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**ORIGINAL ARTICLE**
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# Machine learning-based scoring system to predict cardiogenic shock in acute coronary syndrome

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**Aims** Cardiogenic shock (CS) is a severe complication of acute coronary syndrome (ACS) with mortality rates approaching 50%. The ability to identify high-risk patients prior to the development of CS may allow for pre-emptive measures to prevent the development of CS. The objective was to derive and externally validate a simple, machine learning (ML)-based scoring system using variables readily available at first medical contact to predict the risk of developing CS during hospitalization in patients with ACS.

**Methods and results** Observational multicentre study on ACS patients hospitalized at intensive care units. Derivation cohort included over 40 000 patients from Beth Israel Deaconess Medical Center, Boston, USA. Validation cohort included 5123 patients from the Sheba Medical Center, Ramat Gan, Israel. The final derivation cohort consisted of 3228 and the final validation cohort of 4904 ACS patients without CS at hospital admission. Development of CS was adjudicated manually based on the patients' reports. From nine ML models based on 13 variables (heart rate, respiratory rate, oxygen saturation, blood glucose level, systolic blood pressure, age, sex, shock index, heart rhythm, type of ACS, history of hypertension, congestive heart failure, and hypercholesterolaemia), logistic regression with elastic net regularization had the highest externally validated predictive performance (*c*-statistics: 0.844, 95% CI, 0.841–0.847).

**Conclusion** STOP SHOCK score is a simple ML-based tool available at first medical contact showing high performance for prediction of developing CS during hospitalization in ACS patients. The web application is available at https://stopshock.org/#calculator.

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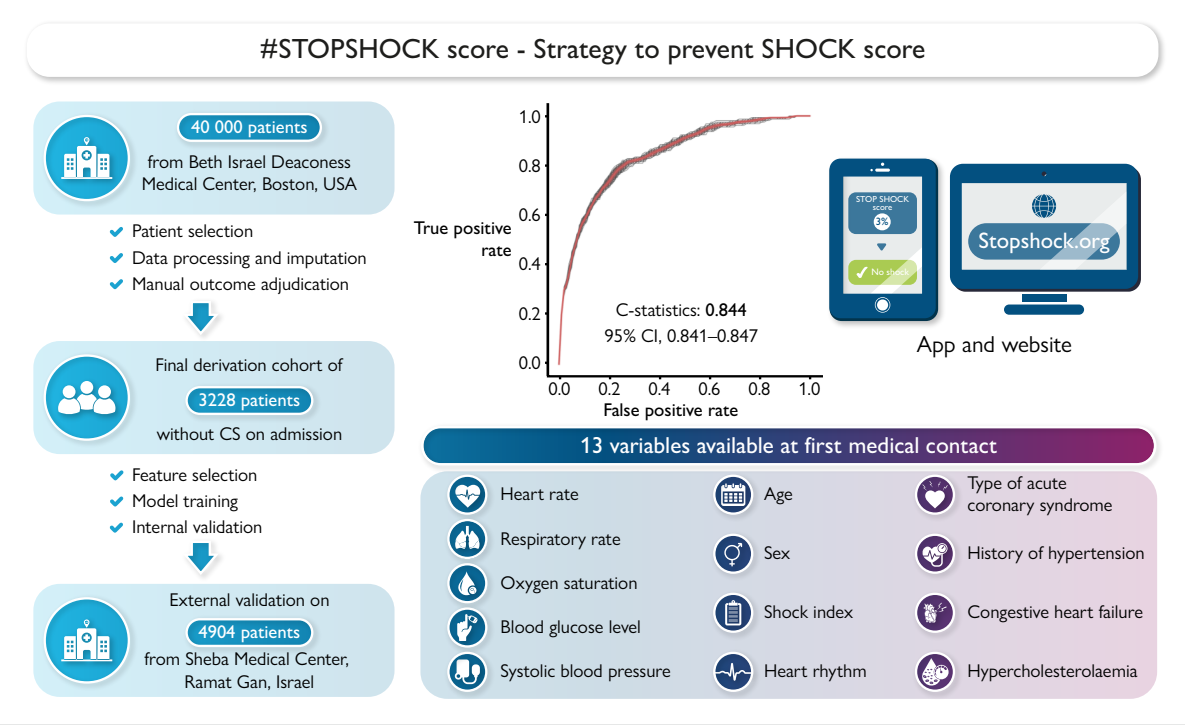
**Graphical Abstract**




**Keywords** Acute coronary syndrome • Cardiogenic shock machine learning • Risk prediction score

# Introduction

Cardiogenic shock (CS) is a serious life-threatening condition affecting 3–10% of patients suffering from acute coronary syndrome (ACS).[1] A common definition is a state of severe tissue and end-organ hypoperfusion caused by primary cardiac dysfunction leading to severe cellular and metabolic abnormalities.[2–4] When left untreated, it can rapidly progress to circulatory collapse and death. Despite recent improvements in diagnostic and treatment options, mortality remains unacceptably high, reaching nearly 50%.[5–8]

Currently available percutaneous mechanical circulatory support devices (pMCS) can temporarily support or even replace the function of the heart and/or lungs, thereby temporarily bypassing the primary cause of the shock state.[9–12] The window for successful treatment is narrow; if missed, even eliminating the underlying primary cause may not be sufficient to reverse this vicious cycle.[13] The ability to identify high-risk patients prior to the development of CS may allow for preemptive measures, such as the early use of pMCS systems to prevent the development of CS.

Few models for predicting CS in ACS patients have been described in the literature with different predictive performances and various clinical applications.[14–16] Perhaps the most robust one is the ORBI score. However, the biggest shortcoming of this score is the fact that CS was not well defined in the registries used for derivation and validation and this outcome was not adjudicated. Furthermore, it uses complex variables that require e.g. catheterization data, and its predictive performance is moderate. As the authors state in their manuscript: '…more sophisticated prediction models such as those involving machine learning (ML), may have provided improved model performance…'[15]

The use of ML algorithms on large datasets has shown encouraging results in disease prediction.[17–24] To the best of our knowledge, there is no externally validated scoring system using ML to predict the risk of CS in ACS available to date. The aim of our study was to derive and externally validate a simple scoring system utilizing ML based on variables readily available at first medical contact to identify the risk of developing CS during hospitalization in patients admitted due to ACS.

# Methods

## Ethical approval

The study was approved by the ethical committee at Sheba Medical Center in Ramat Gan; approval number SMC-9385-22.

