Modelling Uncertainty in the Risk of Intensive Care Unit Readmission I: Data Extraction and Modelling

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1 Introduction

Unplanned readmission to an intensive care unit (ICU) during the same hospital admission is a relatively common event, affecting between 1.3% and 13.7% of all ICU patients (Elliott *et al.*, 2014). Not only do readmissions to ICU represent a substantial strain on hospital resources, but also readmitted patients tend to have worse prognoses, increased length of ICU stay, and greater risks of morbidity and mortality (Markazi-Moghaddam *et al.*, 2020). Despite this, the precise factors contributing to ICU readmission risk remain unclear. Several models for risk prediction have been developed which tend to use very different variable sets, and no model has been widely externally validated. Accordingly, this project does not aim to develop or validate a novel model for ICU readmission, but to tackle an issue that affects the implementation and interpretation of all risk prediction models - how to deal with missing or incomplete data in the predictor variables (Steyerberg, 2008).

1.1 Scope and Aims of Phase I

This document provides a written overview of the first phase of the project. The aims of this phase were twofold:

1. To extract a dataset from the MIMIC-III database of surgical ICU patients, consisting of a clearly defined outcome measure (ICU readmission), and a range of predictors.
2. To compare the performance of a range of published models for the prediction of ICU readmission risk and identify the best model to take forward. This will form the prediction model at the core of a system for quantifying uncertainty and dealing with missing data.

1.2 Readmission prediction models

This report will investigate five models for ICU risk prediction. I will give a brief overview of all five here. Further details on their predictors, statistical approaches and validations are given in Section 2.4. Henceforth, all models will be referred to by the name of the first author, with the exception of the APACHE-II system. The first 'model' is the APACHE-II scoring system devised by Knaus *et al.* (1985). 'Model' is used in inverted commas, as this model was not designed for predicting ICU readmission risk, but instead is a general system to score the severity of a patient's condition using 12 routine physiological variables, age, and medical history. Increasing APACHE-II score has been shown to correlate well with increasing risk of in-hospital mortality for ICU patients. Frost *et al.* (2010) used a logistic regression model to develop a nomogram for predicting ICU readmission risk based on 14,952 patients in a single hospital in Australia. Unfortunately, as they do not present the coefficients from their model directly, only in the form of the nomogram, several of these coefficients can only be approximated, which may hinder external validation of the model.

Fialho *et al.* (2012) developed a model using data mining and fuzzy logic approaches with the MIMIC-II database, precursor to the MIMIC-III used here. Their model focusses on the values of physiological variables during the 24 h before discharge. The fuzzy rules provide a significant barrier to external validation, however. Martin *et al.* (2018) also developed their model into a nomogram, but unlike Frost, also provided coefficients and a precise formula to generate risk estimates. Their model used 3,109 patients in a single academic centre, and narrowed an initial 179 candidate variables down to 7 variables, covering demographics, physiological measurements and medical history. Finally, Hammer *et al.* (2020) developed the 'RISC' score (Readmission to the Intensive care unit in Surgical Critical care patients, henceforth simply called 'Hammer' for consistency with other models) using logistic regression. Their model aimed to include a number of modifiable variables to aid its use as a clinical tool.

2 Methods

2.1 Data Source

This work uses the open-access MIMIC-III critical care database (Johnson *et al.*, 2016), which comprises ICU stay information for 61,532 adult patients at the Beth Israel Deaconess Medical Centre between June 2001 and October 2012. The database includes information such as demographics, vital sign measurements made at the bedside ($\sim$1 data point per hour), laboratory test results, procedures, medications, caregiver notes, imaging reports, and mortality (both in and out of hospital).

