Available online at www.sciencedirect.com

Resuscitation Plus

journal homepage: www.elsevier.com/locate/resuscitation-plus

Clinical paper

Machine learning prediction of refractory ventricular fibrillation in out-of-hospital cardiac arrest using features available to EMS

Rayhan Erlangga Rahadian[a], *Yohei Okada*[b,c,*], *Nur Shahidah*[d,e], *Dehan Hong*[f], *Yih Yng Ng*[a,g], *Michael Y.C. Chia*[h], *Han Nee Gan*[i], *Benjamin S.H. Leong*[j], *Desmond R. Mao*[k], *Wei Ming Ng*[l], *Nausheen Edwin Doctor*[m], *Marcus Eng Hock Ong*[b,d]

Abstract

Background: Shock-refractory ventricular fibrillation (VF) or ventricular tachycardia (VT) is a treatment challenge in out-of-hospital cardiac arrest (OHCA). This study aimed to develop and validate machine learning models that could be implemented by emergency medical services (EMS) to predict refractory VF/VT in OHCA patients.

Methods: This was a retrospective study examining adult non-traumatic OHCA patients brought into the emergency department by Singapore EMS from the Pan-Asian Resuscitation Outcomes Study (PAROS) registry. Data from April 2010 to March 2020 were extracted for this study. Refractory VF/VT was defined as VF/VT persisting or recurring after at least one shock. Features were selected based on expert clinical opinion and availability to dispatch prior to arrival at scene. Multivariable logistic regression (MVR), LASSO and random forest (RF) models were investigated. Model performance was evaluated using receiver operator characteristic (ROC) area under curve (AUC) analysis and calibration plots.

Results: 20,713 patients were included in this study, of which 860 (4.1%) fulfilled the criteria for refractory VF/VT. All models performed comparably and were moderately well-calibrated. ROC-AUC were 0.732 (95% CI, 0.695 – 0.769) for MVR, 0.738 (95% CI, 0.701 – 0.774) for LASSO, and 0.731 (95% CI, 0.690 – 0.773) for RF. The shared important predictors across all models included male gender and public location.

Conclusion: The machine learning models developed have potential clinical utility to improve outcomes in cases of refractory VF/VT OHCA. Prediction of refractory VF/VT prior to arrival at patient's side may allow for increased options for intervention both by EMS and tertiary care centres.

Keywords: Machine learning, Prediction model, OHCA, ECPR, Refractory VF

Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant public health challenge, with an age-adjusted incidence rate of 50 per 100,000 person-years in Singapore.[1] A significant proportion of OHCAs present with ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), so-called "shockable rhythms" that are amenable to defibrillation and are associated with better outcomes as compared to the non-shockable rhythms.[2] According to American Heart Association guidelines, VF/VT is considered shock-refractory if the rhythm persists or recurs after at least 1 shock.[3] This phenomenon has been estimated to occur in more than 60% of VF or pulseless VT OHCAs.[4] VF/VT cardiac arrest survival rates stand at 29%; in contrast, refractory VF/VT are known to have reduced survival of 8–15%.[5] Accordingly, it is crucial to effectively manage OHCA patients with refractory shockable rhythm to improve their outcomes.

In general, the objective of management is to increase the odds of successful defibrillation while preventing the development of recurrent arrhythmias, although there is currently no standardized bundle of care recommended by guidelines.[3] Initial management of refractory VF/VT involves administration of antiarrhythmic drugs such as amiodarone or lignocaine alongside cardiopulmonary resuscitation (CPR).[6] Advanced options for the treatment of refractory

* Corresponding author at: Health Services and Systems Research, Duke-NUS Medical School, National University of Singapore, Singapore and Department of Preventive Services, School of Public Health, Kyoto University, Kyoto, Japan.

E-mail addresses: yohei_ok@duke-nus.edu.sg, yokada-kyf@umin.ac.jp (Y. Okada).

https://doi.org/10.1016/j.resplu.2024.100606

Received 15 December 2023; Received in revised form 22 February 2024; Accepted 4 March 2024

VF/VT include modifications to conventional defibrillation strategies, beta-blocker administration and extracorporeal membrane oxygenation (ECMO) cardiopulmonary resuscitation (ECPR).[7] If refractory VF/VT can be predicted early, such as when ambulances are dispatched, it can guide earlier management plans and preparation for advanced interventions, potentially leading to improved patient outcomes.

While there are some studies that demonstrate models which can predict ECG rhythms in OHCA,[8,9] there are limited studies investigating prediction of refractory VF/VT specifically. One such study developed a random forest algorithm using ECG data with considerable performance.[10] Another previous study using North American OHCA cohorts developed a clinical decision rule derived from decision tree analysis using data available to emergency medical services (EMS) after obtaining the patient's initial ECG rhythm.[7] However, there is no such study done using Asian OHCA datasets, and no studies that attempt prediction using information available prior to EMS arrival at scene. Since Singapore has the National Electronic Health Record (NEHR) system that allows paramedics to access the patient's characteristics such as past medical history before arrival at the scene, we hypothesized that this information could contribute to the prediction of the refractory shockable rhythm.

Therefore, this study aims to provide a proof of concept for an implementation of a predictive model for refractory VF/VT by EMS providers. The model will be trained on a Singaporean OHCA dataset, part of the Pan-Asian Resuscitation Outcomes Study (PAROS) registry that incorporates data obtained by both EMS and hospitals.

Methods

Ethical approval

This study was conducted according to the Declaration of Helsinki. This study was approved by the Centralized Institutional Review Board and Domain Specific Review Board in Singapore granted approval for the SG-PAROS database (ref no: 2013/604/C, 2013/00929 and 2018/2937) and Domain Specific Review Board (ref no: C/10/545 and 2013/00929). Informed consent was waived due to the nature of the observational study and all data were de-identified.