## Data collection

The data for the derivation cohort were obtained from a population of over 40 000 intensive care unit patients from the Beth Israel Deaconess Medical Center, Boston, USA, hospitalized between 2001 and 2012. It is an observational, prospective registry that includes vital signs, medications, laboratory measurements, observations and notes charted by care providers, procedure codes, diagnostic codes, imaging reports, hospital length of stay, survival data, and more.[25] Data were obtained at the end of 2020.

For external validation, a dataset of 5123 consecutive ACS patients from an intensive care unit in the Sheba Medical Center, Ramat Gan, Israel, was used (data from 2014 to 2022, obtained in June and July 2022). This registry

is an observational, prospective registry composed of two databases, where one is collected by automatic hospital systems and the other is entered manually by the attending physicians. The registry includes vital signs, biochemistry, procedures, diagnoses, and notes charted by care providers, hospital length of stay, and outcome data.

## Patient population

Patients aged ≥18 years, admitted for ACS without CS at presentation, and proceeding to invasive coronary angiography were included. Cardiogenic shock was defined as CS in stage C, D, or E according to Society for Cardiovascular Angiography and Interventions (SCAI) clinical expert consensus.[26,27] Both the derivation and validation datasets included patients with (CS group) and without CS (control group) admitted to the intensive care unit. Patients with CS at presentation, cardiac arrest prior to admission, delayed percutaneous coronary intervention or conservative/pharmacological treatment strategy, presentation unknown, or >24 h onset symptoms were excluded. Patients with unknown clinical status were also excluded from the study population. Acute coronary syndrome was defined according to the 10th Revision of the International Classification of Diseases (ICD-10).[27] All ICD-10 codes for CS were manually adjudicated by the investigators based on the patients' reports to confirm the CS diagnosis and discern between patients who were admitted with and without CS. The outcome assessment was blinded with regard to the predictors.

## Statistical analysis

Continuous variables are presented as means and standard deviations, whereas categorical variables are presented as percentages. The normality of data was tested using a Shapiro–Wilk test. Unpaired Student *t*-test and Mann–Whitney tests were used to compare continuous variables as appropriate. $\chi^2$ and Fisher's exact tests were used to compare categorical variables as appropriate. A posteriori sample size calculation with a learning curve approach[28] was performed to determine whether our sample was large enough for model derivation. The analysis showed that doubling the derivation data size led to an increase in classification area under the ROC curve (AUC) of 0.05; therefore, we concluded that our sample size is sufficient for our particular use case.

Data analysis with a ML model was performed according to the previously published report.[29] Briefly, all available data were inspected, plotted, and sorted. Data were cleaned and visually inspected, and the wrong values (extremal values above the common threshold—clearly incorrectly entered values, e.g. the body temperature of 5°C) were removed. Variables stored in the database under multiple codes were clustered into aggregated variables. The first recorded variables were selected. Missing data was imputed using the multiple imputation chain equations method for 10 datasets. This procedure yielded 10 derivation datasets and 10 validation datasets. Three well-known additional imputation algorithms: k-Nearest Neighbors, 'Soft Impute' (performs matrix completion by iterative soft thresholding of singular value decomposition), and 'Iterative singular value decomposition' (performs matrix completion by iterative low-rank singular value decomposition) were selected as a benchmark for stability analysis. Correlation matrixes, diagnostic plots with densities of original non-missing, imputed missing, and imputed data were plotted, and the Kolmogorov–Smirnov test for distribution equivalence was computed in order to examine imputed datasets. To compensate for the class imbalance between the CS group and control group caused by a relatively low incidence of CS between 5% and 10% (data-wise) under-sampling using K-means, oversampling using Synthetic Minority Oversampling Technique and a combination of over- and under-sampling using this technique with the removal of 'noisy' samples using Tomek links and Edited Nearest Neighbors was performed.

Based on ML-team experience and available literature, nine ML models were selected for classification:

(a) logistic regression with *elastic net* regularization;
(b) support vector classifier;
(c) nearest neighbour classifier;
(d) Gaussian Process classifier;
(e) decision tree classifier;
(f) random forest classifier;
(g) neural network (multilayer perceptron);
(h) *XGBoost* classifier; and
(i) *LightGBM* classifier.

All models were recomputed after hyper-parameter fine-tuning of all classification algorithms.

Data were analysed using Python version 3.8.13 (https://www.python.org/) with appropriate libraries (e.g. for statistical analyses, *pingouin* package version 0.5.3: https://pingouin-stats.org/, and for most classification algorithms, *scikit-learn* package version 1.2.2: https://scikit learn.org/stable/).

## Selection of in-hospital cardiogenic shock predictors

Eighty-six variables with clinical and pathophysiological potential to predict CS were selected based on evidence in the literature.[14,30–36] Only variables that would be available at the first medical contact with the patient were selected, i.e. only variables recorded at admission (prior to invasive coronary angiography) were used. A bivariate analysis of differences between the CS and control groups was performed with Benjamini–Yekutieli correction for multiple testing. Based on the results, 19 variables were selected to be used in further ML analysis. This process was blinded with regard to the outcome. Feature importance of all variables for all models was assessed using permutation importance and Shapley Additive Explanations (SHAP). For logistic regression, regression coefficients were assessed. Random forest classifier and gradient boosting classifiers feature importance were assessed for the decision tree classifier. Based on these results, a final list of 13 variables was selected: heart rate, respiratory rate, $SpO_2$, blood glucose level, systolic blood pressure, age, sex, shock index (heart rate/systolic blood pressure), heart rhythm [sinus tachycardia, sinus bradycardia, ventricular tachycardia, 1st degree atrioventricular block (AV block), other rhythm], type of ACS (anterior ST-elevation myocardial infarction (STEMI) or left bundle branch block (LBBB), other STEMI, non-ST-elevation myocardial infarction (NSTEMI), other) history of hypertension, history of congestive heart failure, and history of hypercholesterolaemia.

## Derivation of the STOP SHOCK score

The derivation cohort consisted of 3056 patients in the control group and 703 patients in the CS group (*Figure 1*). A final CS group of 172 patients was obtained after manual review and exclusion of patients with CS at presentation or other forms of shock (e.g. sepsis) resulting in a final cohort of 3228 patients.

Nine pre-selected above-mentioned classification models were trained and recomputed after hyper-parameter fine-tuning. The performance of classifiers was estimated using a repeated stratified K-fold cross-validation technique with five splits and 50 repeats (*Figure 2*).