2.2 Inclusion criteria

An overview of inclusion and exclusion criteria is shown in Figure 1. In brief, we initially include all patients admitted under or transferred to a surgical service, and who underwent a surgical procedure either during or prior to an ICU stay. We exclude patients with invalid surgical procedure codes, or procedure types with $<$20 patients in the dataset. We also exclude patients whose surgical procedure took place after their last ICU stay, or who died during the same hospital admission as their ICU stay. Finally, we exclude patients with data in any of the following categories:

- Missing entire hospital record
- Missing assessment data for predictors
- Missing measurement data for predictors within 24 h prior to ICU discharge
- Physiologically impossible or implausible measurements

2.3 Outcome measure

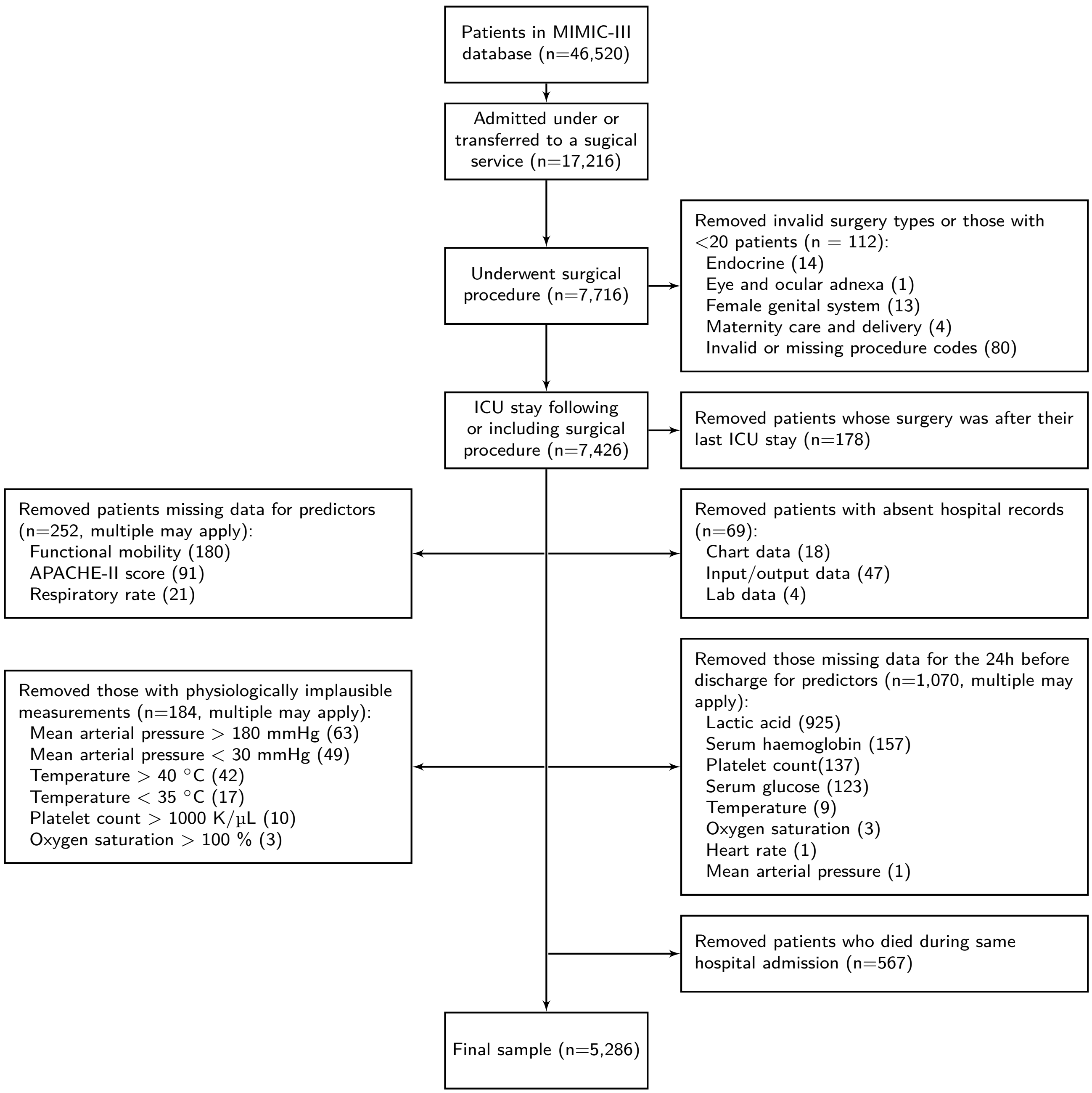
The 'readmission' outcome measure is defined as patients readmitted to the ICU within the same hospitalisation event. Thus, patients discharged fully from the hospital and then readmitted are excluded, even if they were then readmitted to ICU. This is the same outcome measure used by the Frost and Hammer models, whilst the Martin and Fialho models use any readmission within 72 h of discharge.

