteristics curve (AUC), mean calibration (calibration-in-the-large), weak calibration (calibration slope) and moderate calibration performance using a fitted calibration curve from locally estimated scatterplot smoother (LOESS), the Integrated Calibration Index (ICI), the maximum, median and 90th percentile of the absolute difference between the LOESS calibration and the diagonal line (E_{max} , E_{50} , E_{90}), and the Brier score [25–27]. We used a second-degree polynomial with a smoothing parameter set to 0.75 for LOESS. We used a modified large sample Hosmer-Lemeshow test, which was devised from a model attaining a p-value of the traditional Hosmer-Lemeshow test of 0.05 in a sample of one million observations [28]. We used a bootstrap approach for internal model validation based on 100 replicates [13,24]. We assessed temporal and/or geographical transportability, that is, to what extent predictions perform as well in other study populations (in time and/or at different hospitals) and used a proposed framework for interpretation [13,14]. For that purpose, we defined two time periods: Time period one covers the years 2015-2016, whereas time period two covers the year 2017.

In brief, we first assessed to what extent the development and validation samples were related (i.e., to what extent case mix differed between hospitals and time periods). For that purpose, we derived AUC from hierarchical logistic membership models (including the predictors used

for the mortality prediction model and the outcome variable) and reported standardized standard deviations (SDs) of linear predictors (i.e., SDs from validation samples are divided by the SD of the development sample) [14]. Development and validation samples were defined by a "leave-one-unit-out" or a "leave-one-period-out" approach ('internal-external' validation) [15]. Each model performance measure is estimated from the left-out validation samples. We reported pooled estimates and estimates from random effects meta-analyses of AUC and calibration performance measures with 95% CI and prediction intervals (PI) [15]. Results from the meta-analyses include DerSimonian-Laird estimators for between-study standard deviation, I-squared and Cochran's Q-statistic for heterogeneity. Because of the small number of time periods no meta-analytic approach was used for assessing temporal transportability.

We performed several sensitivity analyses. First, we derived a prediction model which used the same predictors as $M_{developed}$ but did not account for APACHE-III diagnosis groups ($M_{sensitivity}$), by using an ordinary logistic regression model. We compared $M_{developed}$ with $M_{sensitivity}$ using analysis of deviance. We further calculated the probability of hospital death from $M_{developed}$, $M_{developed2}$ (same as $M_{developed}$ but without predictor *premorbid functional status*), $M_{sensitivity}$, and the original SAPS-II score, and plotted receiver operating characteristic curves. Second, we used (non-hierarchical) ordinary and penalized logistic regression and least absolute shrinkage and selection operator (LASSO) with APACHE-III diagnostic groups as fixed effects. Penalized estimates were optimized with a modified Akaike Information Criterion [24]. The minimum penalizing factor for LASSO was derived from 30 cross-validation samples. Third, we compared discrimination and calibration performance of the shrunken risk score with its non-shrunken version, that is, when the varying intercept estimates of APACHE-III diagnoses were not set to zero. All analyses were complete case analyses and excluded patients with missing predictor information and were performed in R version 4.0.2.

3. Results

3.1 Study population

The eligible study population included 61,385 patients. We excluded 161 patients (0.3%) because of missing values in age (n=14), admission type (n=126), SAPS-II score (n=15) and APACHE-III diagnosis (n=6). Thus, the final analysis included 61,224 patients with 6,463 (10.6%) in-hospital deaths ([Table 1](#)). The median age was 63 years (IQR 24), the median SAPS-II score was 31 points (IQR 22) and the median modified SAPS-II was 15 points (IQR 19) and 40% were female. Eighty percent of the admissions were emergency admissions and 40% were surgical. Around 30% of all patients had a premorbid functional limitation. The number of admissions and number of deaths per each unit and year is shown in [Supplemental Table 3](#).

3.2 Prediction model

The prediction model ($M_{developed}$) developed for the risk score included 5 variables (age, modified SAPS-II score, admission type, premorbid functional status and APACHE-III diagnostic group) with 15 parameters (1 parameter for intercept, 2 parameters for non-linear age, 2 parameters for non-linear modified SAPS-II score, 4 parameters for interaction effect, 2 parameters for admission type (surgical, emergency), 3 parameters for functional status, 1 parameter for APACHE-III diagnoses grouping variable). [Figure 1](#) shows the joint predictor effects of the categorical variables from the hierarchical logistic regression model. Surgical patients had lower odds of dying than non-surgical patients [OR 0.79, 95%CI (0.64-0.98)]; emergency admissions had higher odds of dying than elective admissions [OR 2.85, 95%CI (2.36-3.45)]. Patients with premorbid functional limitations showed higher odds of dying than patients with normal premorbid functional status. Premorbid functional status was strongly associated with mortality (deviance($M_{developed}$)=27891, deviance($M_{developed2}$)=28052; $\chi^2(3)=161.0$, $p<0.001$). Age and the modified SAPS-II score showed strong evidence for a non-linear relationship (for age: $\chi^2(1)=8.07$, $p=0.004$; for modified SAPS-II score $\chi^2(1)=86.18$, $p<0.001$; [Figure 2](#)). There was strong evidence for an interaction effect of the non-linear modeled variables ($\chi^2(4)=67.22$, $p<0.001$). [Figure 3](#) shows the varying intercept estimates for the APACHE-III diagnoses. The estimated between-diagnoses standard deviation was 0.63; that is, 95% of the ORs of the APACHE-III diagnosis estimates lie between 0.29 (2.5% OR) and 3.43 (97.5% OR). Estimates with 95% CIs overlapping an OR of 1 are shown in red. These