Study design and setting

This study is a secondary analysis of prospective Singapore OHCA data extracted from the PAROS registry cohort. PAROS is an Asia-Pacific cardiac arrest registry that started in 2010 with previously published methodology.[11] Variable definitions in PAROS follow the Utstein recommendations which includes details on prehospital care, medical procedures administered and outcome measures.[12] Singapore's 995 EMS dispatch system is managed by the Singapore Civil Defence Force. The dispatch system is linked to the National Electronic Health Record (NEHR), which can provide information on the patient's medical history. OHCA protocols are based on basic cardiac life support (BLS) principles, and paramedics are trained in defibrillation, advanced airway procedures, and adrenaline administration. The primary aim of PAROS is to enhance the understanding of OHCAs in the Asia-Pacific region and identify strategies for improving outcomes. Notably, 99% of the cardiac arrest patients in this database were transferred to Singapore's eight tertiary care hospitals. The termination of resuscitation (TOR) protocol was implemented in Singapore from January 2019 and the TOR criteria include all the following: (1) Unwitnessed arrest; (2) No shockable rhythm observed or no shock given; (3) No return of spontaneous circulation in out-of-hospital setting following minimum 6 rhythm analyses or CPR cycles at scene. They are also required to seek advice or clearance from an on-duty physician before pronouncing a patient dead at scene.

Study population

OHCA data from April 2010 to March 2020 were used in this study. Adult patients ($\geq$18 years old) who were brought into the hospital emergency department (ED) by EMS were included in the study, while traumatic OHCA was excluded. Since the scope of this study is to develop the model to predict refractory VF in the situation where paramedics have not yet arrived at the scene, the inclusion criteria were not limited to OHCA with initial shockable rhythm.

Outcome

The primary outcome was refractory VF/VT. We used a definition that was in line with the 2018 American Heart Association guidelines,[3] as follows:

1) Shockable first arrest rhythm
2) Shockable rhythm on arrival at the ED
3) No return of spontaneous circulation (ROSC) prior to arrival at the ED
4) At least one shock given prior to arrival at the ED.

Machine learning models

For this study, multivariable logistic regression, least absolute shrinkage and selection operator (LASSO) and random forest (RF) classifiers were developed to predict refractory VF/VT. These methods were selected as they were explainable models that may be familiar to and more well-accepted by clinicians. The *ranger* R package[13] was used for RF implementation. The data were split into derivation (April 2010 – December 2018) and validation (January 2019 – March 2020) cohorts. This temporal split method has been found to be an adequate middle ground between internal and external validation and will help demonstrate applicability in the model in different clinical contexts.[14,15] 10-fold cross-validation method was used to train all models on the derivation cohort.

Feature selection

The full feature set consisted of variables from the PAROS dataset selected by clinical expert opinion that would be available to EMS dispatchers using the NEHR system at the time of receiving the emergency call or to paramedics when they are dispatched. These features are: age (in years); gender; arrest location (home, public, or healthcare setting); history of heart disease; respiratory disease; renal disease; hyperlipidaemia; hypertension; diabetes mellitus; stroke; and cancer.

Statistical analysis

Data analysis and model development were carried out in R version 4.1.2 (R Foundation for Statistical Computing). Descriptive statistics were used to summarize the derivation and validation cohorts. Continuous variables were reported as medians and interquartile ranges while categorical variables were reported as frequencies and percentages. Initially, missing data imputation was planned to be carried out if required. However, since the amount of missing data was found to be a significant minority, complete case analysis was done.

The prediction performance of multivariable logistic regression, LASSO and RF model were quantified using receiver operator characteristic (ROC) area under the curve (AUC) analysis. 95% confidence intervals were generated for the AUC of each model on the validation set using 1000 bootstrapped samples. To understand predictive performance of the models, sensitivity, specificity, positive and negative likelihood ratios were obtained at the cut-off for each model as derived via Youden's J-statistic. Calibration of the models was assessed using a calibration plot on the validation set, quantified using the Brier score where a lower value indicates better calibration. Confidence intervals for Brier score were calculated using 1000 bootstrapped samples. Feature importance plots for each model were also generated for explainability.

Results

Patient characteristics

There were 22,438 OHCA cases recorded in the PAROS database for the period of 1 April 2010 to 31 March 2020. In total, 20,713 cases were included in the study. 17,162 cases were allocated to the derivation cohort while 3551 cases were allocated to the validation cohort. The flow diagram for case selection is displayed in Fig. 1. The baseline statistics for all included cases are displayed in Table 1. In total, 860 (4.1%) patients had refractory VF/VT, while 19,853 (95.9%) patients did not. Results for univariate and multivariable regression analyses of features are presented in Appendix Table A.

Model performance

The AUCs, sensitivity, specificity, positive and negative likelihood ratios for each model are presented in Table 2. The ROC curves are displayed in Fig. 2, while the calibration curves are displayed in Fig. 3. Multivariable logistic regression (AUC = 0.732 [95% CI, 0.695 – 0.769]) and LASSO (AUC = 0.738 [95% CI, 0.701 – 0.774]) models performed comparably to the RF (AUC = 0.731 [95% CI, 0.701 – 0.774]) model. Each model had similar Brier scores for calibration as well (Multivariable logistic regression, 0.0297 [95% CI, 0.0295 – 0.0298]), LASSO, 0.0296 [95% CI, 0.0294 – 0.0297]) and RF 0.0296 ([95% CI, 0.0294 – 0.0297]). Although there was slight overestimation at the range of high predicted probability, the calibration curve indicated that the models were moderately well-calibrated.

