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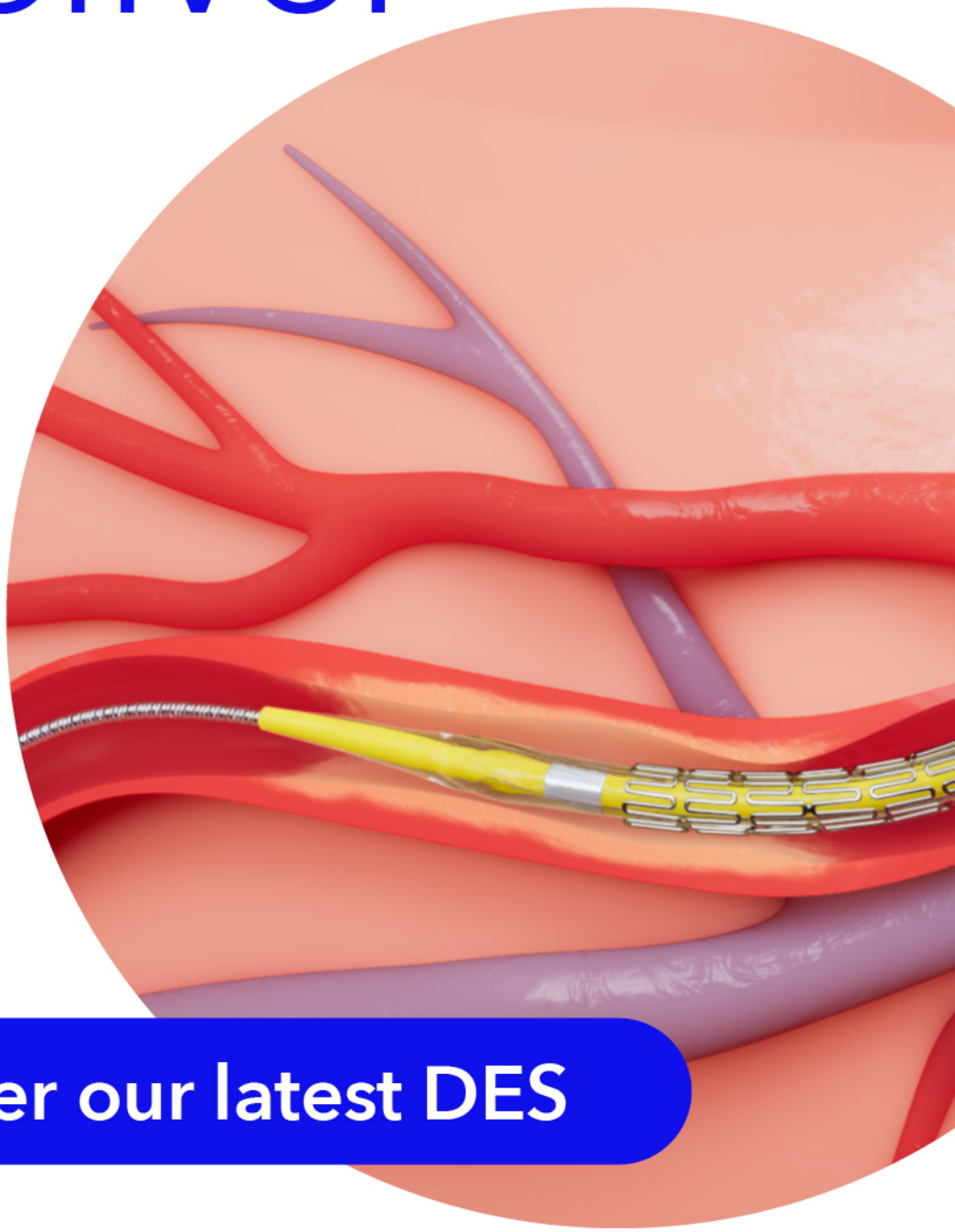

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A machine learning algorithm to predict a culprit lesion after out of hospital cardiac arrest

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Abstract

Background: We aimed to develop a machine learning algorithm to predict the presence of a culprit lesion in patients with out-of-hospital cardiac arrest (OHCA).

Methods: We used the King's Out-of-Hospital Cardiac Arrest Registry, a retrospective cohort of 398 patients admitted to King's College Hospital between May 2012 and December 2017. The primary outcome was the presence of a culprit coronary artery lesion, for which a gradient boosting model was optimized to predict. The algorithm was then validated in two independent European cohorts comprising 568 patients.

Results: A culprit lesion was observed in 209/309 (67.4%) patients receiving early coronary angiography in the development, and 199/293 (67.9%) in the Ljubljana and 102/132 (61.1%) in the Bristol validation cohorts, respectively. The algorithm, which is presented as a web application, incorporates nine variables including age, a localizing feature on electrocardiogram (ECG) (≥2 mm of ST change in contiguous leads), regional wall motion abnormality, history of vascular disease and initial shockable rhythm. This model had an area under the curve (AUC) of 0.89 in the

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development and 0.83/0.81 in the validation cohorts with good calibration and outperforms the current gold standard-ECG alone (AUC: 0.69/0.67/0/67).

Conclusions: A novel simple machine learning-derived algorithm can be applied to patients with OHCA, to predict a culprit coronary artery disease lesion with high accuracy.