## External validation

For model validation, all pre-specified variables with clinical and pathophysiological potential to predict CS in patients meeting all the inclusion criteria and none of the exclusion criteria specified in the Patient population section were selected from the validation dataset. All available data were inspected, plotted, and sorted. Validation datasets were prepared using the same methods as the original dataset. After excluding patients with CS upon admission, the final cohort consisted of 4747 patients without CS and 157 patients who developed CS during the hospital stay (together 4904 patients). To better estimate errors in the validation process, we repeated the train-validate loop 100 times using the all-to-all strategy.

The methods and results of this study are reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement.[37]

An online calculator is available at https://www.stopshock.org.

# Results

A total of 3228 patients (mean age 67.26 ± 12.41, 64.34% male) were included in the derivation and 4904 (mean age 65.56 ± 12.92, 77.84% male) in the validation cohort. *Tables 1* and *2* provide detailed descriptions and comparisons of the baseline characteristics between the two cohorts as well as between the control group and CS group of the derivation cohort. Patients included in the derivation cohort were slightly

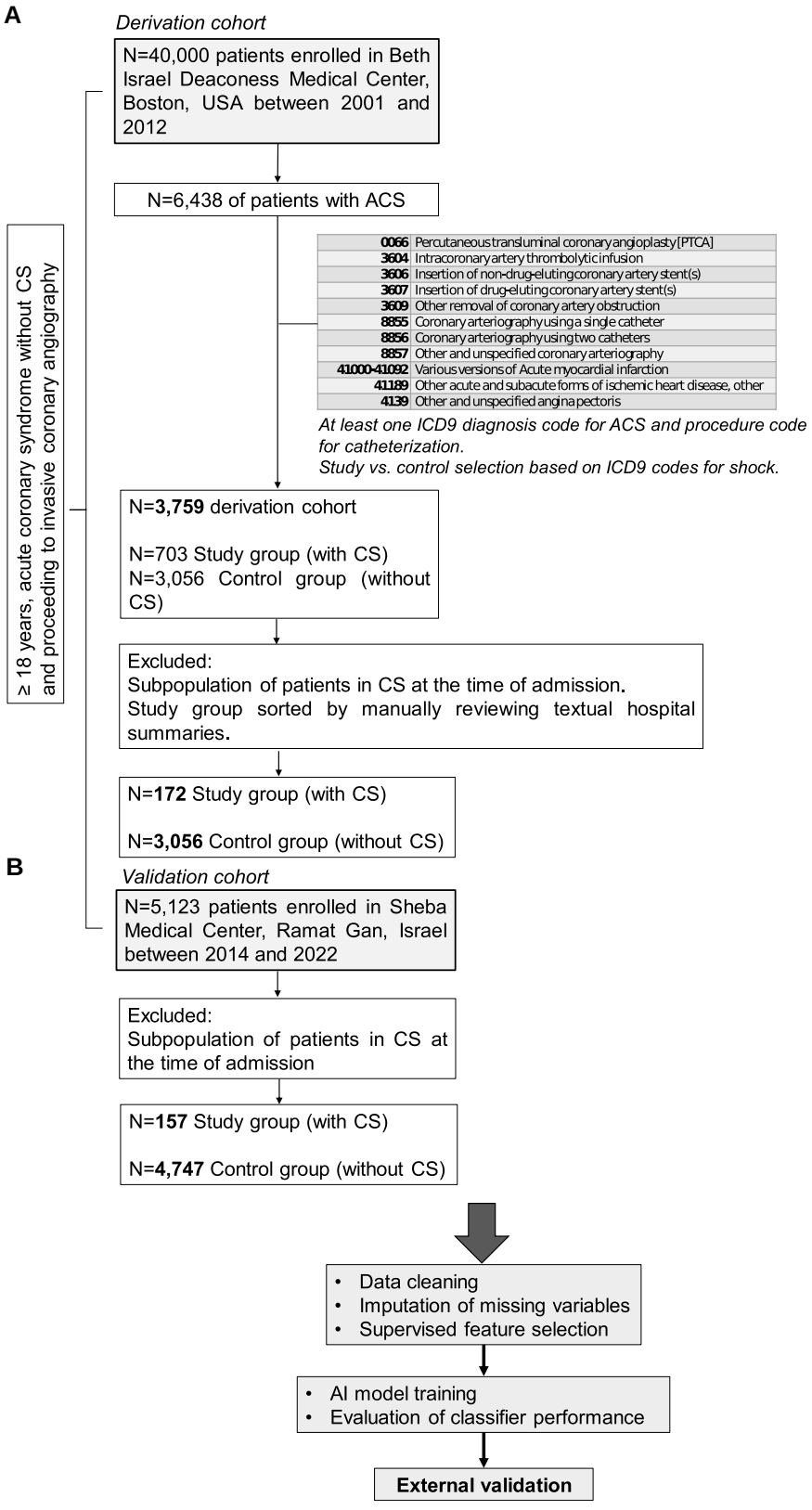



**Figure 1** Flow diagram of the study. Flowcharts of the derivation and validation cohorts. ACS, acute coronary syndrome; CS, cardiogenic shock; ICD, International Classification of Diseases, 10th Revision.