Model features

From feature importance analysis, it was found that the top 3 features for the RF model were age, public arrest location, and heart

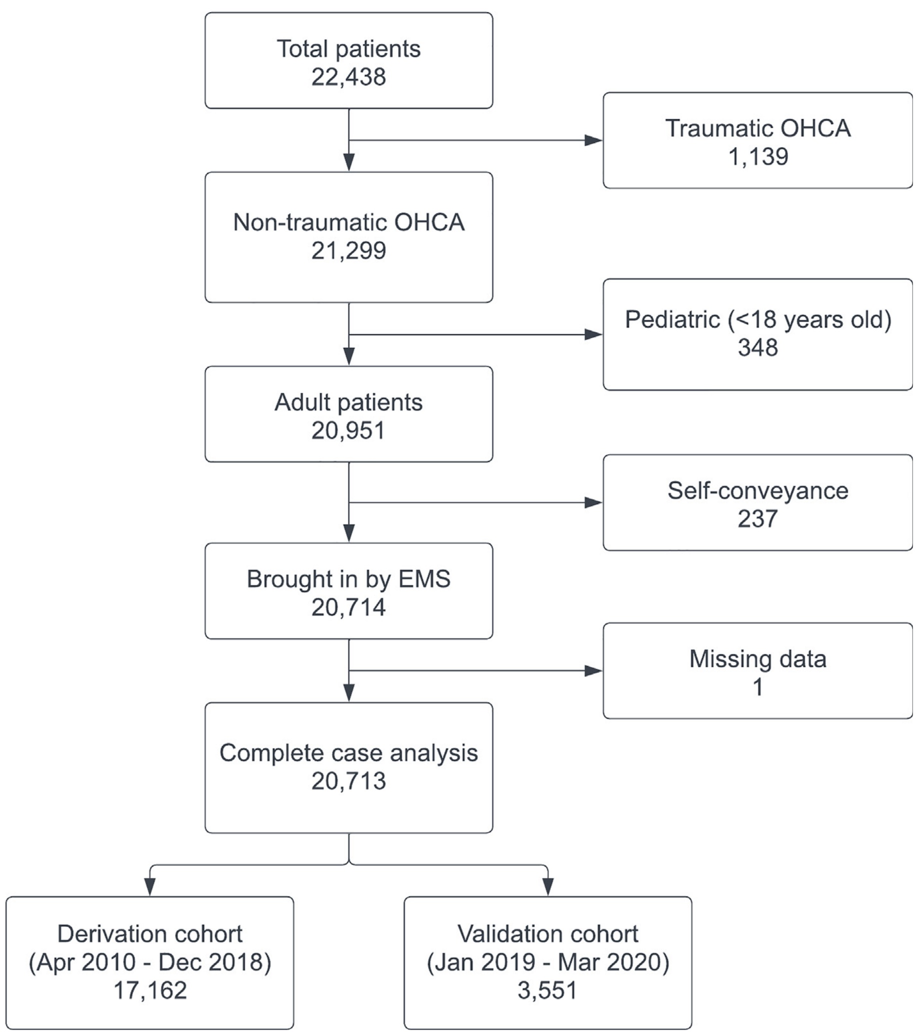

Fig. 1 – Flow diagram for case inclusion and splitting into derivation and validation cohorts.

Table 1 – Descriptive statistics of variables in the derivation and validation cohorts of the OHCA dataset.

	Derivation cohort (n = 17,162)		Validation cohort (*n* = 3551)	
	Refractory VF/VT (*n* = 751)	Without refractory VF/VT (*n* = 16,411)	Refractory VF/VT (*n* = 109)	Without refractory VF/VT (*n* = 3,442)
Age (years)	59 [51–68]	70 [58–81]	61 [56–71]	72 [60–82]
Male gender	641 (85.4)	10,369 (63.2)	100 (91.7)	2,158 (62.7)
Heart disease	331 (44.1)	6034 (36.8)	40 (36.7)	1,191 (34.6)
Diabetes	179 (23.8)	5582 (34.0)	25 (22.9)	1104 (32.1)
Cancer	20 (2.7)	1771 (10.8)	1 (0.9)	392 (11.4)
Hypertension	352 (46.9)	9209 (56.1)	40 (36.7)	1869 (54.3)
Renal disease	66 (8.8)	2399 (14.6)	17 (15.6)	612 (17.8)
Respiratory disease	47 (6.3)	2076 (12.7)	5 (4.6)	378 (11.0)
Hyperlipidaemia	257 (34.2)	6568 (40.0)	36 (33.0)	1491 (43.3)
Stroke	60 (8.0)	2277 (13.9)	12 (11.0)	422 (12.3)
Arrest location				
Home	405 (53.9)	12,310 (75.0)	61 (56.0)	1227 (35.6)
Public	282 (37.5)	2494 (15.2)	40 (36.7)	1771 (51.5)
Healthcare setting	64 (8.5)	1607 (9.8)	8 (7.3)	444 (12.9)
Bystander CPR	433 (57.7)	8186 (49.9)	73 (67.0)	2,075 (60.3)
Bystander AED applied	34 (4.5)	697 (4.2)	15 (13.8)	380 (11.0)
Time from call received to ambulance arrival (mins)	8 [7 –11]	9 [7 –11]	9 [7 –11]	8 [7 –10]

Categorical variables are shown as the number (percentage). Continuous variables are shown as median [Interquartile range (IQR)]. Abbreviations: CPR, cardiopulmonary resuscitation; AED, automated external defibrillator.

Table 2 – Model performance on validation cohort.