estimates were set to zero in the final risk score for model parsimony. APACHE-III code=0 covers “other postoperative” admissions (n=560, 61% various emergencies). Due to the clinical heterogeneity, their estimate was also set to zero. The final prediction model includes 40 APACHE-III diagnoses (calculation formula in [Supplemental Text 2](#)). [Supplemental Figure 1](#) and [Supplemental Figure 2](#) show crude predictor effects. The effect of emergency admissions decreases from a crude model [OR=5.97, 95%CI (5.01-7.10)] to OR=2.85 (reported above) in an adjusted model.

3.3 Discrimination and calibration

[Figure 4](#) shows the internal discrimination and calibration properties of the developed model ($M_{developed}$): AUC 0.886, 95%CI (0.882-0.890), mean calibration -0.004, 95%CI (-0.035-0.027), calibration slope 1.01, 95%CI (0.99-1.03), ICI 0.134, E50 0.032, E90 0.463, Emax 1.000 and a Brier score 0.067. The Hosmer-Lemeshow test for large samples resulted in $p=0.05$. The prediction model without the predictor *premorbid functional* ($M_{developed2}$) had an AUC 0.885, 95%CI (0.881-0.889), mean calibration 0.001 (-0.030-0.031) and calibration slope 1.01, 95%CI (0.99-1.03). Predictions from the original SAPS-II score revealed only slightly lower discrimination ability [AUC=0.864, 95%CI (0.860-0.869)], but poor calibration ([Supplemental Figure 3](#)). [Supplemental Figure 4](#) shows receiver operating characteristic curves from mortality predictions from $M_{developed}$, $M_{developed2}$, $M_{sensitivity}$ and from the original SAPS-II score. Discrimination ability was best for the developed prediction model.

3.4 Validation and interpretation

We assessed the relevance of case mix differences. [Supplemental Figure 5](#) shows AUC estimates from membership models. For geographical validation samples, AUC ranged from 0.65 to 0.96, indicating a substantial heterogeneity between the development and validation samples. Two units with AUC>0.9 are specialized ICUs. The development and validation samples between time periods were similar in terms of the used predictor variables and the outcome (AUC=0.54). [Supplemental Figures 6](#) shows results from standardized SDs of linear predictors (range 0.74 to 1.11), indicating moderate to large case-mix differences between

hospitals. The interpretation of results from linear predictors are comparable to the ones from membership models. One hospital was left out of the membership modelling and the geographical transportability assessment because of a low number of admissions (n=14).

Table 2 shows results from internal and internal-external validation and transportability investigations. We observed very good internal model reproducibility (for example, AUC from the bootstrap samples was 0.888 compared to 0.886 from the development sample). While the overall internal-external calibration was very good, with 95% CIs and PIs overlapping a calibration slope of 1 or a mean calibration value of 0 for all validation approaches (except for the pooled geographical-temporal calibration slope, which was 0.978, 95% CI [0.963-0.993]), we found a moderate to high heterogeneity between ICUs for AUC, calibration slope and mean calibration (I-squared ranging from 53.4%-84.7%). Supplemental Figures 7-15 show the in-depth results for transportability based on pooled estimates and random-effects meta-analyses.

3.5 Sensitivity analyses

In the sensitivity analyses, we compared $M_{developed}$ with a prediction model ($M_{sensitivity}$) which did not account for APACHE-III diagnosis groups but used the same predictors as model $M_{developed}$. $M_{sensitivity}$ is an ordinary logistic regression model with 14 parameters. We found evidence for a better model fit of $M_{developed}$ compared to $M_{sensitivity}$ (deviance($M_{developed}$)=27,891, deviance($M_{sensitivity}$)=28,864; $\chi^2(1)=973.3$, $p<0.001$). Supplemental Figure 16 and Supplemental Figure 17 show the sensitivity analysis results from different modeling strategies. In general, effect estimates from the investigated model approaches were similar. Supplemental Figure 18 shows the discrimination and calibration properties of the non-shrunken model; that is, when the estimated varying intercepts of the APACHE-III diagnosis groups were not set to zero. The results were similar to the implemented risk score from $M_{developed}$.

4. Discussion

Based on data of 61,224 patients in a large international multicenter ICU database, we created a new in-hospital mortality prediction model by adding premorbid functional status to well-established predictors of in-hospital mortality (age, severity of acute illness, diagnosis, admission type). Premorbid functional status was strongly associated with mortality and increased the predictive performance of the model, while the inclusion of diagnosis accounted for the large heterogeneity between diagnosis groups. Overall, the prediction model showed excellent discrimination and calibration performance. We used a proposed framework for interpreting validation results which investigated case-mix differences and transportability properties. We concluded that while a large heterogeneity between ICUs due to case-mix differences exists our prediction model might provide reliable predictions for future monitoring and benchmarking of key performance indicators.