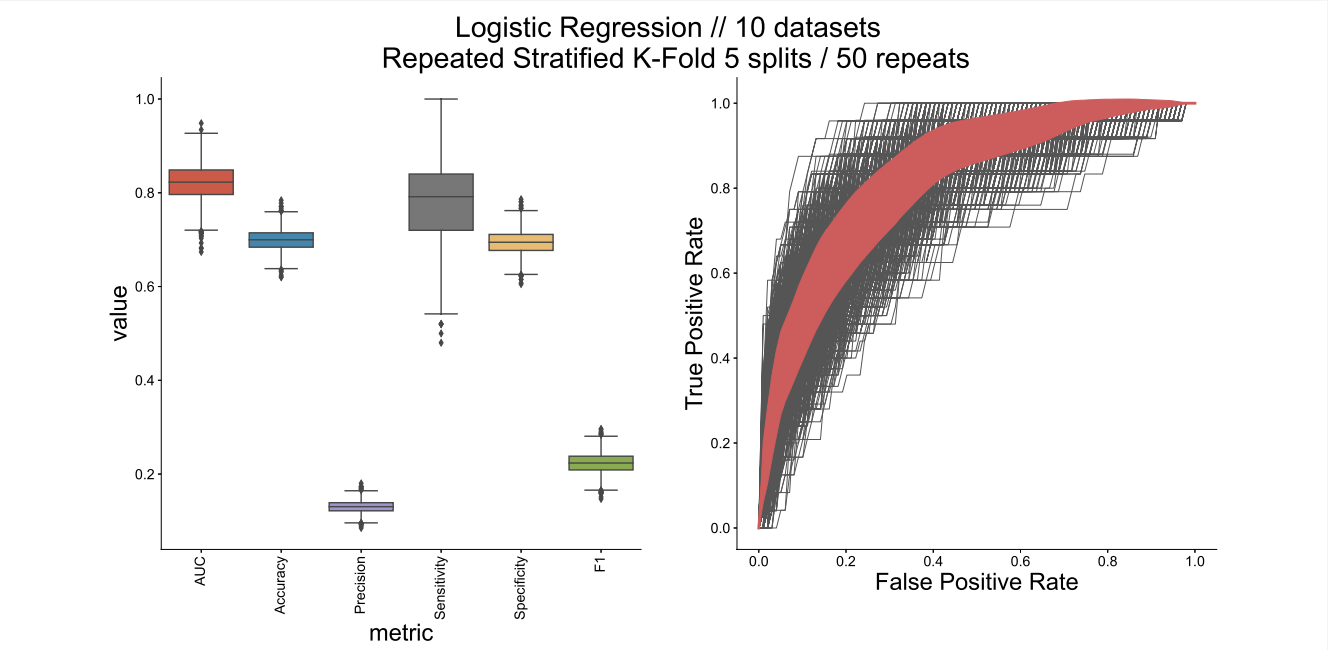



**Figure 2** Logistic regression with elastic net regularization. Box and whisker plot showing performance metrics of the model for all 2500 runs. ROC plot showing all 2500 runs (black) and the average curve (red) with standard deviation.

older ($P < 0.001$), with higher heart rates ($P < 0.001$), higher shock index and oxygen saturation $SpO_2$ ($P < 0.001$), and lower systolic blood pressure and respiratory rate ($P < 0.001$) as compared to the validation cohort. Additionally, they presented a higher rate of chronic heart failure, NSTEMI, and atrial fibrillation.

In the derivation CS group, patients were older ($P = 0.004$), with higher heart rate ($P < 0.001$), higher glucose concentration ($P < 0.001$), higher shock index ($P < 0.001$), and lower systolic blood pressure ($P < 0.001$) compared to controls. Anterior STEMI or LBBB was more common in the CS group. Fewer patients had a history of arterial hypertension (AH; $P = 0.002$), and hypercholesterolaemia ($P = 0.004$), and more patients had a history of chronic heart failure ($P < 0.001$) in the CS group as compared to patients in the control group. The differences between CS group and control group were similar in derivation and validation cohorts.

Cardiogenic shock developed in 5.3% of patients in the validation cohort compared to 3.2% in the derivation cohort ($P = 0.9$). Overall, in-hospital mortality in CS patients was 20% in the derivation and 37% in the validation cohort, respectively. Thirty-day mortality rates of CS patients were 30% in the derivation and 41% in the validation cohort, respectively ($P = 0.06$).

Twelve independent predictors (plus shock index, which is computed as a ratio of heart rate and systolic blood pressure) and their respective weights $\beta$ after training a logistic regression model with elastic net regularization are shown in *Figure 3*.

Logistic regression achieved AUC $0.844 \pm 0.002$ and relatively high sensitivity ($0.805 \pm 0.012$) and specificity ($0.736 \pm 0.006$). *Figure 3* shows individual variables used in the model and their respective average weights $\beta$ in the logistic regression (elastic net regularization) and average *P*-values computed from univariate f-regression. Increased heart rate ($\beta = 0.109 \pm 0.014$, 95% CI 0.085–0.135), respiratory rate ($\beta = 0.158 \pm 0.015$, 95% CI 0.125–0.186), and plasmatic levels of glucose ($\beta = 0.333 \pm 0.015$, 95% CI 0.308–0.365), female sex ($\beta = 0.051 \pm 0.016$, 95% CI 0.019–0.083), higher age ($\beta = 0.424 \pm 0.009$, 95% CI 0.406–0.439), history of chronic heart failure ($\beta = 0.656 \pm 0.009$, 95% CI 0.641–0.670), and increased shock index ($\beta = 0.250 \pm 0.009$, 95% CI 0.236–0.265) were associated with increased chance of developing CS. Higher oxygen saturation ($\beta = -0.046 \pm 0.010$, 95% CI −0.063 to 0.025) and systolic blood pressure ($\beta = -0.221 \pm 0.014$, 95% CI −0.238 to −0.190) and type of ACS (NSTEMI or other) ($\beta = -0.315 \pm 0.014$, 95% CI −0.343 to −0.293) were associated with a decreased chance of developing CS. Type of heart rhythm had only a minor impact on the outcome. All variables except for history of AH and hypercholesterolaemia were statistically significant. For these two variables, the average *P*-value was above the 0.05 threshold but was significant in some of the 100 runs.

Gaussian Process classifier scored second best with AUC $0.811 \pm 0.002$, but in this case, the specificity ($0.829 \pm 0.003$) was higher on average than sensitivity ($0.610 \pm 0.021$). Finally, the multilayer perceptron was deemed as the third best classifier in our task, achieving an AUC of $0.800 \pm 0.011$, albeit with the highest specificity ($0.878 \pm 0.011$) at the cost of sensitivity ($0.478 \pm 0.031$). We ranked our classifiers based on AUC, which offers the most complex view of the classifier performance. Based on sensitivity, the highest scoring classifier was *XGBoost* ($0.942 \pm 0.021$), which is an ensemble method that uses gradient-boosted trees. Conversely, the best scoring classifier based on specificity was the support vector classifier with a radial basis function kernel ($0.882 \pm 0.005$) (*Figure 4*).

In addressing the challenge posed by the skewed class distribution inherent in our dataset, with a low incidence rate for CS, a class balancing technique was employed to mitigate the bias towards the majority class during model training. However, this led to a discrepancy between the model output probabilities and the actual probability of the true outcome. The calibration plot (*Figure 5*) distinctly illustrates the substantial deviation between the true incidence and the model output probabilities, underscoring the necessity for a subsequent calibration step (*Figure 6*).