KEYWORDS

coronary artery disease, early angiography, Out-of-Hospital Cardiac Arrest

1 | INTRODUCTION

Out-of-Hospital Cardiac Arrest (OHCA) occurs in over a quarter of a million patients a year and is a leading cause of mortality in developed countries.[1] Between 50% and 90% of patients have a primary cardiac etiology cardiac arrest with the presence of a culprit coronary lesion.[2,3] Current American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines recommend emergency angiography and percutaneous coronary intervention (PCI) in patients with ST segment elevation or in those without ST elevation with hemodynamic instability and absence of a noncardiac cause.[4–6] The 12 lead electrocardiogram (ECG) remains the current gold standard for guiding pathways of care and decision to perform emergency coronary angiography. However, it is well established that the post return of spontaneous circulation (ROSC) ECG is a poor predictor of the presence of significant coronary artery disease (CAD) and, in particular, a culprit lesion.[2,3,7] Three randomized clinical trials in patients with OHCA without ST elevation recently found unexpectedly low rates of culprit lesions compared with prior observational registries and subsequently no benefit from an early invasive approach, highlighting the critical importance of improved detection.[8–11] There are limited studies addressing identification of culprit lesions in this patient group, which might enable selection of patients for direct conveyance to cardiac arrest centers or for selection for an early invasive approach. To date, the use of biomarkers has been disappointing[12] and a risk score derived from multivariable logistic regression has important limitations and has not been externally validated to date.[13] Accordingly, the purpose of this study was to utilize novel machine learning methods to improve detection of a culprit lesion in patients presenting with OHCA for use before conveyance or after arrival to a specialist heart attack center (HAC).

2 | METHODS

2.1 | Study setting and population

Patients across London, who experience OHCA in the community, are served by the London Ambulance Service (LAS). A standardized systematic protocol was established in 2012 in London, whereby patients who have sustained OHCA with ROSC and an ECG showing ST elevation are taken directly to a HAC. Patients without ST elevation were brought directly to the HAC if there was high suspicion of a cardiac etiology (the presence of chest pain before arrest or a history of established CAD) or after exclusion of noncardiac causes in the emergency department.[5] King's College Hospital (KCH) is the main HAC in South East London, treating a population in excess of one million. On arrival, a decision to perform coronary angiography is made by the admitting interventional cardiologist and after treatment, patients are transferred to the Intensive Care Unit for ongoing supportive care.

We created the King's Out-of-Hospital Cardiac Arrest Registry (KOCAR) as previously described.[14] This registry includes all patients over the age of 18 years, who presented with suspected cardiac etiology OHCA and had ROSC in the field between May 1, 2012 and May 1, 2017. This initial timepoint was chosen to reflect the date that a protocol was established to transfer OHCA patients with ST elevation directly to HACs across London. Inclusion criteria for the registry was all patients with ST elevation on ECG and for patients without ST elevation, if there was no clear noncardiac etiology on initial assessment. Exclusion criteria included an obvious noncardiac cause of arrest (suicide, trauma, drowning, substance overdose), patients with suspected or imaging confirmed intracerebral bleeding, known moderate-to-severe neurological disability (Cerebral Performance Category 3 or 4) or any known survival limiting disease to 6 months preceding the cardiac arrest. Research ethics committee approval was obtained and the study was conducted in accordance with the Declaration of Helsinki.

2.2 | Data collection

Data were collected using a dedicated database based on the Utstein style recommendations. We formed a data collaboration with LAS to ensure high accuracy of prehospital data, including time of cardiac arrest, initial rhythm, administration of bystander cardiopulmonary resuscitation (CPR), and time of ROSC. Patients with a shockable initial rhythm and a witnessed arrest (either by lay responder or emergency medical services [EMS]) were defined as an "Utstein-like" comparator cohort. Medical records were analyzed for hospital data including arterial blood gas results such as pH, lactate and bicarbonate, and blood tests for hemoglobin, creatinine, liver function tests, and C-reactive protein. In total, 175 variables were collected.

Twelve lead ECGs are performed in the prehospital setting before conveyance but only those on admission to the center were analyzed and classified as ST elevation, left bundle branch block (LBBB), ST depression, right bundle branch block (RBBB), or normal. A localizing territory was classified by ≥2 mm ST changes or T wave changes in two contiguous leads in a coronary artery distribution. Localizing features in LBBB were defined according to the Sgarbossa criteria (Concordant ST elevation > 1 mm in leads with a positive QRS complex, Concordant ST depression > 1 mm in V1–V3, and in proportion to the preceding S-wave (or R-wave) as determined by (1) at least 1 mm of ST elevation (or depression) AND (2) an ST/S ratio ≤ −0.25) in accordance with previous literature.[15,16]

Coronary angiography was performed at the interventional cardiologist's discretion. The coronary angiogram was evaluated retrospectively by a blinded clinician. The prespecified primary endpoint was the presence of a culprit lesion, which classified as an athero-thrombotic occlusion with presence of thrombus and/or easy passage of the coronary guidewire. Any lesion over 70% in a single angiographic plane that the clinician treated as a culprit or with evidence of less than TIMI III flow was classed as a culprit in the analysis. These definitions are in accordance with previously published articles in this area.[13,17]

2.3 | Development of machine learning algorithm

We incorporated the patients referred for in-patient coronary angiography in the analysis. Missing predictor variables incorporated into the machine learning algorithm were investigated for associations with other variables, with appropriate multiple imputation methods used to handle missing values in accordance with the recommendations of the TRIPOD guidelines.[18] To generate a statistically significant training sample, we randomly selected 75% of the patient records, with the other 25% available to test the accuracy of our algorithm.

We adopted a Gradient Boosting approach, using the open-source algorithm XGBoost, which is a scalable tree boosting software library commonly used in machine learning and applied in several fields of physics and medicine.[19] This supervised machine learning algorithm is an ensemble of decision trees that are constructed from labeled training data, where each tree is trained individually. In detail, to construct a single tree, a bootstrapped sample of the training sample is selected and the algorithm recursively splits the data using a feature set based on the ability of each node to optimally separate the training data into their constituent classes. Nodes are generated until a maximum depth, minimum number of samples, or user-defined purity is reached. XGBoost uses gradient tree boosting to grow a forest of trees considering all features, where the bootstrapped sample for each new tree is weighted by the accuracy of the previous iteration. Hence, although an individual, optimized, decision tree may return the highest accuracy score for the test data set, a Gradient Boosting approach provides optimal accuracy when considering the variance of the entire training data set. To maximize the predictive power of our algorithm, we used a grid search approach to estimate the maximum depth and number of estimators and optimized the algorithm based on the area under the curve (AUC). The resultant probabilities from the XGBoost are calibrated using a cross-validation technique to lie between 0 and 1.