Valid mortality predictions are essential for use of standardized mortality ratios (SMRs) to assess ICU performance, both for within-ICU evolution and for comparisons between ICUs in benchmarking programs [29,30]. However their use has been criticized for susceptibility to case-mix differences [1]. By using different analyses approaches (membership model approach and internal-external validation) we found substantial differences in case mix among hospitals in our study population. While our findings from internal validation and cross-validated pooled estimates showed very good discrimination and calibration properties, we found a moderate to high variation of prediction model performance measures between ICUs using meta-analytic approaches. Predictions intervals from meta-analytic approaches (that is, the uncertainty interval in which a performance measure of a potentially new ICU will be expected to lie) indicated that the discriminative ability was very good (lowest lower 95% PI: 0.85), while the prediction uncertainties of the mean calibration and calibration slope indicated a potentially not optimal performing prediction model for new ICUs. Heterogeneity between ICUs was mostly expected, given that our data includes admissions from different hospital categories and from different health care systems, and can be explained by difference in case-mix, in resource use or in quality of care. Our joint geographical-temporal transportability results require a careful interpretation because they are prone to potential

model overfitting and biased performance measures because of the small event size of certain hospitals using only admissions from the year 2017 for validation.

The ‘customization’, modernization, and development of new prediction models should offer clear benefits [16,31–34]. The inclusion of diagnoses should help cluster patients into homogenous groups, with similar treatment procedures, resource utilization and patient outcomes [9,35,36]. Nevertheless, it is conceivable that the premorbid functional status may have a relevant impact on risk of in-hospital death and consequently on the performance of mortality prediction models [12,34,37]. Approximately 30% of our study patients had premorbid functional limitation, which was strongly associated with mortality. Ferrando-Vivas et al. found that including the level of assistance needed in daily activities (none, some, total) improved the predictive performance of the ICNARC model [12]. The more detailed WHO ECOG classification we used also improved the performance, emphasizing the need to include premorbid functional status in ICU scoring systems. Demographic changes with an increasing proportion of older people will likely increase the ICU admissions of elderly. Muscedere et al. showed in a systematic review that frailty is an important factor of mortality in elderly treated in the ICU [38]. Dólera-Moreno et al. developed and validated a risk prediction model which uses frailty measures as predictors for all-cause mortality [34]. The implementation of geriatric assessments in ICUs might foster the use of clinical relevant predictors relevant for older persons in future prediction models [39–41].

The statistical approach used for the development and validation of a prediction model should be critically addressed [13]. Due to the a priori decision to include diagnoses, we used a hierarchical regression model to account for grouping of intensive care admissions and discussed its advantages and disadvantages with clinical experts and statisticians [42]. The multicenter study design allowed in-depth validation of the developed risk model and we used the framework proposed by Debray et al. as a guide in interpreting our validation results [14,15]. The internal, geographical, and temporal transportability validation methods provide important key measures for validity and for generalizability for broader study populations. Austin et al. used different admission eligibility criteria for different time periods to assess

temporal and methodological portability [15]. Changes in the structural composition of ICUs in a benchmarking program (for example by the inclusion of specialized ICUs) inherently serve as a new set of admissions of an ICU which allows for the investigation of transportability properties. The FICC, for example, was extended by a neurosurgical ICU in 2017 and was included in the geographical transportability investigation. Our findings from the membership model and the used internal-external validation approaches will be included in regular reports of the FICC benchmarking program and might support the future planning of this program. Further, with the interpretation of measures of heterogeneity from the membership model or the used internal-external validation approaches we have a tool which supports the decision whether a recalibration of the prediction model might be required [14].

4.1 Strengths

First, the large sample size from different hospitals, years, and health care systems, and use of advanced statistical approaches, allows an in-depth investigation of the heterogeneity of performance measures and should enhance the generalizability of the model. For the validation of prediction models an event size of at least 100 events have been recommended [22,43]. Most hospitals in our data have a larger event size when data is combined for all years (i.e., for the assessment of geographical transportability). Second, data validation by trained data managers, use of logical rules, median filtering, and graphic displays should enhance data quality. Third, the FICC cohort study collects relevant patient and clinical information which allows almost unbiased predictions, by using appropriate predictor and grouping information.

4.2 Limitations

All prediction models tend to deteriorate over time as medical care evolves, demographics change, and new diseases appear. Although our model was stable over the recent three years, its predictive ability is likely to change over time. Therefore, regular evaluation of the predictive value of the model should be foreseen and recalibration performed as necessary. The methodology we used will facilitate such a recalibration. Further, future prediction models for intensive care could be improved by using quality of life measures and other study

endpoints or hospital information (like, hospital category, staffing information or hospital volume) to possibly improve the performance and transportability of the prediction model for benchmarking programs [16,31]. Such information was not used for the prediction model development.

4.3 Implications

Our study has important implications for clinicians, health care providers, and health system evaluations. First, the inclusion of premorbid functional status in addition to established clinical predictors in our prediction model improved the performance of the prediction model. Second, the quantification of validation and transportability properties provides important information for future benchmarking programs. As proposed by Debray et al. [14], we encourage in the development of future ICU prediction models to report the transportability properties due to their relevance to changes in case mix, advances in medical technologies or changes in mortality. Third, this modeling strategy might help clinicians, health care providers, guideline developers and regulatory bodies to enhance evaluation of ICU care and finally to improve population health.