2.4 Candidate models

Here, I will give an overview of each model, as well as the model performance metrics given in the paper deriving each model (with the exception of APACHE-II). In general, the performance of binary prediction models can be measured in two separate but related metrics using an unseen validation dataset. Discrimination is usually measured as the area under the Receiver Operating Characteristic curve (called AUROC or AUC). It measures the model's ability, when presented with two patients, one of whom was readmitted and one of whom was not, to give a greater probability of readmission to the patient who was readmitted. Its values range from 0.5, indicating a model no better than guessing, to 1, indicating perfect discrimination. Crudely, discrimination can be classified as poor (0.5–0.6), moderate (0.6–0.7), good (0.7–0.8), very good (0.8–0.9) and excellent ($>$0.9).

Calibration measures the agreement between a model's predicted readmission, and observed readmission. This is usually performed by splitting patients into deciles based on assigned readmission probability, then comparing observed to expected readmission rates within each decile. This goodness-of-fit can then be

Figure 1: Flowchart of inclusion and exclusion criteria for patients in the dataset, alongside sample sizes at each step.



formally assessed using a Hosmer-Lemeshow Chi-squared (χ^2) test, with a well-calibrated model showing no significant differences between observed and expected readmission.

For each model I also present a cross-tabulation of the model's predictors with readmission status from the MIMIC-III dataset, to demonstrate the expected relationship between each predictor and readmission.

APACHE-II. The APACHE-II system was not designed to specifically predict ICU readmission, but rather to assess the severity of a patient's condition. Nonetheless, it has shown to be an informative predictor of ICU readmission (Campbell *et al.*, 2008), and as such is used in both the Hammer and Frost models. This makes it a good 'baseline' predictive model to compare others too. It comprises a scoring system across 12 variables: Core temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation (arterial partial pressure if fraction of inspired oxygen < 0.5, else arterial-alveolar gradient), arterial pH, serum sodium, serum potassium, serum creatinine, haematocrit, white blood cell count and Glasgow coma score. Serum bicarbonate levels are also used if arterial blood gas measurements are not present.

Each variable scores 0 if in a 'normal' range, with increasingly higher scores for abnormally low or high values. The worst value for each variable in the preceding 24 h is used to determine the score. Additional points are then given for increasing age, emergency admissions and the presence of certain comorbidities. The resulting score falls between 0 and 71, with higher values indicating a more severe condition.

Frost. The Frost model is based on a logistic regression model, and includes the following variables (Table 1): Age, sex, elective admission (yes/no), admission source (Operating theatre/recovery ward, emergency department, other hospital or general ward), APACHE-II score at discharge, ICU stay duration > 7 days (yes/no), discharge outside the hours of 08:00–16:00, and acute renal failure during ICU stay (yes/no). Each variable carries a number of points, the sum of which is used to determine readmission risk. Unfortunately, the coefficients linking variables to score, and total score to readmission risk are not presented, and must be inferred from the nomogram. In most cases, variables map clearly onto discrete score values. However, the mapping between total score and readmission is neither linear, nor fully exponential. This relationship has been approximated in my workflow, but may result in poor calibration. The authors report moderate discrimination (AUC = 0.66), and do not quantitatively report calibration, only describing it as 'good'.

Table 1: Cross-tabulation of variables in the Frost model with ICU readmission status in the MIMIC-III dataset. Continuous variables are presented as means ± standard deviation. The APACHE-II is measured at or close to discharge.

Variable	No Readmission	Readmitted to ICU
N	4944 (93.5%)	342 (6.5%)
Age	64.2 ± 14.5	63.5 ± 14.5
Sex		
Male	3121 (63.1%)	207 (60.5%)
Female	1823 (36.9%)	135 (39.5%)
Elective admission	1980 (40%)	104 (30.4%)
Admission source		
Operating theatre	2246 (45.4%)	120 (35.1%)
Emergency room	769 (15.6%)	91 (26.6%)
Other hospital	976 (19.7%)	69 (20.2%)
Ward	953 (19.3%)	62 (18.1%)
APACHE-II score	10.4 ± 4.70	12.0 ± 4.87
ICU stay >7 days	864 (17.5%)	98 (28.7%)
Discharged after hours	2874 (58.1%)	223 (65.2%)
Acute renal failure	788 (15.9%)	125 (36.5%)

Fialho. The Fialho model was built using MIMIC-II, the predecessor of the MIMIC-III database. It was initially trained using a wide range of physiological variables measured in the 24 h before ICU discharge. Sequential forward selection was used to produce a final model with the following variables (Table 2): Mean heart rate, mean temperature, mean oxygen saturation, mean non-invasive arterial pressure, mean platelet count and mean lactic acid.