To develop an algorithm that can be incorporated into clinically relevant, real-time, medical practice, we iteratively selected variables for entry into the decision tree based on clinical relevance and early availability. Based on feature importance and the absence of significant effect on model performance, variables were then iteratively pruned from the algorithm. Final variables incorporated into the machine learning algorithm were age, Utstein-like cohort, normal ECG, ST elevation, RBBB, localizing territory on ECG, regional wall motion abnormality (RWMA) on admission, transthoracic echocardiography (TTE), vascular history (defined as previous stroke, PCI, or coronary artery bypass grafting [CABG]), and initial shockable rhythm.

Calibration slopes were used to plot the mean risk score relative to the observed outcome rate for a given decile of predicted risk and hence measure the calibration of the scores rather than the Hosmer–Lemeshow goodness-of-fit test in accordance with current expert consensus.[20] The accuracy of the best performing model was assessed using the Brier score, which is defined as the mean squared difference between the observed and predicted outcome. Brier scores range from 0 to 1.00, with 0 representing the best possible calibration. An internal validation was performed using 1000 bootstrap iterations, generating bias-corrected and accelerated confidence intervals (CIs). The risk scores were then calculated for patients in the validation cohorts, with the discrimination and calibration measured by the AUC and calibration slope, respectively.

2.4 | Validation cohort study populations

External validation was performed in retrospective cohorts from the University Medical Center, Ljubljana, Slovenia, and Bristol Heart Institute, UK. Both centers are HACs providing primary PCI with an on-site emergency department and serve a population of ~1 million. Similar to the development cohort, both centers followed relevant European Association for Percutaneous Cardiovascular Interventions (EAPCI) and ESC guidelines with regard to pathways of care for OHCA patients, and all patients met inclusion and exclusion criteria. Patients from Ljubljana were recruited from January 2013 to December 2017, and in Bristol from January 2019 to July 2020. The primary endpoint was the presence of a culprit lesion as per study definition.

2.5 | Statistical testing

Statistical analyzes were performed using *T* tests or analysis of variance for parametric variables and Mann–Whitney or Kruskal–Wallis tests for nonparametric variables. Normally distributed variables are expressed as mean with SD and non-normally distributed variables are expressed as median with interquartile range. The χ^2 test was used for categorical variables. A $p < 0.05$ was

considered statistically significant. All analyzes were undertaken using Python version 2.7 (Python service foundation) and SPSS version 25 (IBM).

3 | RESULTS

3.1 | Patient population

Between May 1, 2012 and December 31, 2017, 1055 patients suffered a suspected cardiac etiology OHCA in our catchment area and had attempted resuscitation, of whom 291 failed to regain ROSC with EMS. Of this cohort of survivors, 129 died before reaching KCH. Six hundred and thirty-five patients reached KCH with ROSC, of whom 232 patients were deemed to not have a primary cardiac etiology cause of the cardiac arrest. After excluding patients with prior neurological disability (4 patients) and those lost to follow-up (1 patient), 398 patients were included in the registry (Figure 1).

Patient demographics for the development cohort are summarized in Table 1. The median age was 64.3 years (53.3–75.4) and the majority of patients were male (74.6%). Over half of patients had cardiac arrest at residence (n = 228, 57.3%), 287 patients (72.1%) had shockable rhythms and bystander CPR was performed in 291 (73.1%). Of the admitted 398 patients, 346 (86.9%) had admission TTE and 309 (77.6%) were referred for in-patient coronary angiography within the first 2 h of admission. Patients undergoing coronary angiography were younger and were more likely to have a witnessed arrest, an initial shockable rhythm, a lower creatinine and pH (Table 1).

3.1.1 | ECG analysis

The ECG changes on admission are summarized in Supporting Information: Table 1. Coronary angiography was preferentially performed in patients with ST elevation compared with those without and least likely to be performed in patients with a normal ECG and RBBB. The rates of CAD were highest in those with ST elevation (n = 168/179; 93.9%) but there was also a substantial rate in patients with LBBB (n = 26/40; 65.0%), ST depression (n = 21/31; 67.7%), and in those with a normal ECG (n = 21/45; 46.7%). A similar trend was observed for culprit lesions, with the highest rate in those with ST elevation (159/179; 88.8%). Culprit lesions were detected in 61.3% of patients with ST depression, 37.5% with LBBB, 37.5% with RBBB, and 24.4% of patients with a normal ECG.

3.1.2 | Coronary angiography analysis and rates of CAD

Among the patients who had coronary angiography performed, 209 (70.1%) had evidence of a culprit lesion in a major epicardial vessel by study definitions and the majority of lesions were in the LAD (50.7%). Patient demographics were similar between those with and without a culprit lesion but patients with a culprit lesion were more likely to have a history of smoking and an initial shockable rhythm. Rates of significant CAD (100.0 vs. 34.00%; $p < 0.0001$) and multivessel CAD (50.2 vs. 29.0%; $p < 0.0001$) were higher in patients with a culprit lesion while prior CABG was lower (5.7 vs. 11%, $p = 0.03$). There was no difference in rates of prior