4.4 Conclusions

Premorbid functional status is an important predictor of hospital outcome and improved the predictive performance of our prediction model. Our model showed very good internal validity but a substantial heterogeneity of performance measures between ICUs, providing key information to judge the validity of our model and its adaptation for future use. We used a proposed framework for interpreting model validation findings, which proved helpful in the process of validating our prediction model. We encourage clinicians, health care providers, guideline developers and health service researchers to carefully address the multidimensional aspects of developing ICU prediction models. This includes discussions about the selection of relevant predictors, the interpretation of statistical findings and approaches used, as well as the reporting of key indicators to interpret the model performance and the potential consequences, like transportability to other study settings. We believe that a structured development process improves non-experts' trust in the methodology, supports targeted

458 communication of key performance indicators, and helps assess the reliability of a prediction
459 model in selected settings.

Author contributions

AM: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing - Original Draft, Visualization

MR: Conceptualization, Methodology, Writing - Review & Editing

SJ: Conceptualization, Methodology, Resources, Writing - Review & Editing

TS: Conceptualization, Methodology, Writing - Review & Editing

VP: Conceptualization, Methodology, Writing - Review & Editing

OK: Conceptualization, Methodology, Writing - Review & Editing

TV: Conceptualization, Methodology, Writing - Review & Editing

RR: Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Project administration

JT: Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing - Review & Editing, Visualization, Supervision, Project administration

Conflicts of interest

Dr. Moser has no conflicts of interest.

Dr. Reinikainen has no conflicts of interest.

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492 Dr. Raj has no conflicts of interest.

493 Dr. Takala has no conflicts of interest.

494

495 **Availability of data statement**

496 The study authors had the permission from FINDATA (Social and Health Data Permit
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498 obtained through FINDATA (<https://findata.fi/en/>) according to the Finish Secondary Data
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654

655 **Table 1:** Patient characteristics.

Characteristic	2015	2016	2017	All years
	n/Median (%/IQR)	n/Median (%/IQR)	n/Median (%/IQR)	n/Median (%/IQR)
Age (years)	63 (24)	63 (24)	64 (23)	63 (24)
Gender (male)	11882 (60)	12,335 (60)	12,757 (61)	36,974 (60)
SAPS-II score	31 (22)	31 (23)	31 (22)	31 (22)
Modified SAPS-II score	15 (20)	15 (20)	15 (19)	15 (19)
Surgical admission	7,931 (40)	7,880 (39)	8,460 (40)	24,271 (40)
Emergency admission	15,730 (80)	16,365 (80)	16,643 (79)	48,738 (80)
Functional status				
Normal	14,128 (72)	14,650 (72)	15,002 (71)	43,780 (72)
Light limitation	3,484 (18)	3,656 (18)	3,803 (18)	10,943 (18)
Moderate limitation	1,609 (8)	1,667 (8)	1,695 (8)	4,971 (8)
Severe limitation	521 (3)	502 (3)	507 (2)	1,530 (3)
Non-survivor	2,094 (11)	2,156 (11)	2,213 (11)	6,463 (11)

656 Abbreviations: IQR Interquartile range

657 **Table 2:** Validation and transportability properties.

Measure	Validation	Transportability	Overall estimate (95% CI/PI*)	I-squared (95% CI)
AUC	Internal: Bootstrap**	Reproducibility	0.888 (0.884-0.892)	
	Internal-external: Pooled	Geographical	0.884 (0.880-0.887)	
	Internal-external: Meta-analysis*	Geographical	0.881 (0.847-0.914)	70.8% (55.5%-80.9%)
	Internal-external: Pooled	Temporal	0.886 (0.879-0.893)	
	Internal-external: Meta-analysis*	Temporal	Not reported	Not reported
	Internal-external: Pooled	Geographical-temporal	0.885 (0.880-0.890)	
	Internal-external: Meta-analysis*	Geographical-temporal	0.889 (0.850-0.928)	53.4% (24.3%-71.3%)
Calibration slope	Internal: Bootstrap**	Reproducibility	1.00718 (1.00691-1.00745)	
	Internal-external: Pooled	Geographical	0.980 (0.958-1.002)	
	Internal-external: Meta-analysis*	Geographical	1.033 (0.839-1.227)	71.5% (56.6%-81.2%)
	Internal-external: Pooled	Temporal	1.010 (0.972-1.049)	
	Internal-external: Meta-analysis	Temporal	Not reported	Not reported
	Internal-external: Pooled	Geographical-temporal	1.002 (0.975-1.029)	
	Internal-external: Meta-analysis*	Geographical-temporal	1.066 (0.813-1.319)	58.2% (33.0%-73.9%)
Mean calibration	Internal: Bootstrap**	Reproducibility	0.00632 (0.000582-0.000680)	
	Internal-external: Pooled	Geographical	-0.008 (-0.039-0.022)	
	Internal-external: Meta-analysis*	Geographical	0.065 (-0.322-0.452)	84.7% (78.3%-89.3%)
	Internal-external: Pooled	Temporal	0.011 (-0.042-0.063)	
	Internal-external: Meta-analysis	Temporal	Not reported	Not reported
	Internal-external: Pooled	Geographical-temporal	-0.006 (-0.043-0.031)	
	Internal-external: Meta-analysis*	Geographical-temporal	0.039 (-0.348-0.427)	65.8% (46.4%-78.2%)

658 Abbreviations: CI confidence interval; PI prediction interval.

659 * PI reported.