Model	AUC	Sensitivity	Specificity	LR+	LR-
MVR	0.732 (0.695 – 0.769)	0.927 (0.861 – 0.968)	0.448 (0.431 – 0.465)	1.679 (1.580 – 1.784)	0.164 (0.084 – 0.320)
LASSO	0.738 (0.701 – 0.774)	0.936 (0.872 – 0.974)	0.462 (0.445 – 0.489)	1.738 (1.640 – 1.842)	0.139 (0.068 – 0.285)
Random Forest	0.731 (0.690 – 0.773)	0.624 (0.526 – 0.715)	0.720 (0.705 – 0.735)	2.228 (1.907 – 2.602)	0.523 (0.410 – 0.666)

The 95% confidence intervals are given for each metric. Sensitivity, specificity, LR + and LR- are calculated from the optimal cut-off as derived by Youden's J-statistic.

Abbreviations: LR+, positive likelihood ratio; LR-, negative likelihood ratio; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; MVR, multivariate regression

disease. In comparison, the top 3 features for the multivariable logistic regression and LASSO model were cancer, public arrest location, and male gender. While hypertension and hyperlipidaemia had little to no effect in the multivariable regression and LASSO models, they were significant predictors in the RF model. Conversely, healthcare setting arrest location was a relevant predictor in the multivariable regression and LASSO models but had no significance in the RF model. The feature importance plots are presented in Fig. 4.

Discussion

Key observation

In this study, we developed 3 machine learning-based models trained on a Singaporean OHCA dataset to predict refractory VF/VT. Multivariable logistic regression, LASSO and random forest models were found to have appreciable classification performance and moderately good calibration when trained on the Singapore PAROS cohort. As a proof of concept, this study has managed to show that machine learning models have potential for use in the prediction of refractory VF/VT in the prehospital setting.

Strengths

This study has several strengths compared to previous studies. One study developed an ECG-based algorithm to predict patients with refractory VF with significant predictive performance (AUC = 0.85 [95% CI, 0.79–0.89]).[10] Another study developed a clinical decision rule that included variables such as bystander AED application, EMS-witnessed arrest, gender, initial rhythm, and time to arrival at the scene. In both studies, arriving at the scene and contacting the patients were essential to predict refractory VF. In contrast, this study focused on the phase before the paramedics arrived at the scenes, suggesting novel insight into the resuscitation strategy. Notably, this study is among the first to use the definition of refractory VF/VT as VF/VT persisting or recurring after at least one shock, as stated in the AHA guidelines. This contrasts with other studies on refractory VF/VT that used a three-shock definition instead of one shock.[5,16,17] The previously mentioned clinical decision rule used this three-shock definition of refractory VF/VT and achieved an AUC of

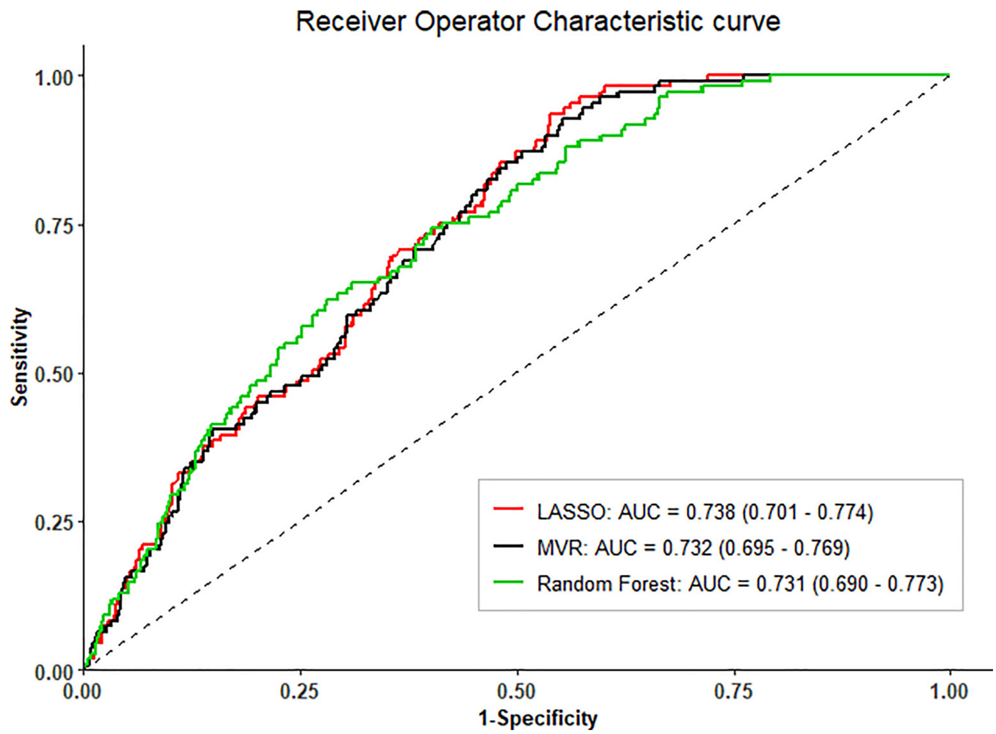

Fig. 2 – Receiver operator characteristic curves.