Unlike the other models discussed here, the Fialho model is based on fuzzy logic, rather than a classical logistic regression model. This takes the form of, in this case, three logistic regression-like models. Which model to use for a given individual depends on the fuzzy rules, for example:

> **If** mean heart rate is normal/high **and** mean temperature is normal **and** mean oxygen saturation is normal **and** mean non-invasive blood pressure (mean) is normal/high **and** mean platelets is high **and** mean lactic acid is very low, **then** y1 = 0.17 $\times$ mean heart rate - 0.64 $\times$ mean temperature + 0.08 $\times$ mean oxygen saturation - 0.27 $\times$ mean non-invasive blood pressure (mean) - 0.1 $\times$ mean platelets + 1.3 $\times$ mean lactic acid + 0.54

As the name 'fuzzy rules' implies, these rules are not clearly defined by the system, which makes them very hard to implement, let alone validate, in any other setting. My approach here was to find which of the three 'fuzzy classes' an individual best fits, based on using quantiles to determine 'high'/'low' etc. The Fialho model reports good discrimination (AUC = 0.76) and moderate calibration (Hosmer-Lemeshow χ^2 p-value = 0.06, where $p < 0.05$ indicates significant differences between observed and expected readmission).

Table 2: Cross-tabulation of variables in the Fialho model with ICU readmission status in the MIMIC-III dataset. Continuous variables are presented as means $\pm$ standard deviation. Mean arterial pressure is estimated from non-invasive systolic and diastolic blood pressure measurements. All variables represent the mean value over the final 24 h before discharge from ICU.

Variable	No Readmission	Readmitted to ICU
N	4944 (93.5%)	342 (6.5%)
Heart rate (bpm)	83.9 $\pm$ 12.2	84.8 $\pm$ 13.4
Temperature (°C)	36.8 $\pm$ 0.51	36.8 $\pm$ 0.55
Oxygen saturation (%)	96.8 $\pm$ 1.64	96.8 $\pm$ 1.69
Mean arterial pressure (mmHg)	81.2 $\pm$ 14.6	85.0 $\pm$ 16.0
Platelets (K/µL)	221 $\pm$ 131	241 $\pm$ 154
Lactic acid (mmol/L)	1.68 $\pm$ 0.82	1.58 $\pm$ 0.82

Martin. Whilst the Martin model presents a nomogram to aid implementation by clinicians, it is based on a logistic regression model, and full coefficients are also presented. The model was built using 3,109 surgical ICU patients in a single centre over 5 years. Its predictors comprise 7 common demographic and physiological variables (Table 3): Age, respiratory rate, blood urea nitrogen concentration, serum glucose, serum chloride, history of atrial fibrillation (yes/no) and history of renal insufficiency (yes/no).

The Martin model was built with any readmission to ICU within 72 h of discharge as the outcome measure. It used the least absolute shrinkage and selection operator (lasso) approach to regression, which aims to reduce very small coefficents to zero, thus performing automated feature selection. The authors report good discrimination (AUC = 0.71), and whilst they claim in the methods that '...the model's goodness of fit of was assessed using the Hosmer-Lemeshow test', no calibration results are reported statistically or visually.

Hammer. The Hammer model is a logistic regression model with the specific goal of including modifiable predictors, to increase the model's usability as a clinical tool. It was built using 7,126 patients from the same medical centre that the MIMIC-III database comes from, though the data collection dates do not overlap. To further aid clinical usage, the model contains only binary yes/no variables (Table 4): Sex, general surgical procedure, cardiac surgical procedure, APACHE-II score of >20 on admission, ICU stay of >5 days and, within the last 24 h, hyperglycaemia, severe anaemia and no ambulation. The paper presents the results

Table 3: Cross-tabulation of variables in the Martin model with ICU readmission status in the MIMIC-III dataset. Continuous variables are presented as means ± standard deviation.