660 ** From 100 bootstrap replicates.

661 **Figure 1:** Joint predictor effects of categorical variables.

662

663 **Figure 2:** Predictor effects of nonlinear modelled interaction effect between age and
 664 modified SAPS-II.

x-axis ticks indicate 5th, 25th, 50th, 75th and 95th percentiles.
 * Reference is median age (63 years).
 ** Estimates adjusted for median modified SAPS-II score (15 points), admission type (non-surgical, elective) and normal functional status.
 ** Values chosen based on 5th, 25th, 50th, 75th, 95th population percentiles.

666 **Figure 3:** Varying intercept estimates of APACHE-III diagnosis groups from a hierarchical
 667 logistic regression model.

668

669 **Figure 4:** Discrimination and calibration properties of developed prediction model.

670

Supplementary material to:

**Mortality prediction in intensive care units including premorbid functional status
improved performance and internal validity**

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Supplemental Text 1: Modified SAPS-II score formula.

Modified SAPS-II score = SAPS-II score – 7*I[Age>=40 & Age<60] – 12*I[Age>=60 & Age<70] – 15*I[Age>=70 & Age<75] – 16*I[Age>=75 & Age<80] – 18*I[Age>=80] – 6*I[OPERATIVE=0] – 8*I[OPERATIVE=1 & EMERGENCY=1],

where I[X] is an indicator function, i.e. I[X]=1 if X is fulfilled, and 0 otherwise.

Supplemental Text 2: In-hospital mortality prediction formula.

$\text{logit}^{-1}(Y) = -4.123 + 0.406 * \text{AGE_STD} - 0.004 * \{ ((\text{AGE_STD} - k1_AGE)^3)^+ - [\text{AGE_STD}]^3 \} + \frac{(k3_AGE - k1_AGE)}{k3_AGE} - \frac{((\text{AGE_STD} - k3_AGE)^3)^+ * k1_AGE}{k3_AGE} \} / (k3_AGE - k1_AGE)^2 + 1.252 * \text{SAPSMODIFIED_STD} - 0.677 * \{ ((\text{SAPSMODIFIED_STD} - k1_SAPSMODIFIED)^3)^+ - [\text{SAPSMODIFIED_STD}]^3 \} + \frac{(k3_SAPSMODIFIED - k1_SAPSMODIFIED)}{k3_SAPSMODIFIED} - \frac{((\text{SAPSMODIFIED_STD} - k3_SAPSMODIFIED)^3)^+ * (k1_SAPSMODIFIED)}{k3_SAPSMODIFIED} \} / (k3_SAPSMODIFIED - k1_SAPSMODIFIED)^2 - 0.036 * \text{AGE_STD} * \text{SAPSMODIFIED_STD} - 0.052 * \{ ((\text{AGE_STD} - k1_AGE)^3)^+ - [\text{AGE_STD}]^3 \} + \frac{(k3_AGE - k1_AGE)}{k3_AGE} - \frac{((\text{AGE_STD} - k3_AGE)^3)^+ * k1_AGE}{k3_AGE} \} / (k3_AGE - k1_AGE)^2 * \text{SAPSMODIFIED_STD} - 0.066 * \text{AGE_STD} * \{ ((\text{SAPSMODIFIED_STD} - k1_SAPSMODIFIED)^3)^+ - [\text{SAPSMODIFIED_STD}]^3 \} + \frac{(k3_SAPSMODIFIED - k1_SAPSMODIFIED)}{k3_SAPSMODIFIED} - \frac{((\text{SAPSMODIFIED_STD} - k3_SAPSMODIFIED)^3)^+ * (k1_SAPSMODIFIED)}{k3_SAPSMODIFIED} \} / (k3_SAPSMODIFIED - k1_SAPSMODIFIED)^2 + 0.108 * \{ ((\text{AGE_STD} - k1_AGE)^3)^+ - [\text{AGE_STD}]^3 \} + \frac{(k3_AGE - k1_AGE)}{k3_AGE} - \frac{((\text{AGE_STD} - k3_AGE)^3)^+ * k1_AGE}{k3_AGE} \} / (k3_AGE - k1_AGE)^2 * \{ ((\text{SAPSMODIFIED_STD} - k1_SAPSMODIFIED)^3)^+ - [\text{SAPSMODIFIED_STD}]^3 \} + \frac{(k3_SAPSMODIFIED - k1_SAPSMODIFIED)}{k3_SAPSMODIFIED} - \frac{((\text{SAPSMODIFIED_STD} - k3_SAPSMODIFIED)^3)^+ * k1_SAPSMODIFIED}{k3_SAPSMODIFIED} \} / (k3_SAPSMODIFIED - k1_SAPSMODIFIED)^2 - 0.233 * \text{OPERATIVE} + 1.049 * \text{EMERGENCY} + 0.233 * \text{FUNCTIONAL_STATUS1} + 0.492 * \text{FUNCTIONAL_STATUS2} + 0.699 * \text{FUNCTIONAL_STATUS3} +$