A straightforward output calibration was performed using a calibration ratio in *Table 3* to align the shock risk probabilities more closely with. This recalibration serves to fine-tune the predictive probabilities,

**Table 1 Baseline continuous variables of the datasets used in the derivation and validation of the STOP SHOCK score**

| | Validation cohort Overall ($n = 4904$) Mean (SD) | Derivation cohort Overall ($n = 3228$) Mean (SD) | *P*-value | Derivation cohort Control group ($n = 3056$) Mean (SD) | Derivation cohort CS group ($n = 172$) Mean (SD) | *P*-value |
|---|---|---|---|---|---|---|
| Heart rate (b.p.m.) | 78.57 (18.46) | 82.73 (16.71) | <0.001 | 82.08 (16.34) | 94.07 (18.91) | <0.001 |
| Respiratory rate (b.p.m.) | 18.27 (6.57) | 17.30 (5.61) | <0.001 | 17.14 (5.55) | 20.08 (5.92) | <0.001 |
| Saturation $SpO_2$ (%) | 96.55 (3.74) | 97.69 (3.17) | <0.001 | 97.77 (3.04) | 96.29 (4.70) | 0.005 |
| Glucose (mg/dL) | 166.37 (81.91) | 161.60 (85.79) | 0.463 | 157.79 (80.43) | 227.45 (135.49) | <0.001 |
| Systolic BP (mmHg) | 142.82 (27.17) | 124.72 (24.23) | <0.001 | 125.63 (24.11) | 108.89 (20.54) | <0.001 |
| Age (y) | 65.56 (12.92) | 67.26 (12.41) | <0.001 | 67.04 (12.40) | 71.03 (12.00) | 0.004 |
| Weight (kg) | 80.80 (16.43) | 81.55 (18.56) | >0.999 | 81.80 (18.67) | 77.09 (15.99) | 0.077 |
| Height (cm) | 170.42 (8.99) | 169.78 (12.86) | 0.293 | 169.84 (12.90) | 168.78 (12.22) | >0.999 |
| Shock index | 0.57 (0.19) | 0.70 (0.23) | <0.001 | 0.68 (0.22) | 0.90 (0.29) | <0.001 |
| BMI ($kg/m^2$) | 27.72 (4.78) | 28.35 (6.64) | 0.995 | 28.42 (6.70) | 27.13 (5.38) | 0.565 |
| BSA ($m^2$) | 1.98 (0.23) | 1.98 (0.26) | >0.999 | 1.98 (0.26) | 1.92 (0.24) | 0.157 |

For continuous variables, the table shows mean and standard deviation per dataset and per group and bivariate differences using an appropriate test based on normality, including a *P*-value. For categorical variables, the table shows percentages of each category and $\chi^2$ test, including a *P*-value.
BP, blood pressure; BMI, body mass index; BSA, body surface area; CS group, patients who developed in-hospital cardiogenic shock; control group, patients who didn't develop in-hospital cardiogenic shock; SD, standard deviation.

**Table 2 Baseline categorical variables of the datasets used in the derivation and validation of the STOP SHOCK score**

| | Validation cohort Overall ($n = 4904$) | Derivation cohort Overall ($n = 3228$) | *P*-value | Derivation cohort Control group ($n = 3056$) | Derivation cohort CS group ($n = 172$) | *P*-value |
|---|---|---|---|---|---|---|
| Sex—female (%) | 32.16 | 35.66 | <0.001 | 35.54 | 37.7 | >0.999 |
| Heart rhythm | NA | NA | <0.001 | NA | NA | <0.001 |
| Sinus tachycardia (%) | 7.88 | 11.28 | NA | 10.27 | 28.69 | NA |
| Sinus bradycardia (%) | 9.61 | 1.23 | NA | 5.3 | 1.64 | NA |
| Ventricular tachycardia (%) | 0.10 | 0.18 | NA | 0.14 | 0.82 | NA |
| 1st degree atrioventricular block (%) | 8.65 | 0.89 | NA | 0.85 | 1.64 | NA |
| Other (%) | 73.76 | 82.55 | NA | 83.44 | 67.21 | NA |
| History of arterial hypertension (%) | 61.18 | 51.54 | <0.001 | 52.53 | 34.43 | 0.002 |
| History of chronic heart failure (%) | 9.9 | 37.4 | <0.001 | 35.68 | 67.21 | <0.001 |
| History of hypercholesterolaemia (%) | 32.0 | 26.26 | <0.001 | 27.07 | 12.3 | 0.004 |
| ECG | NA | NA | <0.001 | NA | NA | <0.001 |
| Anterior STEMI or LBBB (%) | 16.37 | 18.43 | NA | 17.61 | 32.79 | NA |
| Other STEMI (%) | 32.71 | 25.19 | NA | 24.85 | 31.15 | NA |
| NSTEMI (%) | 38.35 | 46.17 | NA | 47.18 | 28.69 | NA |
| Other (%) | 12.57 | 10.2 | NA | 10.36 | 7.38 | NA |
| Diabetes (%) | 36.02 | 31.95 | 0.005 | 31.99 | 31.15 | >0.999 |
| Chronic obstructive pulmonary disease/ asthma (%) | 8.16 | 5.68 | 0.001 | 5.73 | 4.92 | >0.999 |
| Cerebrovascular accident (%) | 9.43 | 2.46 | <0.001 | 2.37 | 4.1 | >0.999 |
| Chronic kidney disease (%) | 11.6 | 11.1 | >0.999 | 11.07 | 9.84 | >0.999 |
| Pulmonary Hypertension (%) | 1.2 | 6.58 | <0.001 | 6.44 | 9.02 | >0.999 |
| Dementia (%) | 0.73 | 0.58 | >0.999 | 0.52 | 1.64 | >0.999 |
| Atrial fibrillation (%) | 6.8 | 25.6 | <0.001 | 24.66 | 31.97 | 0.565 |

CS group, patients who developed in-hospital cardiogenic shock; control group, patients who didn't develop in-hospital cardiogenic shock; ECG, electrocardiogram; LBBB, left bundle brunch block; NA, not applicable; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