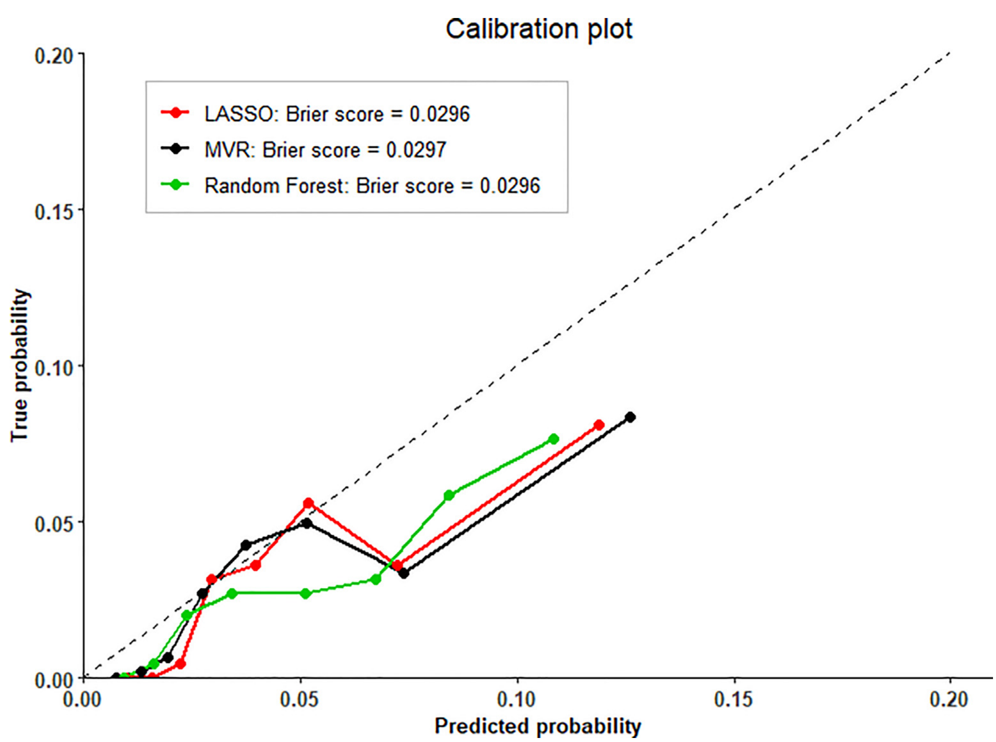

Fig. 3 – Calibration plots for all 3 models in the validation cohort.

0.671, although only patients who have received at least one shock were included in their complete case analysis.[7] Some definitions require the use of antiarrhythmics and vasopressors in addition to the three shocks.[18] However, there is currently no universally agreed upon definition of refractory VF/VT, which may pose a challenge in comparing between strategies or models reported in literature.[19] In this study, we defined refractory VF/VT as VF/VT rhythm with at least one shock given but no return of spontaneous circulation (ROSC) prior to arrival at the ED based on the guidelines, with the intention to consider revising the strategy in the earlier phase. Thus, this study

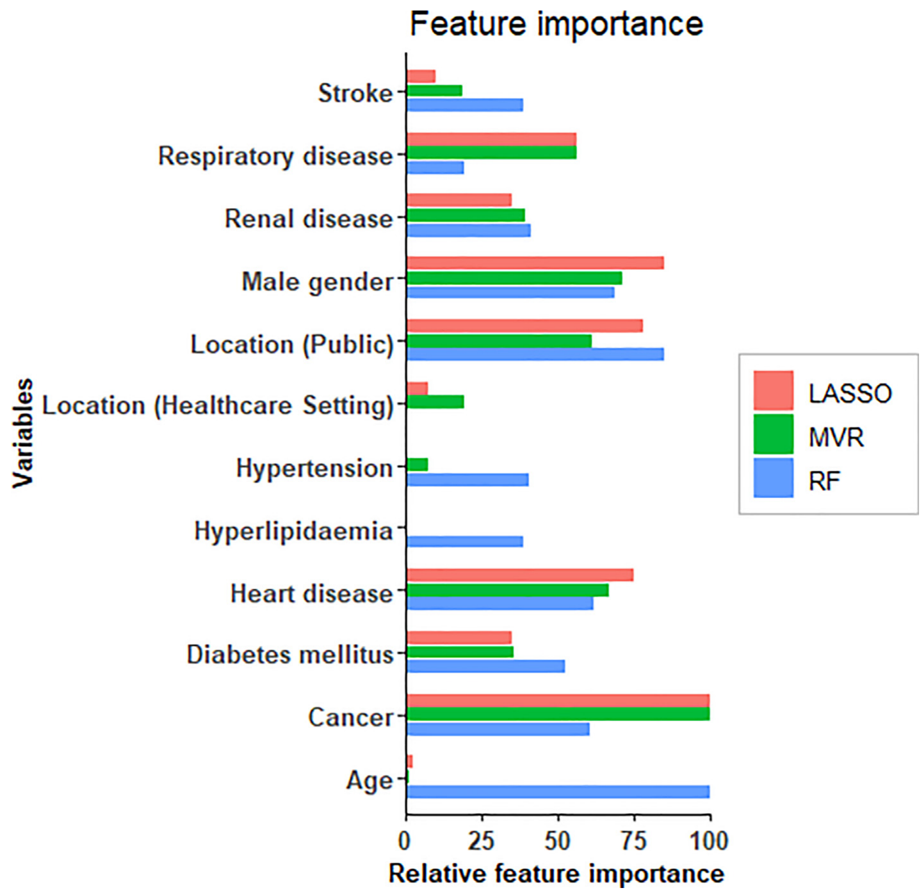

Fig. 4 – Feature importance plots.

is more applicable to clinical settings compared to previous studies conducted on refractory VF/VT. However, future studies should conduct sensitivity analyses comparing multiple definitions of the outcome on model performance.

Clinical implication

This study suggests the potential of utilizing the models to build a novel resuscitation strategy, using data available at the time when the dispatcher receives the emergency call, where data available are limited. No previous study has conducted an analysis of the predictive ability of models in this context. Earlier prediction of refractory VF/VT may allow an EMS provider to initiate targeted, effective intervention strategies to improve outcomes in this patient population. For example, prediction of refractory VF/VT can identify patients who may benefit from more aggressive resuscitation techniques, earlier administration of antiarrhythmics, earlier activation of ECPR facilities and teams, or transport to more specialized cardiac arrest centres.[20] Notably, previous studies have indicated that a shorter time to implement ECPR may result in better outcomes, highlighting the potential importance of early recognition of refractory VF/VT and prompt activation of the ECPR team to enhance patient outcomes.[21–23,34] Furthermore, prehospital ECPR systems have already been implemented in some regions.[24,25] We expect that the models in this study have potential to improve the criteria to activate prehospital ECPR teams. Although the available information is limited compared to those after the paramedics contact with the patients, we expect that prediction at an earlier time point may be advantageous.