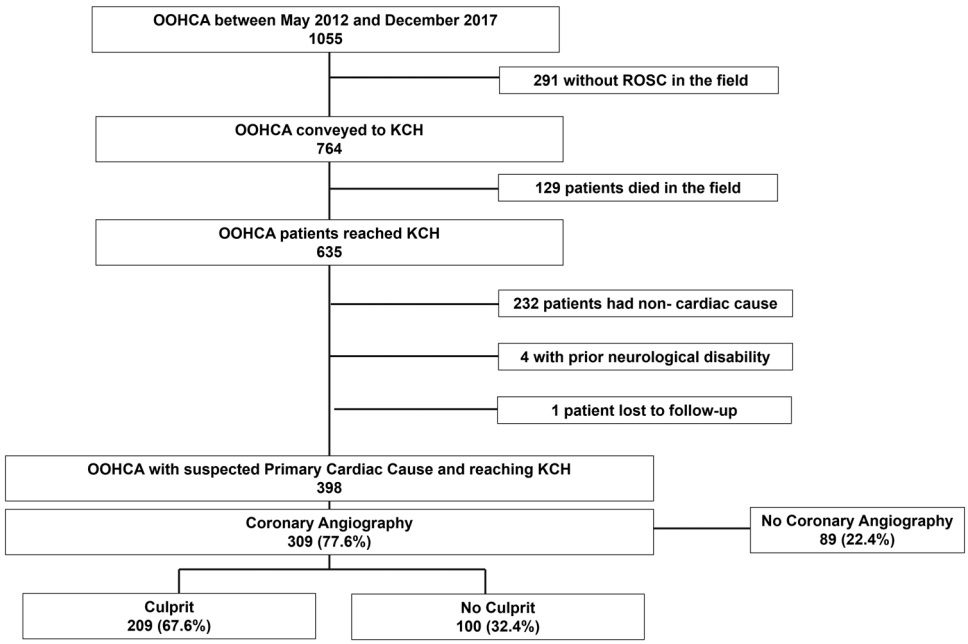

FIGURE 1 Flow chart of patient flow from the King's Out-of-Hospital Cardiac Arrest Registry (KOCAR) registry cohort in the study. Between May 1, 2012 and December 31, 2017, 1055 patients suffered out-of-hospital cardiac arrest (OOHCA), of whom 398 survived to our institution and met inclusion criteria for the study. ROSC, return of spontaneous circulation.

TABLE 1 Comparison of baseline characteristics between development and validation cohorts.

	Total (*n* = 966)	King's College (*n* = 398)	Ljubljana (*n* = 346)	Bristol (*n* = 222)	*p*
Age (years) – Median (IQR)	63.8 (54.0–74.0)	64.3 (53.3–75.4)	63.0 (55.0–73.0)	63.0 (52.0–74.0)	0.926
Male – no/total no. (%)	750/966 (77.6)	297/398 (74.6)	282/346 (81.5)	171/222 (77.0)	0.078
Hypertension	**475/962 (49.4)**	**189/398 (47.5)**	**203/342 (59.4)**	**83/222 (37.4)**	**<0.0001**
Type 2 DM	172/962 (17.9)	72/398 (18.1)	66/342 (19.3)	34/222 (15.3)	0.478
Smoker	388/816 (47.5)	237/398 (59.5)	118/196 (60.2)	33/222 (14.9)	<0.0001
Prior PCI	70/962 (7.3)	32/298 (8.0)	20/342 (5.8)	18/222 (8.1)	0.448
Prior CABG	94/963 (9.8)	31/398 (7.8)	44/343 (12.8)	19/222 (8.6)	0.055
Arrest circumstances – no/total no. (%)					
Witnessed	**825/966 (85.6)**	**319/398 (80.2)**	**318/346 (91.9)**	**188/222 (84.7)**	**<0.0001**
Bystander CPR	**676/913 (69.6)**	**291/398 (73.1)**	**190/293 (64.8)**	**195/222 (87.8)**	**<0.0001**
Initial shockable rhythm	**744/963 (77.3)**	**287/398 (72.1)**	**284/344 (82.6)**	**173/221 (78.8)**	**0.003**
Utstein-like cohort	**653/963 (67.8)**	**241/398 (60.6)**	**259/344 (75.3)**	**153/221 (69.2)**	**<0.0001**
Investigations					
RWMA	**386/846 (45.6)**	**198/346 (57.2)**	**100/298 (33.6)**	**88/202 (43.6)**	**<0.0001**
Serum creatinine (μmol/L)	105 (85–162)	107 (86–134)	104 (84–124)	94 (80–118)	0.24
Blood lactate (mmol/L)	4.3 (2.1–7.8)	4.8 (2.4–8.7)	3.5 (1.8–7.3)	4.7 (2.1–6.9)	<0.0001
pH	7.24 (7.12–7.32)	7.22 (7.09–7.31)	7.27 (7.18–7.35)	7.2 (7.1–7.3)	<0.0001
12 lead ECG - no/total no. (%)					**<0.0001**
STEMI	405/963 (42.1)	182/398 (45.7)	154/346 (45.7)	69/219 (31.5)	
LBBB	114/963 (11.8)	52/398 (13.1)	37/346 (10.9)	25/219 (11.4)	
ST depression	133/963 (13.8)	41/398 (10.3)	60/346 (17.8)	32/219 (14.6)	
RBBB	107/963 (11.1)	45/398 (11.3)	37/346 (11.0)	25/219 (11.4)	
Normal	196/963 (20.4)	78/398 (19.6)	50/346 (14.8)	68/219 (31.1)	
Localizing territory	**552/957 (57.7)**	**242/396 (61.1)**	**160/342 (46.8)**	**150/219 (68.5)**	**<0.0001**
Admission – no/total no. (%)					
Cardiogenic shock	**387/958 (40.4)**	**192/398 (48.9)**	**117/343 (34.1)**	**78/222 (35.1)**	**<0.0001**
Coronary angiography	**734/963 (76.2)**	**309/398 (77.6)**	**293/343 (85.4)**	**132/222 (59.5)**	**<0.0001**
Culprit	510/734 (69.4)	209/309 (67.4)	199/293 (67.9)	102/132 (61.1)	0.269

Note: Bold values are statistically significant.

Abbreviations: CABG, coronary artery bypass grafting; CPR, cardiopulmonary resuscitation; DM, diabetes mellitus; ECG, electrocardiogram; IQR, interquartile range; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; RWMA, regional wall motion abnormality.

PCI or presence of a chronic total occlusion (Supporting Information: Table 2).

