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Machine learning risk prediction of mortality for patients undergoing surgery with perioperative SARS-CoV-2: the COVIDSurg mortality score

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Introduction

Since the beginning of the COVID-19 pandemic tens of millions of operations have been cancelled[1] as a result of excessive postoperative pulmonary complications (51.2 per cent) and mortality rates (23.8 per cent) in patients with perioperative SARS-CoV-2 infection[2]. There is an urgent need to restart surgery safely in order to minimize the impact of untreated non-communicable disease.

As rates of SARS-CoV-2 infection in elective surgery patients range from 1–9 per cent[3–8], vaccination is expected to take years to implement globally[9] and preoperative screening is likely to lead to increasing numbers of SARS-CoV-2-positive patients, perioperative SARS-CoV-2 infection will remain a challenge for the foreseeable future.

To inform consent and shared decision-making, a robust, globally applicable score is needed to predict individualized mortality risk for patients with perioperative SARS-CoV-2 infection. The authors aimed to develop and validate a machine learning-based risk score to predict postoperative mortality risk in patients with perioperative SARS-CoV-2 infection.

Methods

Cohort study design

An international, multicentre, prospective, cohort study (COVIDSurg Cohort Study) included consecutive patients who were diagnosed with SARS-CoV-2 in the 7 days before or the 30 days after surgery. Patients undergoing any type of surgery were included from 1 February 2020 to 31 July 2020. Full study methodology has been published previously[2].

Machine learning methods were used to analyse the COVIDSurg Cohort Study dataset. Sixteen patient and operative variables were entered into the analysis and, based on time, data were split into a derivation set, where all analysis and modelling were performed, and a validation set, where the final model was assessed. Five features were selected following variable importance measurements from both linear and non-linear modelling. These features were then combined into 26 different predictor sets, which were fitted through three different algorithms (logistic regression, decision trees and random forest), generating a total of 78 different models. These models were tuned with a 10-fold cross-validation, fitted in the 75 per cent split of the derivation set and assessed in the remaining 25 per cent. In order to ascertain the model's stability, this training and testing split was randomly repeated 100 times (bootstraps). Finally, to decide which model to select, performance was evaluated through the mean area under the receiver operating characteristic curve (AUROC) value. A full description of methods is available in *Appendix S1*.

Results

Patients

From 10 029 patients in the cohort study, data from 8492 patients entered the machine learning processes (*Fig. 1*). The most common surgical procedures were abdominal (40.6 per cent, 3446 of 8492 patients), orthopaedic (33.8 per cent, 2867 of 8492) and head and neck surgery (9.8 per cent, 835 of 8492). Emergency surgery accounted for 80.8 per cent (6862 of 8492 patients) and benign disease for 57.3 per cent (4868 of 8492) (*Table S1*).

Of the 8492 patients, data from 6777 patients who had surgery from February to May 2020 (726 hospitals, 65 countries) were entered into the derivation set and data from 1715 who had surgery from June to July 2020 (296 hospitals, 53 countries) were entered into the validation set. Despite changes in patient demographics and treatment options, such as the recommendations from the RECOVERY trial[10] in June 2020, model performance remained robust between the derivation and validation sets. Mortality rates were 17.2 per cent overall (1462 of 8492 patients), 18.9 per cent (1279 of 6777) in the derivation set and 10.7 per cent (183 of 1715) in the validation set. Missing data handling is described in *Appendix S2*.