Variable	No Readmission	Readmitted to ICU
N	4944 (93.5%)	342 (6.5%)
Age	64.2 ± 14.5	63.5 ± 14.5
Respiratory rate	18.4 ± 3.89	19.2 ± 3.91
Blood urea nitrogen (mg/dl)	22.8 ± 16.3	27.8 ± 20.9
Serum glucose (mg/dl)	129 ± 29.0	126 ± 29.2
Serum chloride (mmol/L)	105 ± 4.4	105 ± 4.7
History of atrial fibrillation	1565 (31.7%)	129 (37.7%)
History of renal insufficiency	261 (5.3%)	31 (9.1%)

as a nomogram, but almost all model coefficients can be found in the supplementary information, with the exception of the intercept, which was estimated using the nomogram.

The authors report good discrimination (AUC = 0.78) and good calibration using a Brier score. Additionally, the authors implemented the Frost and Martin models within the same dataset, and report that their model shows superior discrimination, though the AUC values for the other models are not reported.

Table 4: Cross-tabulation of variables in the Hammer model with ICU readmission status in the MIMIC-III dataset. APACHE-II score is calculated upon admission, hyperglycaemia, anaemia and ambulation are measured during the last 24 h, and positive fluid balance is over the whole ICU stay.

Variable	No Readmission	Readmitted to ICU
N	4944 (93.5%)	342 (6.5%)
Sex		
Male	3121 (63.1%)	207 (60.5%)
Female	1823 (36.9%)	135 (39.5%)
General surgery	1167 (23.6%)	136 (39.8%)
Cardiac surgery	2423 (49%)	93 (27.2%)
Hyperglycaemia (>180 mg/dl)	475 (9.6%)	35 (10.2%)
Severe anaemia (<7 g/dl)	35 (0.7%)	1 (0.3%)
APACHE-II > 20	2397 (48.5%)	164 (48%)
Positive fluid balance >5L	768 (15.5%)	95 (27.8%)
No ambulation	3882 (78.5%)	298 (87.1%)
ICU stay >5 days	1244 (25.2%)	124 (36.3%)