3.2 | Model development in the development cohort

The final and complete decision tree model combines nine variables, which are readily available on arrival to a HAC, and includes ~512 potential permutations. The most discriminant variable across the entire decision tree was the presence of a localizing ECG change on the 12 lead ECGs. The following variables in conjunction predicted the presence or absence of a culprit lesion with high accuracy—age, a localizing feature on the ECG, presence of ST elevation, RBBB, normal ECG, presence of an initial shockable rhythm, Utstein-like cohort, prior vascular history, and an RWMA on TTE. Supporting Information: Figure 1 shows one example of a single decision tree within the random forest ensemble determined by XGBoost for illustrative purposes and frequencies of predictions as probabilities are shown in Supporting Information: Figure 2.

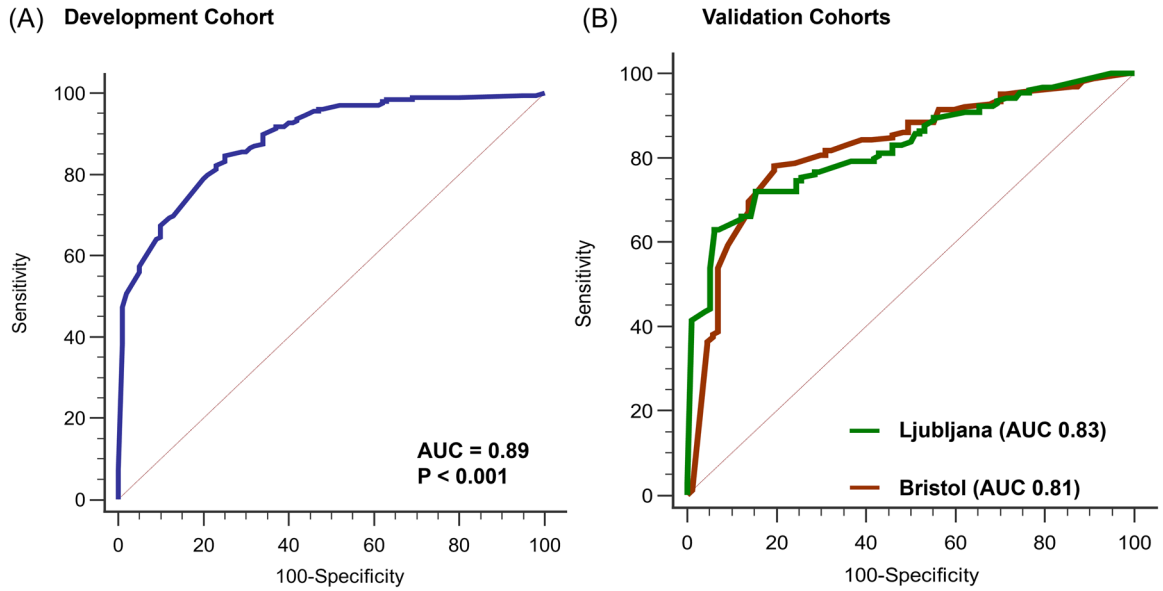

FIGURE 2 Receiver operating curve for the development and external validation cohorts. (A) The area under the curve (AUC) in the development cohort was 0.83 and (B) was 0.81 in the Ljubljana cohort (green) and 0.91 in Bristol (red). [Color figure can be viewed at wileyonlinelibrary.com]

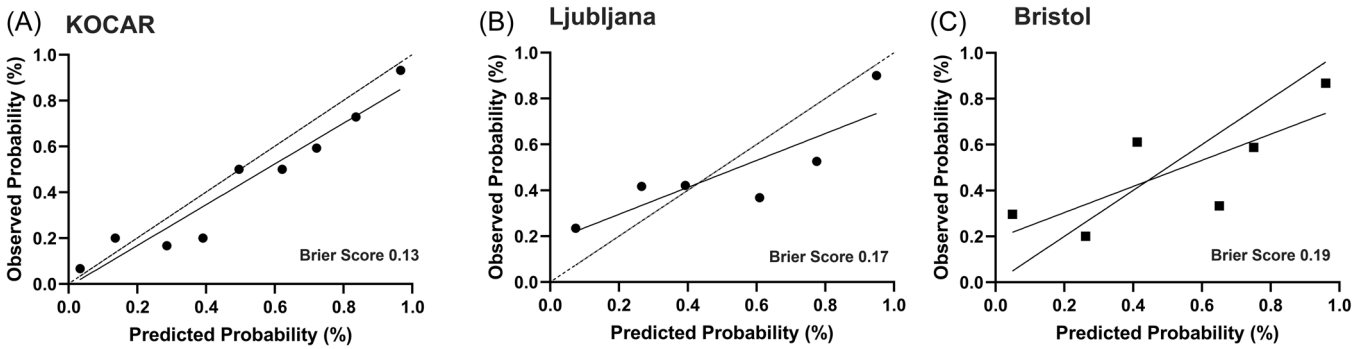

FIGURE 3 Calibration plots for the decision tree. (A) The performance of the decision tree in the King's Out-of-Hospital Cardiac Arrest Registry (KOCAR) development cohort, (B) in the Ljubljana cohort, and (C) in the Bristol cohort.

The KOCAR Culprit predictor had a discrimination of 0.89 AUC (CI 0.858–0.918) (Figure 2). The model showed good calibration with a Brier score of 0.13 and a Cohen's κ of 0.558 (Figure 3). The performance of the model was significantly superior to the use of the presence of ST elevation on ECG alone (AUC 0.69).

3.3 | Validation cohorts

Three hundred and forty-six patients were recruited in the Ljubljana and 222 were recruited in the Bristol cohort (Table 1). The external validation cohorts had differing rates of baseline characteristics and frequency of predictor variables used in the final algorithm described above than the development cohort. The KOCAR algorithm had an AUC of 0.825 in the Ljubljana validation cohort with a Brier Score of 0.173, whereas in the Bristol cohort, the AUC was 0.811 and the Brier score was 0.196. In both cohorts, the KOCAR culprit predictor algorithm had superior discrimination than ECG alone, where this had an AUC of 0.669 and 0.665 in the Ljubljana and Bristol cohorts, respectively (Figure 2).