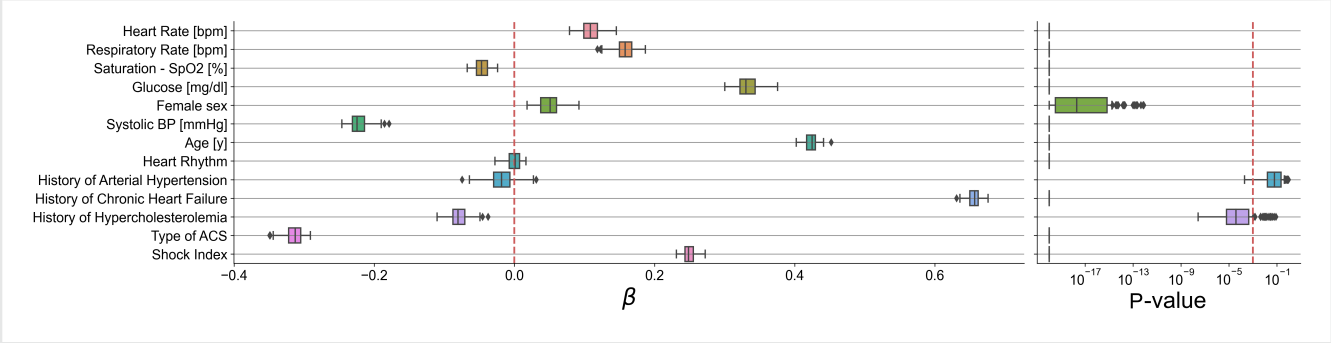



**Figure 3** Predictors of the STOP SHOCK logistic regression model in the derivation cohort and their respective weights $\beta$ in the logistic regression (elastic net regularization) and *P*-values computed from univariate f-regression. *P*-values were clipped to the minimum of 10–20. The box plots show distributions of $\beta$s and *P*-values over 100 runs of the model in the all-to-all validation strategy. Since numerical variables were scaled to a standard normal distribution (zero mean and unit variance), the value of $\beta$ directly represents the magnitude of their effect on the model prediction. Positive $\beta$ represents a direct relationship, while negative $\beta$ represents a reverse indirect relationship. As can be seen from the respective *P*-values (*P*-values were computed using an f-regression, a univariate regression procedure testing the effect of a single regressor), almost all variables have a significant effect on the model output. ACS, acute coronary syndrome; BP, blood pressure.

engendering a more reliable and interpretable model that clinicians can use. The table entries are average values of 10 × 10 runs.

# Discussion

We developed a novel STOP SHOCK score that predicts the risk of in-hospital CS development in patients with ACS. The score is composed of 13 variables readily available at first medical contact—and can be calculated with an online calculator. According to our knowledge, STOP SHOCK is the first, externally validated, ML-based score for CS risk prediction with a superior predictive performance.

In the variable selection process, the most significant predictors of CS were identified and included based on their superior performance in the analysis.[29] Although well-established criteria such as left ventricular ejection fraction, mechanical ventilation, and others are recognized as important predictors, they did not enhance the model's predictive accuracy to the same extent as the selected variables. Furthermore, to ensure the tool's practicality and ease of use in urgent clinical settings, it was essential to limit the number of variables and to include only those that are available at first medical contact. Maintaining a reasonable number of predictors facilitates rapid and efficient risk assessment, making the tool more feasible for everyday clinical practice without compromising reliability. While a model with more variables might achieve better performance, it would become impractical for real-world application. A model capable of perfect prediction holds little value if it cannot be easily utilized by clinicians in critical situations where timely decision-making is paramount.

Machine learning algorithms have shown great promise in risk prediction models. However, it is important to know when and how to use them. Many studies showed logistic regression yielding similar or higher predictive value than advanced ML algorithms.[38,39] Our study demonstrated similar results in terms of the predictive performance of different classifiers, where logistic regression achieved the highest ROC AUC compared to other more complex and advanced ML algorithms. However, achieving this predictive performance would never be possible without implementing ML in the data pre-processing such as imputation, class balancing techniques, and feature selection. Our research shows that ML is not an omnipotent tool, but it can improve predictive performance substantially when used correctly and for particular tasks.

The study results are drawn from two large observational prospective registries collecting consecutive homogeneous patients for admission from North America and Middle East countries 10–15 years apart. This entails potential differences in demographic features and guideline driven approaches between scientific societies (North American and European) and throughout the collection period (2001–12; 2014–22). Nevertheless, the prediction model demonstrated excellent and comparable performance in derivation and validation cohorts.

All the variables included in the model pertain clinical and demographic information that are part of the standard clinical practice at patients' first medical contact, without requiring any additional investigation or intervention outside the widely adopted standard of care even prior to invasive coronary angiography. Ability to stratify patients in this early stage gives the potential to implement pre-emptive measures such as intensive monitoring or therapeutical intervention.

The prevalence of CS was significantly and the mortality numerically different amongst the two populations. These data are in line with other reports over the years.[1,40] Besides the different geographical and timeline distribution of the cohorts, several clinical and demographic variables were also different. The robustness of the score in cohorts with different characteristics, although unified by the same aetiology, represents *per se* an additional value to the score itself.

Since the development of the SCAI stage classification, several validation studies have unsurprisingly provided good evidence of an exponential increase in mortality with advanced stages.[41,42] However, most existing papers included only patients with ongoing CS. Therefore, the focus on the early stage of haemodynamic alteration preceding the development of hypoperfusion (pre-shock) is ubiquitously recognized as one of the top priorities.

Jentzer *et al.*[43] highlighted in a cohort of 10 000 retrospective patients that hypotension either isolated [adjusted OR, 1.7 (95% CI, 1.4–2.2)] or combined with hypoperfusion [adjusted OR, 2.8 (95% CI, 2.1–3.6)] was a major variable associated with increased mortality. Additionally, in the pre-shock patients with ACS, blood glucose, heart rate, elevated shock index, and reduced blood pressure were also found to be strictly related to mortality.[43,44]

Past medical history of heart failure, on top of the clinical and haemodynamic parameters included in the analysis, was commonly listed as a strong predictor of mortality in ACS patients in different scores over the years.[45] Interestingly, AH and dyslipidaemia were weakly associated with lower risk of CS development in our study. Rather than