Interpretation

We suggest some explanations to interpret the models. Based on the model features, male and public location were the variables which highly contributed to the model. We believe it may be reasonable due to the following reasons. Generally, males were reported to be the predominant population of occurrence of VF in most age groups,[26] and most OHCA patients treated with ECPR due to refractory VF were also male.[27] Furthermore, from the perspective of electrophysiology, males may have a higher risk of early repolarization, idiopathic VF, and Brugada syndrome.[28] Previous clinical rules to predict refractory VF also included males as a predictor. Furthermore, OHCA cases with VF were reported to occur more commonly in public locations compared to residential locations.[29] In contrast, the variable cancer exhibited high importance in both the logistic regression model and LASSO, with a notably low odds ratio (OR), suggesting its significance in excluding the likelihood of refractory VF/VT. Based on these results, we postulate that OHCA patients with cancer were more likely to have non-cardiac causes and less likely to experience VF/VT. Therefore, it appears reasonable that these factors played a significant role in the prediction models utilized in this study.

Limitations

There are several limitations in this study. Firstly, information on patients' past medical history in the PAROS datasets were collected by the clinicians and/or research assistants. These data are not the same as those in the NEHR system which are currently restricted only for clinical use and not permitted for research. Secondly, since this study included OHCA patients with both initial shockable and non-shockable rhythms, the number of refractory VF/VT cases was limited; this imbalance in the dataset may place machine learning models at risk of overfitting and worsen its performance on an unseen dataset.[30] Strategies such as down sampling the majority class or up sampling the majority class in the derivation cohort prior to model training may improve prediction performance but may run the risk of information loss, introducing bias, or worsening calibration.[31] Thirdly, due to limited available variables, the performance might still be insufficient to make a definitive decision only by the models. While the PAROS dataset does include variables that may strengthen the model performance, such as arrest witness and bystander CPR, such information may not be available at the point of dispatch or not routinely collected by the dispatcher. The models possibly require further refinement before it can be deployed in EMS processes. However, we consider that the AUC obtained in this study is sufficiently significant to validate the concept of our study and to warrant and future studies into developing more accurate models to predict refractory VF in OHCA. Once more detailed data can be obtained, model performance is expected to improve. Finally, the generalizability of the findings to other settings may also be limited as our models were developed with the primary intention of application in Singapore. Differences in patient demographics and EMS systems can significantly influence the incidence and outcomes of OHCA.[32] Information bias may also arise from differences in methods of data collection between healthcare systems.[33] Therefore, while our models show appreciable performance in the Singaporean context, the applicability of the model to other contexts may require careful consideration. Future work should involve external validation to assess the robustness of the models in different contexts.

Conclusion

This study developed and validated three machine learning models trained on a Singaporean OHCA dataset to predict refractory VF/VT. Multivariable logistic regression, LASSO, and random forest models performed comparably in predictive ability on the validation set. As a proof of concept, this study has managed to show that machine learning models have potential for use in the prediction of refractory VF/VT in the prehospital setting.

Consent for publication

Not applicable.

Availability of data and materials

This study's datasets and/or analyses are not publicly available because the ethics committee did not permit it.

Funding

This study was supported by a scientific research grant from the JSPS KAKENHI of Japan (JP22K21143 to YO), the ZOLL Foundation (YO), National Medical Research Council, Clinician Scientist Awards, Singapore (NMRC/CSA/024/2010, NMRC/CSA/0049/2013 and NMRC/CSASI/014/2017) to MEHO, and Ministry of Health, Health Services Research Grant, Singapore (HSRG/0021/2012) to MEHO. These organizations have no role in conducting this research.

CRediT authorship contribution statement

Rayhan Erlangga Rahadian: Writing – original draft, Formal analysis, Conceptualization. **Yohei Okada:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization. **Nur Shahidah:** Writing – review & editing, Project administration, Investigation, Data curation. **Hong Dehan:** Writing – review & editing, Project administration, Data curation. **Yih Yng Ng:** Writing – review & editing, Project administration, Data curation. **Michael Y.C. Chia:** Writing – review & editing, Data curation. **Han Nee Gan:** Writing – review & editing, Project administration, Data curation. **Benjamin S.H. Leong:** Writing – review & editing, Project administration, Data curation. **Desmond R. Mao:** Writing – review & editing, Project administration, Data curation. **Wei Ming Ng:** Writing – review & editing, Project administration, Data curation. **Nausheen Edwin Doctor:** Writing – review & editing, Project administration, Data curation. **Marcus Eng Hock Ong:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YO has received a research grant from the ZOLL Foundation and an overseas scholarship from the FUKUDA Foundation for Medical Technology and the International Medical Research Foundation. MEHO reports grants from the Laerdal Foundation, Laerdal Medical, and Ramsey Social Justice Foundation for funding of the Pan-Asian Resuscitation Outcomes Study; an advisory relationship with Global Healthcare SG, a commercial entity that manufactures cooling devices; and funding from Laerdal Medical on an observation program to their Community CPR Training Centre Research Program in Norway. MEHO is a Scientific Advisor to TIIM Healthcare SG and Global Healthcare SG. These organizations have no role in the design of the study, the collection, analysis, or interpretation of data, or in writing the manuscript. All other authors reported no competing interests.