3.4 | Discrimination performance of the KOCAR culprit predictor algorithm

The discrimination performance of the KOCAR culprit predictor algorithm was evaluated at two predictive thresholds: >70% and >90%.

3.4.1 | Greater than 70%

A total of 75.8%, 71.3%, and 61.8% patients had a predicted threshold above 70% in the KOCAR, Ljubljana, and Bristol cohorts. At this threshold, there was a high rate of culprit lesions, with a positive

predictive value of 85.0% in the KOCAR development cohort and 82.8%/82.9% in the external validation cohorts.

3.4.2 | Greater than 90%

A total of 40.4%, 37.7%, and 30.6% patients had a threshold above 90% in the KOCAR, Ljubljana, and Bristol cohorts, respectively. In KOCAR, this threshold had a positive predictive value of 96.0% and a specificity of 0.950. In the Ljubljana cohort, this had a positive predictive value of 93.7% and a specificity of 0.931. In the Bristol cohort, a threshold of >90% had a positive predictive value of 93.8% and a specificity of 0.952 (Tables 2 and 3).

3.5 | Implementation of algorithm into a web-based application

For ease of use for physicians in clinical practice, we constructed a web-based application that provides a probability of the presence of a culprit coronary artery lesion in patients admitted to HAC after OHCA given the nine input parameters described above (beta version available at http://tinyurl.com/miracle2score/kocar) (Figure 4).

4 | DISCUSSION

In this study, we derived and validated a novel machine learning algorithm to predict the presence of a culprit coronary artery lesion after OHCA on admission to a HAC, which has an AUC of 0.89 in the development cohort and 0.83/0.81 in the external validation cohorts. Importantly, this algorithm outperforms the 12-lead ECG, which is the current gold-standard for guiding pathways of care.[21] The algorithm, which is implemented in a practical web-based application, has the potential to be integrated into research studies and clinical practice to support early decision-making either before conveyance or after admission to a HAC.

There is an increasing appreciation of an underlying cardiac and, in particular, CAD etiology of OHCA. The post-ROSC ECG is a poor predictor of a culprit lesion with several studies, indicating a relatively high rate of culprit lesions in patients without ST-elevation myocardial infarction (STEMI) and a proportion of patients with STEMI not having a culprit lesion, possibly due to acidemia and post-ROSC changes.[10] Nonetheless, the AHA, ESC, and EAPCI societies currently recommend the use of the 12-lead ECG as the key determinant in this decision-making process.[4,5,21] Owing to the poor discrimination of the 12-lead ECG, these guidelines currently recommend that patients without STEMI particularly, receive an assessment to exclude obvious noncardiac causes, which might lead to substantial delays in treatment. The recently reported COACT, PEARL, and TOMAHAWK trials showed no benefit from early coronary angiography in this patient group but found a lower rate of culprit lesions (13.3%–45%) than previously reported registries, which may have attenuated the benefits of an invasive approach.[8,10] These studies highlight the importance for objective methods to predict culprit lesions in patients with OHCA and particularly in those without ST elevation.[9] Although the interpretation of lesion significance in this population remains unclear, our study definition of a culprit lesion was similar to these trials and prior reports with inclusion of patients with a lesion of >70%.[8,9,11]

Although there is evidence that rates of CAD vary between 50% and 90% in all-comers with OHCA,[2,3] there remains limited data for the predictors of a culprit lesion. Cardiac biomarkers and the 12-lead ECG, which are the gold standard in acute coronary syndromes, are poor predictors of a culprit lesion in the OHCA cohort.[3,12,22] A study by Waldo et al.[13] found that 4 variables in 247 patients with OHCA, including angina, congestive cardiac failure, initial shockable rhythm, and the presence of ST elevation, could predict a culprit lesion with an AUC of 0.86 but performed less well in patients without ST elevation (AUC 0.76) and has important limitations. For example, this study included in-hospital cardiac arrests, had a relatively lower rate of shockable rhythms, uses subjective variables (some of which may not be apparent at the time of admission such as chest discomfort and presence of heart failure) and was not externally validated, so may

TABLE 2 Diagnostic performance of the decision tree in the development cohort.

Performance	KOCAR Culprit > 0.70 Value (95% CI)	KOCAR Culprit > 0.90 Value (95% CI)	ECG alone Value (95% CI)
AUC	0.888 (0.858–0.918)	0.888 (0.858–0.918)	0.691 (0.647–0.738)
Sensitivity	0.871 (0.834–0.914)	0.574 (0.524–0.631)	0.833 (0.792–0.875)
Specificity	0.680 (0.600–0.763)	0.950 (0.912–0.981)	0.550 (0.469–0.632)
Accuracy	0.809 (0.777–0.851)	0.696 (0.657–0.741)	0.741 (0.702–0.783)
Positive likelihood ratio	2.721 (2.171–3.674)	11.483 (6.437–30.055)	1.850 (1.554–2.279)
Negative likelihood ratio	0.190 (0.125–0.248)	0.448 (0.386–0.508)	0.304 (0.219–0.400)
Positive predictive value	0.850 (0.809–0.889)	0.960 (0.929–0.985)	0.795 (0.749–0.840)
Negative predictive value	0.716 (0.644–0.802)	0.516 (0.458–0.582)	0.611 (0.529–0.703)

Abbreviations: AUC, area under the curve; CI, confidence interval; ECG, electrocardiogram; KOCAR, King's Out-of-Hospital Cardiac Arrest Registry.

TABLE 3 Diagnostic performance of the decision tree in the validation cohorts.