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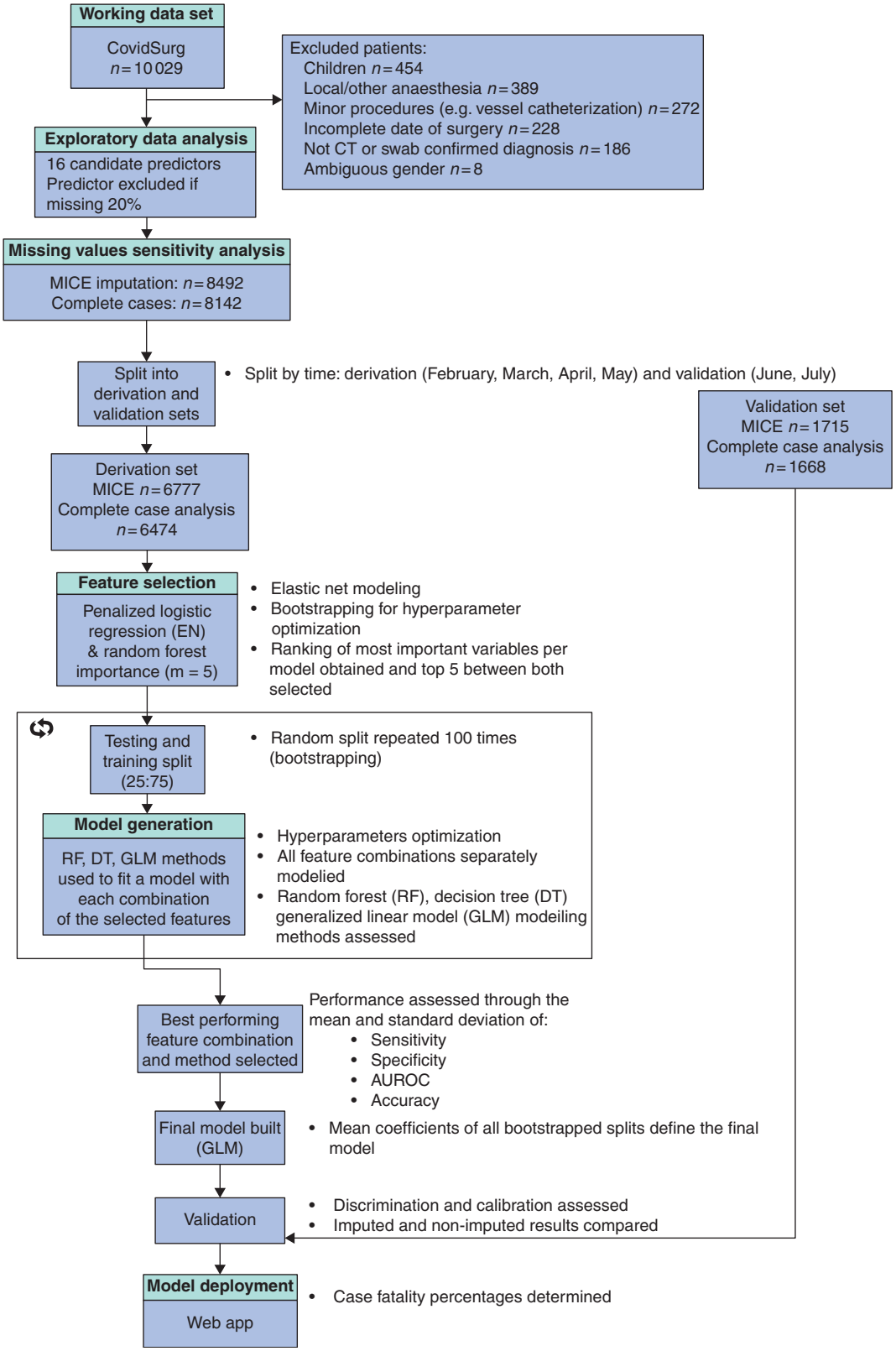

Fig. 1 Cohort study patient inclusion and model derivation and validation flow

MICE, multiple imputation by chained equations; EN, elastic net.

Feature selection

A full breakdown of feature and model selection are in *Tables S3–S7*. Random forest and elastic net were applied to the derivation set and the most important features were ranked (*Fig. S1*). Logit model performance of all different feature combination (runs) divided by each of the features is shown in *Fig. 2a*. The five features taken forward into model building were age, preoperative respiratory support, ASA grade, specialty and revised cardiac risk index (RCRI) score.

Model building and validation

Multivariable models were built using all possible combinations of the five selected features, resulting in 26 model runs (*Table S8*). The smallest, higher-performing and most robust model was a logistic regression model with four features (age, ASA grade, RCRI score and preoperative respiratory support). A full description is in *Appendix S2*.

The AUROC for the final score was 0.73 (95 per cent c.i. 0.71 to 0.74) in the derivation set and 0.80 (95 per cent c.i. 0.77 to 0.83) in the validation set (*Fig. 2b*). Calibration in the validation set is shown in *Fig. S2* (Brier score 0.084, intercept 0.078, slope 1.08).

Mortality rates were studied for different probability risk cut-offs (*Fig. S3*), with a balance between distribution and clinical importance leading to cut-off values at approximately 2, 10, 30 and 45 per cent mortality. These showed high concordance between derivation and validation sets (*Table S7*) with the final mortality percentages in the combined dataset being very similar.

Deployment

The COVIDSurg Mortality Score has been deployed online at http://covidsurgrisk.app/.