Acknowledgements

The authors are deeply grateful to all EMS personnel for collecting the Utstein data. The authors would also like to thank Ms. Maeve Pek and the late Ms. Susan Yap from the Department of Emergency Medicine, Singapore General Hospital; Ms. Noor Azuin, Ms. Nurul Asyikin and Ms. Liew Le Xuan from Unit for Prehospital Emergency Care, Singapore General Hospital; Ms Woo Kai Lee from National University Heart Centre Singapore for their contributions and support to the Singapore PAROS registry, and all other Singapore PAROS investigators (Andrew FW Ho, Singapore General Hospital, Singapore; Ling Tiah, Changi General Hospital, Singapore; Si Oon Cheah, Urgent Care Clinic International, Singapore; Shun Yee Low, Sengkang General Hospital, Singapore; Wei Ling Tay, Ng Teng Fong

General Hospital, Singapore; Shir Lynn Lim, National University Heart Centre Singapore) that contributed to the study. The authors thank the JSPS Overseas Research Fellowships, the FUKUDA Foundation for Medical Technology, and the International Medical Research Foundation for their support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100606.

Author details

[a]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore [b]Health Services and Systems Research, Duke-NUS Medical School, Singapore, Singapore [c]Department of Preventive Services, Graduate School of Medicine, Kyoto University, Kyoto, Japan [d]Department of Emergency Medicine, Singapore General Hospital, Singapore, Singapore [e]Pre-hospital and Emergency Research Centre, Duke-NUS Medical School, Singapore [f]Emergency Medical Services Department, Singapore Civil Defence Force, Singapore [g]Department of Preventive and Population Medicine, Tan Tock Seng Hospital, Singapore, Singapore [h]Emergency Department, Tan Tock Seng Hospital, Singapore, Singapore [i]Accident & Emergency, Changi General Hospital, Singapore, Singapore [j]Emergency Medicine Department, National University Hospital, Singapore, Singapore [k]Department of Acute and Emergency Care, Khoo Teck Puat Hospital, Singapore, Singapore [l]Emergency Medicine Department, Ng Teng Fong General Hospital, Singapore, Singapore[m]Department of Emergency Medicine, Sengkang General Hospital, Singapore, Singapore

REFERENCES

1. Ho AFW, Lim MJR, Earnest A, et al. Long term survival and disease burden from out-of-hospital cardiac arrest in Singapore: a population-based cohort study. Lancet Reg Health West Pac 2023;32. https://doi.org/10.1016/j.lanwpc.2022.100672.
2. Goto Y, Maeda T, Nakatsu-Goto Y. Prognostic implications of conversion from nonshockable to shockable rhythms in out-of-hospital cardiac arrest. Crit Care 2014;18:528. https://doi.org/10.1186/s13054-014-0528-7.
3. Panchal AR, Berg KM, Kudenchuk PJ, et al. American heart association focused update on advanced cardiovascular life support use of antiarrhythmic drugs during and immediately after cardiac arrest: an update to the American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2018;2018:138. https://doi.org/10.1161/CIR.0000000000000613.
4. Shanmugasundaram M, Lotun K. Refractory out of hospital cardiac arrest. Curr Cardiol Rev 2018;14:109–14. https://doi.org/10.2174/1573403X14666180507155622.
5. Bartos JA, Carlson K, Carlson C, et al. Surviving refractory out-of-hospital ventricular fibrillation cardiac arrest: Critical care and extracorporeal membrane oxygenation management. Resuscitation 2018;132:47–55. https://doi.org/10.1016/j.resuscitation.2018.08.030.
6. Ching C, Leong B, Nair P, et al. Singapore advanced cardiac life support guidelines 2021. Singapore Med J 2021;62:390–403. https://doi.org/10.11622/smedj.2021109.
7. Lupton JR, Jui J, Neth MR, Sahni R, Daya MR, Newgard CD. Development of a clinical decision rule for the early prediction of shock-refractory out-of-hospital cardiac arrest. Resuscitation 2022;181:60–7. https://doi.org/10.1016/j.resuscitation.2022.10.010.
8. Figuera C, Irusta U, Morgado E, et al. Machine learning techniques for the detection of shockable rhythms in automated external defibrillators. PLoS One 2016;11:e0159654. https://doi.org/10.1371/journal.pone.0159654.
9. Manibardo E, Irusta U, Del Ser J, et al. ECG-based Random Forest Classifier for Cardiac Arrest Rhythms. In: 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE; 2019. p. 1504–8. https://doi.org/10.1109/EMBC.2019.8857893.
10. Coult J, Yang BY, Kwok H, et al. Prediction of shock-refractory ventricular fibrillation during resuscitation of out-of-hospital cardiac arrest. Circulation 2023. https://doi.org/10.1161/circulationaha.122.063651.
11. Ong MEH, Do SS, De Souza NNA, et al. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: The Pan Asian Resuscitation Outcomes Study (PAROS). Resuscitation 2015;96:100–8. https://doi.org/10.1016/j.resuscitation.2015.07.026.
12. Ong MEH, Do SS, Tanaka H, et al. Pan-Asian Resuscitation Outcomes Study (PAROS): Rationale, methodology, and implementation. Academic Emergency Medicine 2011;18:890–7. https://doi.org/10.1111/j.1553-2712.2011.01132.x.
13. Wright MN, Ziegler A. ranger: A fast implementation of random forests for high dimensional data in C++ and R. J Stat Softw 2017;77. https://doi.org/10.18637/jss.v077.i01.
14. Sperrin M, Riley RD, Collins GS, Martin GP. Targeted validation: validating clinical prediction models in their intended population and setting. Diagn Progn Res 2022;6:24. https://doi.org/10.1186/s41512-022-00136-8.
15. Ramspek CL, Jager KJ, Dekker FW, Zoccali C, van Diepen M. External validation of prognostic models: what, why, how, when and where? Clin Kidney J 2021;14:49–58. https://doi.org/10.1093/ckj/sfaa188.
16. Nakashima T, Noguchi T, Tahara Y, et al. Patients with refractory out-of-cardiac arrest and sustained ventricular fibrillation as candidates for extracorporeal cardiopulmonary resuscitation: Prospective multi-center observational study. Circulation Journal 2019;83:1011–8. https://doi.org/10.1253/circj.CJ-18-1257.
17. Cheskes S, Dorian P, Feldman M, et al. Double sequential external defibrillation for refractory ventricular fibrillation: The DOSE VF pilot randomized controlled trial. Resuscitation 2020;150:178–84. https://doi.org/10.1016/j.resuscitation.2020.02.010.
18. Lee YH, Lee KJ, Min YH, Ahn HC, Sohn YD, Lee WW, et al. Refractory ventricular fibrillation treated with esmolol. Resuscitation 2016;107:150–5. https://doi.org/10.1016/j.resuscitation.2016.07.243.
19. Nas J, Thannhauser J, Bonnes JL, Brouwer MA. Importance of the distinction between recurrent and shock-resistant ventricular fibrillation: Call for a uniform definition of refractory VF. Resuscitation 2019;138:312–3. https://doi.org/10.1016/j.resuscitation.2019.01.042.
20. Bartos JA, Grunau B, Carlson C, et al. Improved survival with extracorporeal cardiopulmonary resuscitation despite progressive metabolic derangement associated with prolonged resuscitation. Circulation 2020;141:877–86. https://doi.org/10.1161/CIRCULATIONAHA.119.042173.
21. Okada Y, Irisawa T, Yamada T, et al. Clinical outcomes among out-of-hospital cardiac arrest patients treated by extracorporeal cardiopulmonary resuscitation: The CRITICAL study in Osaka. Resuscitation 2022;178:116–23. https://doi.org/10.1016/j.resuscitation.2022.06.007.
22. Matsuyama T, Irisawa T, Yamada T, et al. Impact of low-flow duration on favorable neurological outcomes of extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest. Circulation 2020;141:1031–3. https://doi.org/10.1161/CIRCULATIONAHA.119.044285.