+0.377*I[APACHE-III DIAGNOSIS CODE=10010]
+0.392*I[APACHE-III DIAGNOSIS CODE=10020]
+0.424*I[APACHE-III DIAGNOSIS CODE=10070]
+0.531*I[APACHE-III DIAGNOSIS CODE=10075]
+1.198*I[APACHE-III DIAGNOSIS CODE=11010]
+1.254*I[APACHE-III DIAGNOSIS CODE=11030]
+0.438*I[APACHE-III DIAGNOSIS CODE=11060]
+0.509*I[APACHE-III DIAGNOSIS CODE=11065]
-0.594*I[APACHE-III DIAGNOSIS CODE=11090]

+0.475*I[APACHE-III DIAGNOSIS CODE=11990]
+1.128*I[APACHE-III DIAGNOSIS CODE=12010]
+0.382*I[APACHE-III DIAGNOSIS CODE=12020]
+0.629*I[APACHE-III DIAGNOSIS CODE=12030]
+0.388*I[APACHE-III DIAGNOSIS CODE=12990]
+0.652*I[APACHE-III DIAGNOSIS CODE=13010]
+0.362*I[APACHE-III DIAGNOSIS CODE=13020]
+0.423*I[APACHE-III DIAGNOSIS CODE=13030]
-0.491*I[APACHE-III DIAGNOSIS CODE=13040]
-1.442*I[APACHE-III DIAGNOSIS CODE=13070]
-0.386*I[APACHE-III DIAGNOSIS CODE=13990]
+0.392*I[APACHE-III DIAGNOSIS CODE=14010]
-1.087*I[APACHE-III DIAGNOSIS CODE=14020]
-0.212*I[APACHE-III DIAGNOSIS CODE=15010]
-1.385*I[APACHE-III DIAGNOSIS CODE=16020]
-1.943*I[APACHE-III DIAGNOSIS CODE=16030]
-0.869*I[APACHE-III DIAGNOSIS CODE=16990]
+0.632*I[APACHE-III DIAGNOSIS CODE=17010]
+0.910*I[APACHE-III DIAGNOSIS CODE=17990]
-0.237*I[APACHE-III DIAGNOSIS CODE=18010]
-0.532*I[APACHE-III DIAGNOSIS CODE=19010]
+0.410*I[APACHE-III DIAGNOSIS CODE=20010]
+0.694*I[APACHE-III DIAGNOSIS CODE=20020]
+0.611*I[APACHE-III DIAGNOSIS CODE=22010]
+0.594*I[APACHE-III DIAGNOSIS CODE=22020]
+0.415*I[APACHE-III DIAGNOSIS CODE=22030]
+0.252*I[APACHE-III DIAGNOSIS CODE=22060]
-0.679*I[APACHE-III DIAGNOSIS CODE=22070]
+0.643*I[APACHE-III DIAGNOSIS CODE=22990]
-0.450*I[APACHE-III DIAGNOSIS CODE=23020]
+0.390*I[APACHE-III DIAGNOSIS CODE=23030],

where

$$\text{logit}^{-1}(x) = \exp(x) / (1 + \exp(x)),$$

$$[x]^+ = 0 \text{ if } x < 0 \text{ and } [x]^+ = x \text{ if } x \geq 0,$$

I[X] is an indicator function, i.e. I[X]=1 if X is fulfilled, and 0 otherwise,

$$\text{SAPSMODIFIED_STD} = (\text{SAPSMODIFIED} - 15) / 10,$$

$$k1_SAPSMODIFIED = -1.3,$$

$$k3_SAPSMODIFIED = 2.6,$$

$$\text{AGE_STD} = (\text{AGE} - 63) / 10,$$

k1_AGE=-3.3,

k3_AGE=1.7.

We note that the central knots k2_SAPSMODIFIED and k2_AGE are both equal to zero due to standardization and are not shown in the formula.

For APACHE-III diagnosis code names see [Supplemental Table 1](#).

Supplemental Text 3: In-hospital mortality prediction formula: Calculation example.

We consider a patient with age 83, a SAPS-II score of 34 and a severe functional disability (FUNCTIONAL_STATUS3=1). This patient is treated as a non-surgical (OPERATIVE=0) but emergency (EMERGENCY=1) admission with an APACHE-III diagnosis ‘aspiration pneumonia’ (APACHE-III DIAGNOSIS CODE=11020).

First, we calculate the modified SAPS-II score (SAPSMODIFIED=10; see [Supplemental Text 1](#)). Second, we calculate the values for the standardized age and modified SAPS-II score of AGE_STD=2.1 and SAPSMODIFIED_STD=-0.5 as described in the formulas above. All calculated numbers can then be put in the formula:

$$\begin{aligned} \text{logit}^{-1}(Y) = & -4.123 \text{ [“Intercept”]} + 0.406 * 2.1 \text{ [“first AGE_STD spline term”]} - 0.004 * 5.214 \\ & \text{[“second AGE_STD spline term”]} + 1.252 * (-0.5) \text{ [“first SAPSMODIFIED_STD spline"} \\ & \text{term”]} - 0.677 * 0.0337 \text{ [“second SAPSMODIFIED_STD spline term”]} - 0.036 * 2.1 * (-0.5) \\ & \text{[“first interaction spline term”]} - 0.052 * 5.214 * (-0.5) \text{ [“second interaction spline term”]} \\ & - 0.066 * 2.1 * 0.0337 \text{ [“third interaction spline term”]} + 0.108 * 5.214 * 0.0337 \text{ [“fourth"} \\ & \text{interaction spline term”]} + 1.049 \text{ [“EMERGENCY”]} + 0.699 \text{ [“FUNCTIONAL_STATUS3”]} \\ = & \underline{\underline{-2.0044}} \end{aligned}$$

The calculated probability of death is then $P(\text{Death}) = \exp(-2.0044) / [1 + \exp(-2.0044)] = \underline{\underline{0.119}}$.