Discussion

Understanding risks related to SARS-CoV-2 and COVID-19 will remain important for the foreseeable future. There is an urgent need to restart elective surgery in order to reduce the backlog of cancelled operations[11]. Vaccination programmes are expected to take years to deliver, particularly in low- and middle-income countries[9], and may not protect against new variants[12]. COVID-19-free surgical pathways are unlikely to be universally implemented, particularly in emergency settings[3], leaving patients at

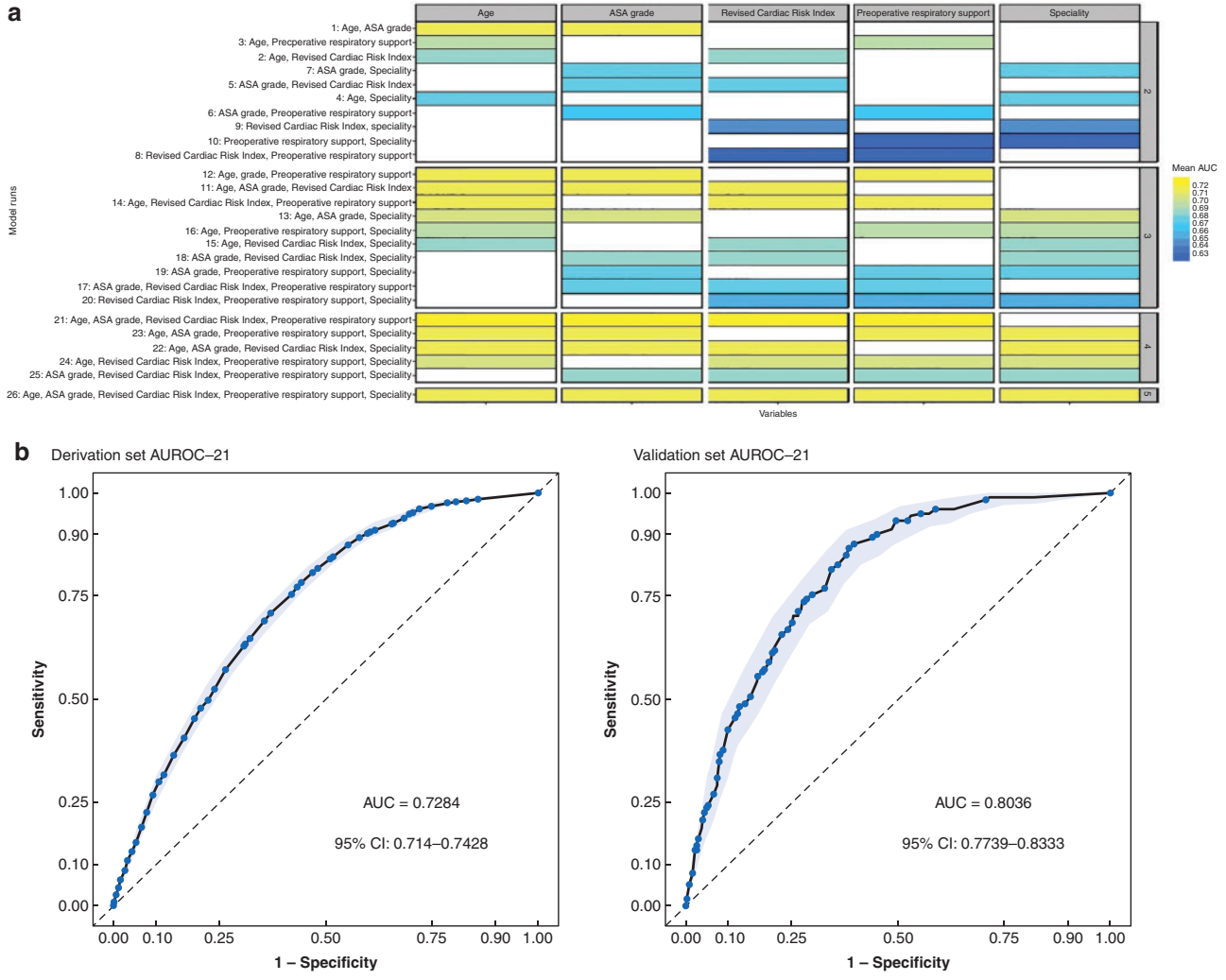

Fig. 2 Model performance and evaluation.