	Ljubljana			Bristol		
Performance	KOCAR Culprit > 0.70 Value (95% CI)	KOCAR Culprit > 0.90 Value (95% CI)	ECG alone Value (95% CI)	KOCAR Culprit > 0.70 Value (95% CI)	KOCAR Culprit > 0.90 Value (95% CI)	ECG alone Value (95% CI)
AUC	0.825 (0.774–0.870)	0.825 (0.774–0.870)	0.669 (0.614–0.718)	0.811 (0.756–0.870)	0.811 (0.756–0.870)	0.665 (0.605 –0.733)
Accuracy	0.770 (0.722–0.813)	0.675 (0.627–0.722)	0.690 (0.639–0.738)	0.739 (0.682–0.803)	0.663 (0.602–0.723)	0.662 (0.599–0.726)
Sensitivity	0.818 (0.767–0.864)	0.539 (0.471–0.602)	0.739 (0.683–0.792)	0.716 (0.641–0.798)	0.474 (0.388–0.558)	0.653 (0.573–0.742)
Specificity	0.678 (0.597–0.762)	0.931 (0.882–0.976)	0.598 (0.506–0.684)	0.774 (0.683–0.864)	0.952 (0.898–0.986)	0.677 (0.576–0.770)
Positive Likelihood Ratio	2.542 (1.993–3.454)	7.821 (4.482–20.066)	1.838 (1.459–2.368)	3.170 (2.218–5.254)	9.789 (3.686–30.674)	2.023 (1.504–2.959)
Negative Likelihood Ratio	0.268 (0.195–0.359)	0.495 (0.423–0.574)	0.436 (0.336–0.575)	0.367 (0.253–0.478)	0.553 (0.458–0.647)	0.513 (0.374–0.665)
Positive Predictive Value	0.828 (0.778–0.875)	0.937 (0.892–0.976)	0.777 (0.722–0.831)	0.829 (0.761–0.893)	0.938 (0.872–0.982)	0.756 (0.675–0.835)
Negative Predictive Value	0.663 (0.575–0.741)	0.862 (0.793–0.928)	0.516 (0.449–0.579)	0.640 (0.549–0.735)	0.541 (0.467–0.625)	0.560 (0.475–0.661)

Abbreviations: AUC, area under the curve; CI, confidence interval; ECG, electrocardiogram; KOCAR, King's Out-of-Hospital Cardiac Arrest Registry.

have been at risk of over-fitting. Pertinently, validation of this model was not possible in the development and validation cohorts owing to an absence of robust recording of these variables. By contrast, our cohort consists of a real-world cohort of patients with OHCA and a primary cardiac etiology incorporating only objective variables into the decision tree model and, in addition, with robust external validation.

We applied a random forest classifier to provide a practical and individualized decision algorithm to a complex, heterogeneous, and nonlinear population. The variables in our decision tree identified by the machine learning algorithm are corroborated by previous studies evaluating features associated with the presence of CAD. Although several of these parameters are traditionally believed to be associated with culprit CAD, there is limited data to support this and the algorithm also provides a simple tool which incorporates the relevant variables. From the 12 lead ECG, a localizing ECG was the most important predictor of a culprit lesion, suggesting that this algorithm might be equally applied to patients with or without ST elevation. Although rates of ST elevation were high in both the development and validation cohorts, this parameter had relatively lower feature importance, providing validity of use in those without STEMI. Importantly, a RWMA on admission trans-thoracic echocardiography in patients with or without a localizing ECG change was an important predictor of a culprit lesion. Postarrest myocardial dysfunction, which is usually global in nature, is a well-established process after OHCA and has recently been associated with poor outcome.[23] However, this study suggests that presence of a RWMA may be an important factor in guiding decision-making to perform coronary angiography and is corroborated by recent data.[24] This lends support to the notion that all patients with OHCA should have a bedside/admission assessment of LV function by rapid TTE as part of the diagnostic process for a decision to perform immediate cardiac intervention, either prehospital or after admission.

The decision tree was developed in a cohort with broad clinical inclusion of patients with presumed cardiac etiology OHCA based on current consensus pathways of care and so is likely to be generalizable to a wide cohort of patients. Patients with a clear noncardiac cause were excluded but as coronary angiography is unlikely to be considered in this cohort, the model remains relevant to current clinical practice. The higher AUC of the algorithm in the development and validation cohorts compared with ECG alone (i.e., those with STEMI on 12-lead ECG) confirms a potential role in future clinical practice. Importantly, validation of this algorithm immediately after ROSC might facilitate direct transfer to a HAC, thereby minimizing delays in revascularization and ensuring appropriate patients receive optimal care. It is known that increased time from ROSC to ECG acquisition reduces the false positive rate of ECGs for the presence of significant CAD.[25] In our study, the 12 lead ECG was performed on arrival to a HAC, which will improve the accuracy of ECG findings. In future model development, particularly in a prehospital setting before conveyance, timing of ECG acquisition will need to taken into account. The intention of the algorithm is to guide clinicians to perform immediate invasive CAG and might be combined with the presence of hemodynamic instability and risk of neurological futility.