Supplemental Table 1: TRIPOD checklist*.

Section/Topic	Item	Checklist Item	Section*
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title page
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	1
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	1
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	2.1
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	2.2
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	2.2
	5b	Describe eligibility criteria for participants.	2.1
	5c	Give details of treatments received, if relevant.	2.1
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	2.4
	6b	Report any actions to blind assessment of the outcome to be predicted.	-
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	2.5
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	-
Sample size	8	Explain how the study size was arrived at.	2.2
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	2.6
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	2.6
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	2.6
	10c	For validation, describe how the predictions were calculated.	2.6
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	2.6
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	-
Risk groups	11	Provide details on how risk groups were created, if done.	-
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	2.6
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	3.1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	3.1
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	3.4
Model development	14a	Specify the number of participants and outcome events in each analysis.	Suppl Table 3
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	3.1
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Suppl Text 2
	15b	Explain how to use the prediction model.	Suppl Text 3
Model performance	16	Report performance measures (with CIs) for the prediction model.	3.3; 3.4
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	3.4
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	4
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	4

	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	4
Implications	20	Discuss the potential clinical use of the model and implications for future research.	4
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Suppl Material; Availability of data statement
Funding	22	Give the source of funding and the role of the funders for the present study.	Funding

Source: www.tripod-statement.org

* The last column has been changed from the original TRIPOD checklist from “Page” to “Section”.

Supplemental Table 2: APACHE-III diagnosis coding (Source: Knaus et al. [20]).

APACHE-III diagnosis	Name
10010	Cardiogenic shock
10020	Cardiac arrest
10030	Aortic aneurysm
10040	Congestive heart failure
10045	Cardiomyopathy
10050	Peripheral vascular disease
10060	Rhythm disturbance
10065	Chest pain without infarction
10070	Acute myocardial infarction
10075	Acute myocardial infarction with thrombolysis
10080	Hypertension
10990	Other cardiovascular disease
11010	Parasitic pneumonia
11020	Aspiration pneumonia
11030	Respiratory neoplasm (including larynx, trachea)
11040	Respiratory arrest
11050	Pulmonary edema (non-cardiogenic)
11060	Bacterial/viral pneumonia
11065	Virus pneumonia
11070	Chronic obstructive pulmonary disease
11080	Pulmonary embolism
11090	Mechanical airways obstruct
11100	Asthma
11990	Other respiratory disease
12010	Hepatic failure
12020	GI perforation/obstruction
12030	GI bleeding due to varices
12040	GI inflammatory disease (ulcerative colitis/Crohn's/pancreatitis)
12050	GI bleeding due to ulceration/laceration
12060	GI bleeding due to diverticulosis
12990	Other GI disease
13010	Intracerebral hemorrhage
13020	Subarachnoid hemorrhage
13030	Stroke
13040	Neurologic infection
13050	Neurologic neoplasm
13060	Neuromuscular disease
13070	Seizure
13990	Other neurologic disease
14010	Sepsis (other than urinary tract)

14020	Sepsis of urinary tract origin
15010	Head trauma (with/without multiple trauma)
15020	Multiple trauma (excluding head trauma)
16010	Metabolic coma
16020	Diabetic ketoacidosis
16030	Drug overdose
16990	Other metabolic disease
17010	Coagulopathy/neutropenia/thrombocytopenia
17990	Other hematologic disease
18010	Renal disease
19010	Other medical disease
20010	Postoperative: Dissecting/ruptured aorta
20020	Postoperative: Peripheral vascular disease (no bypass graft)
20040	Postoperative: Elective abdominal aneurysm repair
20050	Postoperative: Peripheral artery bypass graft
20060	Postoperative: Carotid endarterectomy
20990	Postoperative: Other cardiovascular disease
21010	Postoperative: Respiratory infection
21020	Postoperative: Lung neoplasm
21030	Postoperative: Respiratory neoplasm (mouth, sinus, larynx, trachea)
21990	Postoperative: Other respiratory disease
22010	Postoperative: GI perforation/rupture
22020	Postoperative: GI inflammatory disease
22030	Postoperative: GI obstruction
22040	Postoperative: GI bleeding
22050	Postoperative: Liver transplant
22060	Postoperative: GI neoplasm
22070	Postoperative: GI cholecystitis/cholangitis
22990	Postoperative: Other GI disease
23010	Postoperative: Intracerebral hemorrhage
23020	Postoperative: Subdural/epidural hematoma
23030	Postoperative: Subarachnoid hemorrhage
23040	Postoperative: Laminectomy/other spinal cord surgery
23050	Postoperative: Craniotomy for neoplasm
23990	Postoperative: Other neurologic disease
24010	Postoperative: Head trauma (with/without multiple trauma)
24020	Postoperative: Multiple trauma (excluding head trauma)
25010	Postoperative: Renal neoplasm
25990	Postoperative: Other renal disease
26010	Postoperative: Hysterectomy
26990	Postoperative: Other gynecologic disease
27010	Postoperative: Hip or extremity fracture
0	Postoperative: Other elective surgery

Supplemental Table 3: Number of admissions and number of deaths, by unit and year.