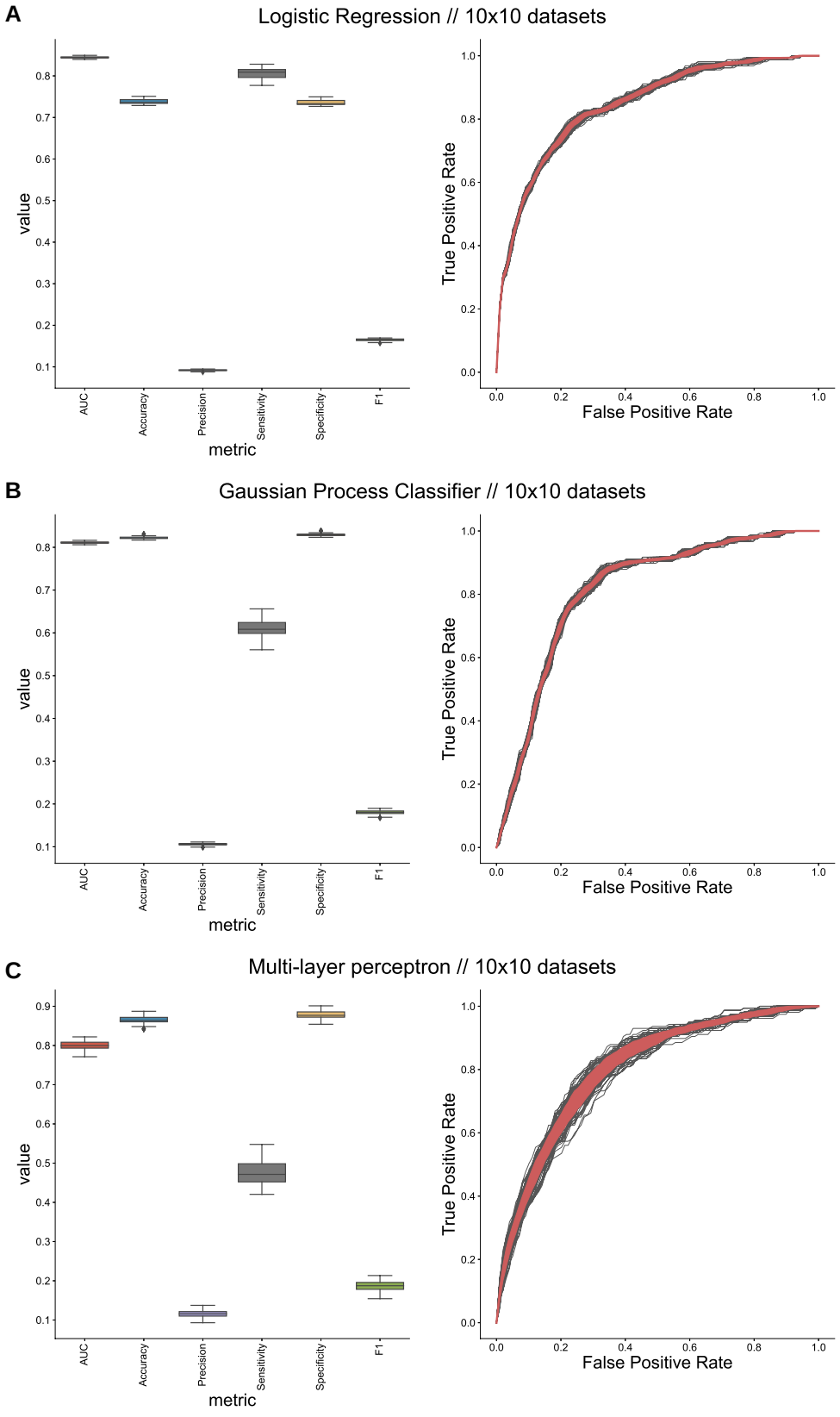



**Figure 4** Classifier performance on external validation cohort using three classification models. (*A*) Logistic regression with elastic net regularization, (*B*) Gaussian Process classifier with rational quadratic kernel, and (*C*) multilayer perceptron classifier with three layers (500, 200, and 100 neurons) with hyperbolic tangent activation function.

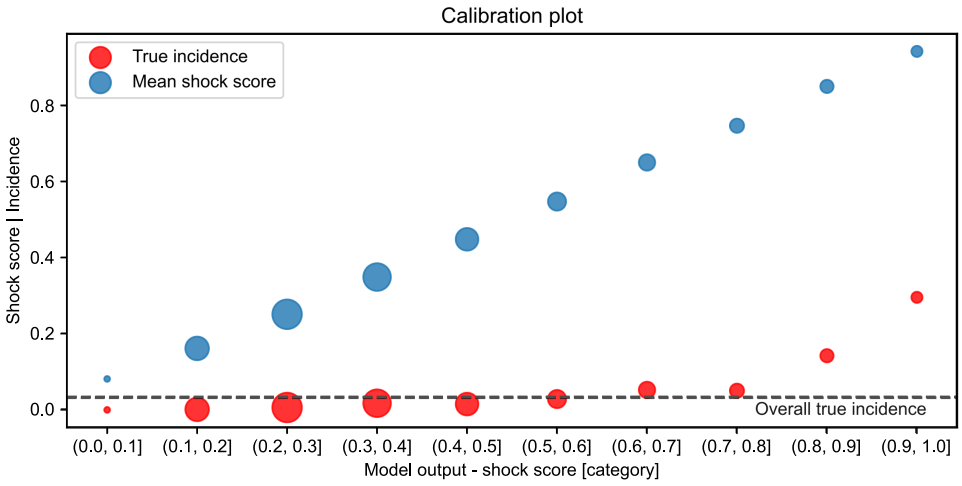



**Figure 5** Calibration plot before recalibration. The calibration plot illustrating the substantial deviation between the true incidence and the model output probabilities due to skewed class distribution inherent in our dataset, with a low incidence rate for cardiogenic shock, underscoring the necessity for a subsequent calibration step.

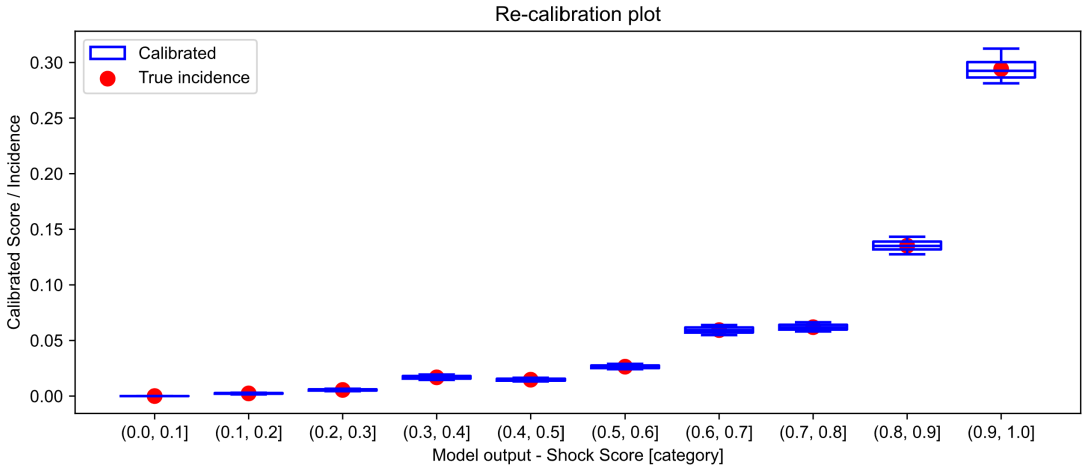



**Figure 6** Calibration plot after recalibration vs. true incidence. Calibration plot after recalibration showing model output probabilities and the actual probability of the true outcome. This fine-tuned model is more reliable and easily interpretable in clinical use.