23. Okada Y, Kiguchi T, Irisawa T, et al. Development and validation of a clinical score to predict neurological outcomes in patients with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation. JAMA Netw Open 2020;3():e2022920. https://doi.org/10.1001/jamanetworkopen.2020.22920.
24. Okada Y, Fujita K, Ogura T, et al. Novel and innovative resuscitation systems in Japan. Resusc Plus 2024;17:100541. https://doi.org/10.1016/j.resplu.2023.100541.
25. Richardson SAC, Anderson D, Burrell AJC, et al. Pre-hospital ECPR in an Australian metropolitan setting: a single-arm feasibility assessment—The CPR, pre-hospital ECPR and early reperfusion (CHEER3) study. Scand J Trauma Resusc Emerg Med 2023;31:100. https://doi.org/10.1186/s13049-023-01163-0.
26. Tseng W-C, Wu M-H, Chen H-C, Kao F-Y, Huang S-K. Ventricular fibrillation in a general population – a national database study. Circulation Journal 2016;80:2310–6. https://doi.org/10.1253/circj.CJ-16-0602.
27. Okada Y, Shahidah N, Ng YY, et al. Outcome assessment for out-of-hospital cardiac arrest patients in Singapore and Japan with initial shockable rhythm. Crit Care 2023;27:351. https://doi.org/10.1186/s13054-023-04636-x.
28. Tadros R, Ton A-T, Fiset C, Nattel S. Sex differences in cardiac electrophysiology and clinical arrhythmias: epidemiology, therapeutics, and mechanisms. Canadian Journal of Cardiology 2014;30:783–92. https://doi.org/10.1016/j.cjca.2014.03.032.
29. Kiguchi T, Kiyohara K, Kitamura T, et al. Public-access defibrillation and survival of out-of-hospital cardiac arrest in public vs. residential locations in Japan. Circulation Journal 2019;83:1682–8. https://doi.org/10.1253/circj.CJ-19-0065.
30. Basit MS, Khan A, Farooq O, Khan YU, Shameem M. Handling imbalanced and overlapped medical datasets: a comparative study. In: 2022 5th International Conference on Multimedia, Signal Processing and Communication Technologies (IMPACT), IEEE. p. 1–7. https://doi.org/10.1109/IMPACT55510.2022.10029111.
31. van den Goorbergh R, van Smeden M, Timmerman D, Van Calster B. The harm of class imbalance corrections for risk prediction models: illustration and simulation using logistic regression. Journal of the American Medical Informatics Association 2022;29:1525–34. https://doi.org/10.1093/jamia/ocac093.
32. Lim SL, Smith K, Dyson K, et al. Incidence and outcomes of out-of-hospital cardiac arrest in Singapore and Victoria: a collaborative study. J Am Heart Assoc 2020;9. https://doi.org/10.1161/JAHA.119.015981.
33. Bower JK, Patel S, Rudy JE, Felix AS. Addressing bias in electronic health record-based surveillance of cardiovascular disease risk: finding the signal through the noise. Curr Epidemiol Rep 2017;4:346–52. https://doi.org/10.1007/s40471-017-0130-z.
34. Low CJW, Ling RR, Ramanathan K, Chen Y, Rochwerg B, Kitamura T, Iwami T, Ong MEH, Okada Y. Extracorporeal cardiopulmonary resuscitation versus conventional CPR in cardiac arrest: an updated meta-analysis and trial sequential analysis. Crit Care 2024;28(1):57. https://doi.org/10.1186/s13054-024-04830-5.