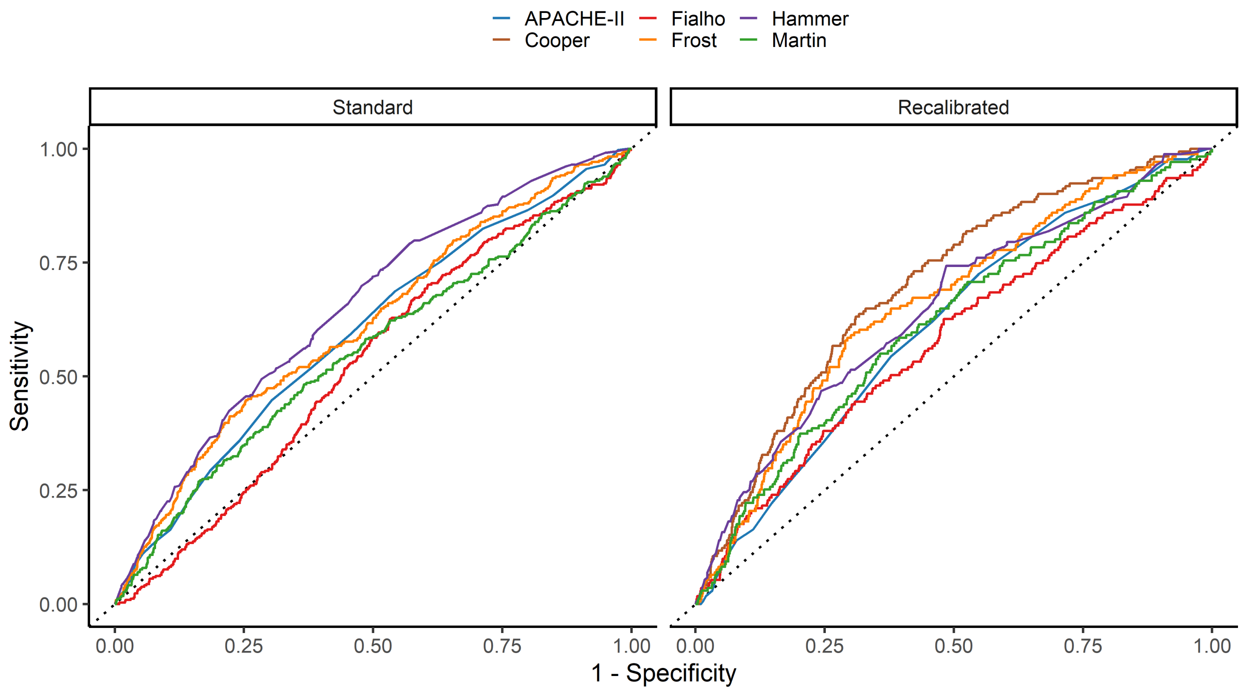


Figure 2

2.5 Model comparisons

2.6 Recalibration

2.7 Novel model

3 Results

3.1 Discrimination

Table 5

Model	AUC	χ^2	AUC$_{rc}$	χ^2_{rc}
APACHE-II	0.60	296.8	0.61	**6.29**
Cooper	—	—	0.70	**6.17**
Fialho	0.53	19010.1	0.58	**6.70**
Frost	0.61	402.3	0.66	17.48
Hammer	0.65	130	0.65	**7.57**
Martin	0.56	273.7	0.61	**6.06**

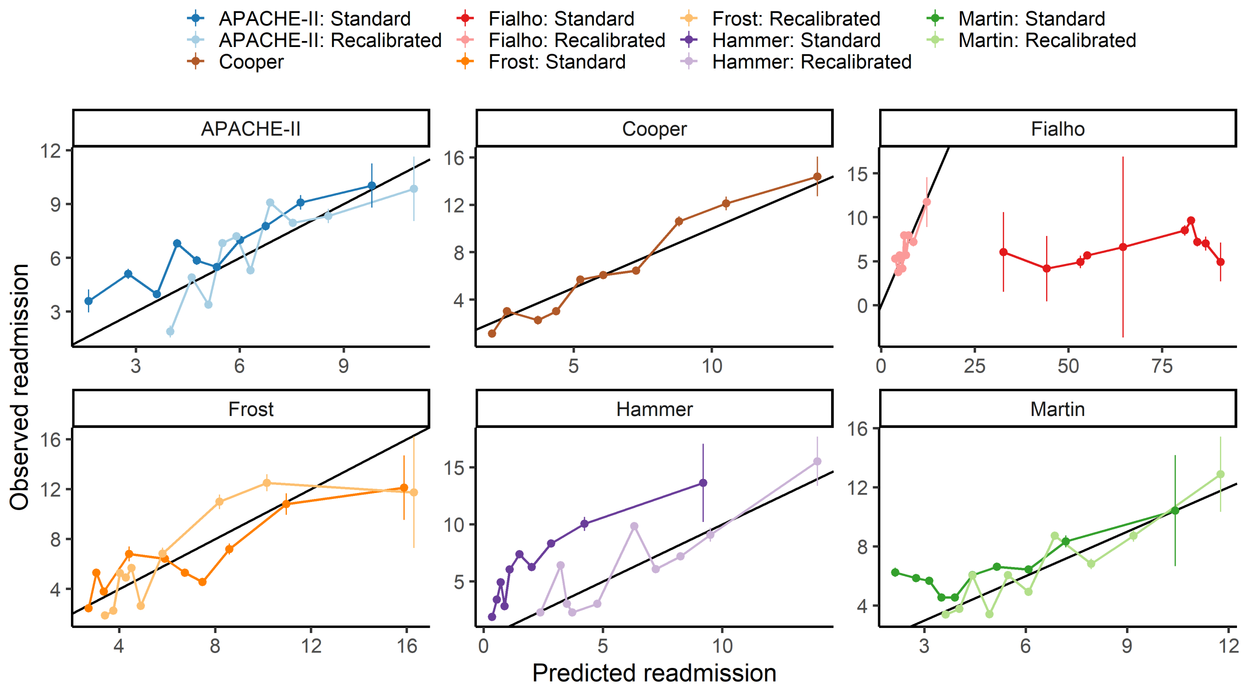


Figure 3

3.2 Calibration

3.3 Variables retained in novel model

4 Discussion

4.1 Model performance

4.2 Next steps

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