Unit	Year	Number of admissions	Number of deaths
A	2015	584	91
A	2016	685	87
A	2017	588	79
B	2015	336	34
B	2016	395	57
B	2017	397	50
C	2015	463	67
C	2016	474	80
C	2017	504	59
D	2015	432	49
D	2016	450	46
D	2017	405	63
E	2015	350	61
E	2016	350	51
E	2017	302	43
F	2015	342	46
F	2016	346	44
F	2017	386	53
G	2015	319	41
G	2016	290	52
G	2017	318	52
H	2015	260	51
H	2016	285	58
H	2017	273	53
I	2015	284	50
I	2016	271	43
I	2017	347	49
J	2015	442	79
J	2016	471	72
J	2017	373	55
K	2015	233	39
K	2016	230	18
K	2017	230	40
L	2015	267	38
L	2016	318	38
L	2017	335	48
M	2015	1255	134
M	2016	1286	132
M	2017	1332	121
N	2015	87	10

N	2016	151	11
N	2017	131	15
O	2015	428	39
O	2016	337	46
O	2017	371	44
P	2017	380	18
Q	2015	964	85
Q	2016	970	59
Q	2017	952	82
R	2015	5218	461
R	2016	5190	467
R	2017	5120	489
S	2015	1866	145
S	2016	1844	159
S	2017	1690	140
T	2015	1588	140
T	2016	1742	143
T	2017	1769	136
U	2015	1585	136
U	2016	1573	141
U	2017	1700	153
V	2015	1099	128
V	2016	1473	167
V	2017	1704	192
W	2015	1326	167
W	2016	1344	185
W	2017	1400	179
Z	2015	14	3

Supplemental Figure 1: Crude and adjusted predictor effects of categorical variables.

* Estimates from hierarchical model with APACHE-III diagnosis as grouping variable.

** Adjusted for all listed variables, age and modified SAPS-II score.

*** Uses one single variable of the listed variables.

Supplemental Figure 2: Crude and adjusted predictor effects of nonlinear modelled age and modified SAPS-II score.

x-axis ticks indicate 5th, 25th, 50th, 75th and 95th percentiles.
 * Estimates from a hierarchical model with APACHE-III diagnosis as grouping variable.
 Reference is a median age (63 years) for crude and adjusted models.
 ** Estimates adjusted for median modified SAPS-II score (15 points), admission type (non-surgical, elective) and normal functional status.

x-axis ticks indicate 5th, 25th, 50th, 75th and 95th percentiles.
 * Estimates from a hierarchical model with APACHE-III diagnosis as grouping variable.
 Reference is a median modified SAPS-II score (15 points) for crude and adjusted models.
 ** Estimates adjusted for median age (63 years), admission type (non-surgical, elective) and normal functional status.

Supplemental Figure 3: Discrimination and calibration performance of mortality predictions from the original SAPS-II score.

Supplemental Figure 4: Receiver operating characteristics curves for mortality predictions from developed prediction models, the sensitivity prediction model and the original SAPS-II score.

* From an hierarchical logistic regression model with predictors age, a modified SAPS-II score, admission type, functional status, and accounting for APACHE-III diagnosis groups.

** Excluding predictor pre-morbid functional status from the developed prediction model.

*** From an ordinary logistic regression model with same predictors as the developed prediction model, but not accounting for APACHE-III diagnosis groups.

Supplemental Figure 5: AUC estimates from membership models from leave-one-hospital-out validation samples.

Supplemental Figure 6: Standardized standard deviations for assessing the relatedness of the leave-one-hospital-out validation samples and the development sample.

* Standard deviation of validation sample divided by standard deviation of development sample.
Mean value of all units indicated by vertical lines: 0.962, 95% CI (0.923, 1.001)

Supplemental Figure 7: Geographic transportability: Pooled estimates.

Supplemental Figure 8: Geographic transportability: AUC random effects meta-analysis.

Supplemental Figure 9: Geographic transportability: Mean calibration random effects meta-analysis.

Supplemental Figure 10: Geographic transportability: Calibration slope random effects meta-analysis.

Supplemental Figure 11: Temporal transportability: Pooled estimates.

Supplemental Figure 12: Geographic-temporal transportability: Pooled estimates.

Supplemental Figure 13: Geographic-temporal transportability: AUC random effects meta-analysis.

Supplemental Figure 14: Geographic-temporal transportability: Mean calibration random effects meta-analysis.

Supplemental Figure 15: Geographic-temporal transportability: Calibration slope random effects meta-analysis.

Supplemental Figure 16: Effect estimates of categorical variables from different sensitivity models.

Supplemental Figure 17: Effect estimates of age and the modified SAPS-II score from different sensitivity models.

* Reference is median age (63 years) and median modified SAPS-II score (15 points). Estimates adjusted for admission type (non-surgical, elective) and normal functional status.
 ** Values chosen based on 5th, 25th, 50th, 75th, 95th population percentiles.

Supplemental Figure 18: Discrimination and calibration properties of the developed risk when the varying estimates of APACHE-III diagnoses are not set to zero.