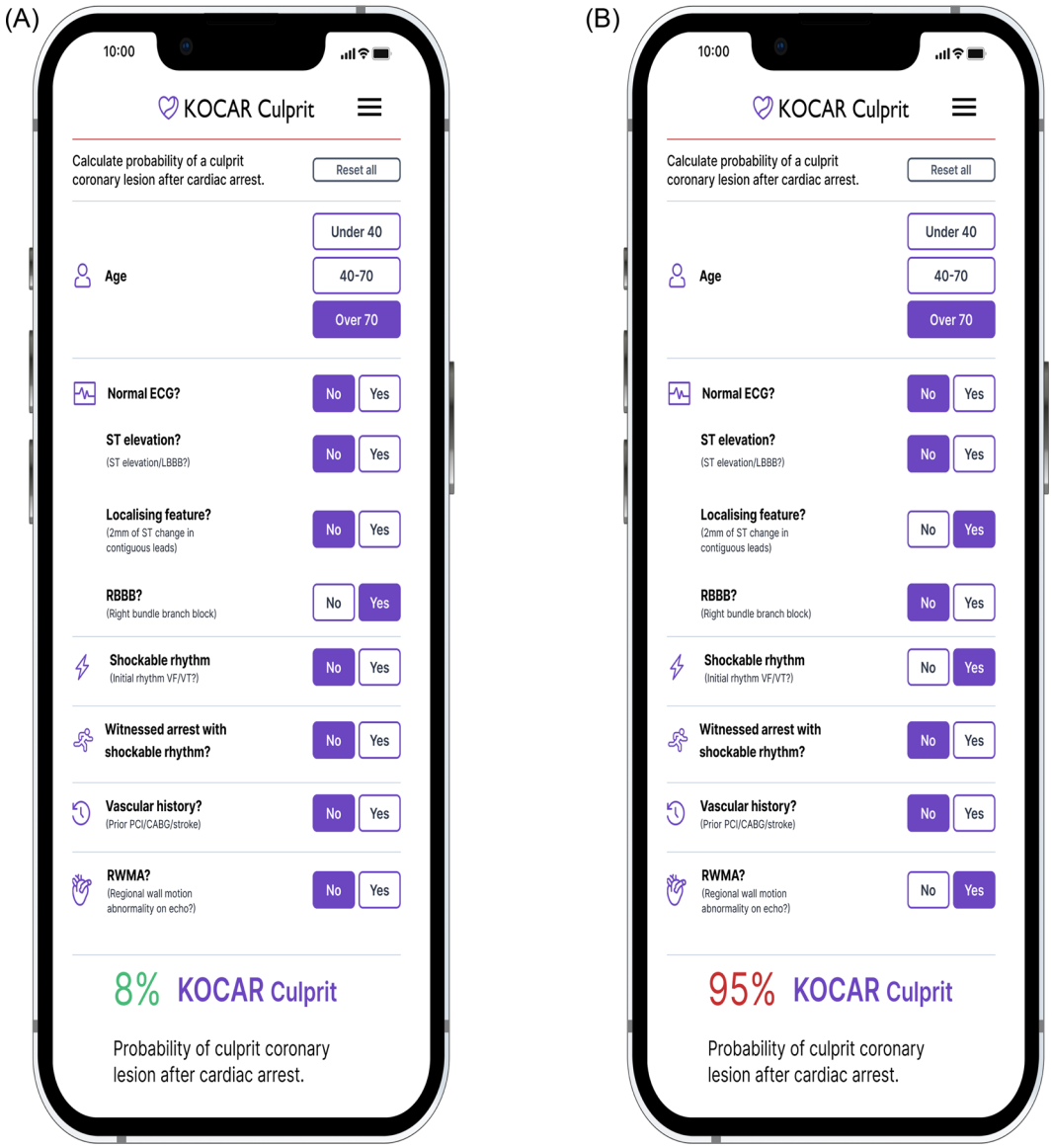

FIGURE 4 King's Out-of-Hospital Cardiac Arrest Registry (KOCAR) culprit lesion prediction tool web application. The figure provides an illustrative representation of the decision tree algorithm in the web application format. (A) A patient with a final diagnosis of a pulmonary embolism with a low risk of a culprit lesion (8%), (B) a patient without ST elevation but at high risk of a culprit lesion (95%). [Color figure can be viewed at wileyonlinelibrary.com]

With further prospective validation in large studies, this algorithm might be incorporated into research trials evaluating optimal pathways of care for patients with OHCA, particularly in those without ST elevation, with the potential for integration into clinical guidelines.

5 | LIMITATIONS

The risk score was derived and validated in retrospective cohorts, albeit with a thorough methodology and with internal and external validation. Although this enabled collection of a high-fidelity data set with a protocolized protocol of care, it introduces the possibility of a selection bias. In particular, the retrospective nonconsecutive nature of this study does not enable the rates of CAD and culprit lesions to be ascertained in patients that were not selected for coronary angiography based on clinical discretion who may be at particularly low risk. This also includes some patients with STEMI/LBBB, who might have been deemed not suitable for angiography for other clinical reasons such as futility or severe hemodynamic instability. However, only those undergoing coronary angiography were included which minimized adverse effects on algorithm development. Prediction of a culprit lesion might be most beneficial in those without STEMI on 12-lead ECG but this study was not powered to reflect this group due to lower numbers of non-STEMI patients and culprit lesions. Furthermore, the

definition of a culprit lesion in this patient cohort is challenging and based to some extent on clinical discretion but we used established definitions in accordance with previous studies.[13,17] We did not perform a core lab analysis and without evidence of thrombus or other angiographic features suggestive of a culprit lesion might simply represent stable bystander CAD. Ultimately, intra-coronary imaging might be able to clarify the pathophysiological significance of these plaques but in the meantime, flow-limiting lesions can reasonably be considered to be culprit lesions. We excluded patients with a clear noncardiac diagnosis, such as trauma, cerebral bleed or overdose, as by current treatment algorithms, a decision to perform emergency coronary angiography is made only in their absence. As a result, a significant proportion of patients had STEMI and there was a high rate of shockable rhythms and culprit lesions, which might affect the performance of the algorithm in undifferentiated OHCA populations. There were differing rates of baseline characteristics and predictive variables in the validation cohorts which might also have negatively affected the performance of the algorithm, although the discrimination performance remained accurate. Finally, the predictive accuracy of this algorithm may not be transferrable to other systems of care, such as in non-HAC without access to 24 h cardiac imaging and coronary angiography on arrival. Our findings and algorithm require further prospective validation in larger cohorts across multiple centers, in different systems of care and potentially before conveyance before routine clinical use.

6 | CONCLUSIONS

A novel simple machine learning-derived algorithm can be applied to patients with OHCA to predict a culprit CAD lesion with high accuracy. The algorithm requires further validation but may play a role in research studies or in supporting clinical pathways of care.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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