a Logistic model performance of all different runs divided by each of the features. Colour coded according to performance values (mean area under the curve (AUC) of 100 bootstraps). **b** Receiver operating characteristic curves for model evaluation. After generating the final model made up by the averaged coefficients of the bootstraps of run 21, it was evaluated in both the derivation set as a whole (Area under receiver operating characteristic curve (AUROC) = 0.7284, 95 per cent c.i. 0.7140 to 0.7428) and the validation set AUROC = 0.8036, 95 per cent c.i. 0.7739 to 0.8333). Results are depicted with AUROC and confidence intervals generated through the pROC and plotROC packages. 95 per cent confidence intervals were computed with default 2000 stratified bootstrap replicates.

risk of in-hospital SARS-CoV-2 transmission. Research is critical to mitigate impact. The COVIDsurg Morality Score is a tool that can help overcome these challenges and has clear clinical applications. It can inform consent and shared decision making by patients and surgeons. If individual patient mortality risk is too high, they may choose to postpone surgery. If surgery is unavoidable, risks should be clearly documented as part of informed consent, and postoperative critical care can be identified and justified. It can also identify patients who are at very low risk, where surgery can continue as planned.

The COVIDSurg Mortality Score shows high discrimination for predicting mortality in patients with perioperative SARS-CoV-2. The AUROCs in the derivation (0.73) and validation (0.80) sets are consistent with published non-surgical COVID risk scores[13]. The COVIDSurg Mortality Score is globally applicable and consists of variables that are readily available across all resource settings. The score was derived and validated in a global data set (all types of surgery, 756 hospitals, 69 countries) and demonstrated validity across geographic regions and over time as community SARS-CoV-2 infection rates fluctuated.

The COVIDSurg cohort study was prospectively collected and conducted, but it had limitations. Variables were coded following standardized medical criteria but a further analysis of continuous variables as well as the inclusion of interactions[14] could be incorporated in future studies. As there are no other international, multispecialty data sets for SARS-CoV-2 surgical patients, further external validation was not possible, but should be considered if such data sets emerge. High mortality percentages (approximately 47 per cent) at higher probability outputs (greater than 0.5) should be interpreted with caution, as numbers of patients with these feature combinations were low. The authors acknowledge that the model will warrant updates as more data become available.

PROBAST: Prediction model Risk Of Bias ASsessment Tool
Step 1: Specify your systematic review question(s) – not applicable.
Step 2: Classify the type of prediction model evaluation – development and validation.
Step 3: Assess risk of bias and applicability

Risk of Bias			
Participants	**Predictors**	**Outcome**	**Analysis**
Were appropriate data sources used, e.g., cohort, RCT, or nested case–control study data? **Yes**	Were predictors defined and assessed in a similar way for all participants? **Yes**	Was the outcome determined appropriately? **Yes**	Were there a reasonable number of participants with the outcome? **Yes**
Were all inclusions and exclusions of participants appropriate? **Yes**	Were predictor assessments made without knowledge of outcome data? **Yes**	Was a prespecified or standard outcome definition used? **Yes**	Were continuous and categorical predictors handled appropriately? **Yes**
	Are all predictors available at the time the model is intended to be used? **Yes**	Were predictors excluded from the outcome definition? **Yes**	Were all enrolled participants included in the analysis? **No**
		Was the outcome defined and determined in a similar way for all participants? **Yes**	Were participants with missing data handled appropriately? **Yes**
		Was the outcome determined without knowledge of predictor information? **Yes**	Was selection of predictors based on univariable analysis avoided? **No**
		Was the time interval between predictor assessment and outcome determination appropriate? **Yes**	Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately? **Yes**
			Were relevant model performance measures evaluated appropriately? **Yes**
			Were model overfitting, underfitting, and optimism in model performance accounted for? **Yes**
			Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? **Yes**

ROB = risk of bias. + indicates low ROB/low concern regarding applicability; − indicates high ROB/high concern regarding applicability; and ? indicates unclear ROB/unclear concern regarding applicability.

Step 4: Overall judgment

ROB				Applicability			Overall	
Participants	**Predictors**	**Outcome**	**Analysis**	**Participants**	**Predictors**	**Outcome**	**ROB**	**Applicability**
+	+	+	+	NA	NA	NA	+	NA

Despite differences in mortality between the derivation and validation sets, model performance remained robust. There are likely to have been structural and system differences between hospitals that were not captured in the cohort study. These differences are further compounded by variation in community SARS-CoV-2 across time and across geographical locations. Nonetheless, the score performed well in the validation set, suggesting the score can be used reliably both during COVID waves and troughs.

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Supplementary material

Supplementary material is available at *BJS* online.

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