considering these two comorbidities as protective factors, several explanations may clarify this finding. Patients with diagnosed AH or dyslipidaemia may reflect access to better chronic health care that could have influence the risk of CS development or there is a potential protective mechanism of common antihypertensive drugs such renin–angiotensin–aldosterone blockade or pleiotropic anti-inflammatory effect of statins.[21,46–48]

A known disparity exists between the treatment of ACS in females and males.[49–51] Females are less likely to receive invasive coronary angiography, timely revascularization, and secondary prevention medication.[52] A recent analysis by Ton *et al.*[53] showed that women with CS have worse outcomes than men. In our study, female sex was associated with increased risk of CS that further underlines potential disparities in ACS treatment and calls to action.

We deliberately chose variables that are potentially available at the first medical contact in the ambulance or emergency department in order to allow the immediate predictable severity stratification. Considering that some of the important elements related to angiographic findings (e.g. no-reflow) or laboratory findings (e.g. lactate or troponin) are not included, it may be worthwhile considering the development of specific scores accounting for them on top of the common features.

In the light of the futile effort of treating evolved CS with pMCS underlined by the results of a recent meta-analysis,[13] it is certain that the approach to the CS treatment needs a substantial change. The CRISP AMI trial and following sub-study showed that implantation of the pMCS in high-risk STEMI patients without CS was associated with numeric reduction in all-cause mortality and in-hospital development

**Table 3 Recalibration**

| Shock score category | True incidence | *n* | Mean shock score | Calibration ratio |
|---|---|---|---|---|
| (0.0, 0.1] | 0.00% | 55 | 8.07% | 0.0000 |
| (0.1, 0.2] | 0.24% | 731 | 16.02% | 0.0149 |
| (0.2, 0.3] | 0.55% | 1088 | 25.02% | 0.0220 |
| (0.3, 0.4] | 1.68% | 955 | 34.76% | 0.0485 |
| (0.4, 0.5] | 1.47% | 651 | 44.71% | 0.0329 |
| (0.5, 0.6] | 2.64% | 439 | 54.68% | 0.0483 |
| (0.6, 0.7] | 5.93% | 339 | 64.96% | 0.0913 |
| (0.7, 0.8] | 6.19% | 264 | 74.63% | 0.0830 |
| (0.8, 0.9] | 13.52% | 222 | 84.89% | 0.1592 |
| (0.9, 1.0] | 29.41% | 155 | 94.12% | 0.3125 |

of CS.[54,55] This suggests that if pMCS is implanted to the right patients at the beginning of haemodynamic deterioration while microcirculation is still functioning and systematic inflammatory response syndrome has not yet developed, CS might be prevented.

Whether STOP SHOCK score could be used to guide pre-emptive pMCS implantation in order to prevent CS warrants further research. The future plans include prospectively validating the model in clinical settings with consecutive patient cohorts. By predicting CS, the STOP SHOCK score may facilitate pre-emptive measures, such as pre-emptive pMCS implantation. Additionally, since the score is available at first contact, it can be utilized for patient triage, for example enabling the intensive monitoring and faster coronary angiography for stable NSTEMI patients who do not exhibit any specific signs of CS. Upon confirming the model's prospective performance, randomized trials comparing pre-emptive MCS implantation based on STOP SHOCK score predictions vs. standard of care are intend to be designed to evaluate whether the implementation of the score would lead to improved patient outcomes.

## Study limitations

The present study has several limitations. The selection of variables has been to some extent biased by the availability of parameters in both databases. Considering the different time course, some standard treatments, may not be included in the standard of care in the oldest cohort. The data collection timeframe (from 20 to 6 years ago) may also represent a general limit to applicability in contemporary cohorts. Both registries involved predominantly Caucasian ethnicity, therefore, applicability of the results to other ethnic groups requires caution. Finally, significant class imbalance was present in this study. Despite the high ROC AUC and specificity, the positive predictive value of the STOP SHOCK score was low. While the current findings support the tool's reliability and predictive capability, further prospective studies are necessary to confirm its effectiveness in diverse clinical settings and to establish appropriate management protocols based on the predicted risk of shock.

# Conclusion

The STOP SHOCK risk score is a simple and efficient ML-based tool that may be calculated at the first medical contact in routine practice to identify the risk of in-hospital development of CS in patients with ACS. Apart from risk stratification and facilitation of clinical decision-making, this tool provides the scientific basis for future research of the concept of pre-emptive pMCS implantation to prevent CS in ACS patients.

## Author contribution

A.B.—Conceptualization, Methodology, Writing—original draft preparation, Supervision, A.S.—Investigation, Writing—reviewing and editing, N.J.—Conceptualization, Methodology, Visualization, Writing—original draft preparation, Data curation, K.A.K.—Writing—reviewing and editing, G.T.—Writing—reviewing and editing, M.S.—Investigation, Writing—reviewing and editing, M.K.—Writing—reviewing and editing, Project administration, I.B.—Investigation, Visualization, J.J.—Visualization, Formal analysis, F.G.—Investigation, E.P.—Writing—reviewing and editing, A.R.—Software, M.J.—Investigation, V.S.J.—Writing—reviewing and editing, K.P.—Project administration, S.M.—Supervision, C.S.—Supervision, K.H.—Supervision, B.B.—Conceptualization, Methodology, Investigation, Writing—original draft preparation, Validation. All authors listed have made a substantial, direct, and intellectual contribution to the work. All authors critically revised and approved the manuscript for the submission.

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## Data availability

All data requests should be submitted to the corresponding author for consideration. Access to anonymized data for scientific research may be granted following review.

# Lead author biography

Allan Böhm is cardiologist, scientists, and lecturer interested in acute cardiology, prevention, thromboses, arrhythmias, and artificial intelligence. From 2015–23, he worked at the National Institute of Cardiovascular Diseases in Bratislava. In 2015, he founded the biomedical organization Premedix Academy. In 2017, he helped establish the Committee for Digital Health. Subsequently, he brought this form of medicine to Slovakia, and established Premedix Clinic. In 2020, he became board member of the ESC; in 2022, was awarded with the silver medal of the ESC and chosen amongst top five young scientists in Slovakia. In 2022, he founded a medtech start-up Seerlinq.

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