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Clinical paper

Outcome prediction of out-of-hospital cardiac arrest with presumed cardiac aetiology using an advanced machine learning technique

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Abstract

Background: Outcome prediction for patients with out-of-hospital cardiac arrest (OHCA) has the possibility to detect patients who could have been potentially saved. Advanced machine learning techniques have recently been developed and employed for clinical studies. In this study, we aimed to establish a prognostication model for OHCA with presumed cardiac aetiology using an advanced machine learning technique.

Methods and Results: Cohort data from a prospective multi-centre cohort study for OHCA patients transported by an ambulance in the Kanto area of Japan between January 2012 and March 2013 (SOS-KANTO 2012 study) were analysed in this study. Of 16,452 patients, data for OHCA patients aged ≥18 years with presumed cardiac aetiology were retrieved, and were divided into two groups (training set: n = 5718, between January 1, 2012 and December 12, 2012; test set: n = 1608, between January 1, 2013 and March 31, 2013). Of 421 variables observed during prehospital and emergency department settings, 35 prehospital variables, or 35 prehospital and 18 in-hospital variables, were used for outcome prediction of 1-year survival using a random forest method. In validation using the test set, prognostication models trained with 35 variables, or 53 variables for 1-year survival showed area under the receiver operating characteristics curve (AUC) values of 0.943 (95% CI [0.930, 0.955]) and 0.958 (95% CI [0.948, 0.969]), respectively.

Conclusions: The advanced machine learning technique showed favourable prediction capability for 1-year survival of OHCA with presumed cardiac aetiology. These models can be useful for detecting patients who could have been potentially saved.

Keywords: Out-of-hospital cardiac arrest, Resuscitation, Outcome prediction, Machine learning

Introduction

Out-of-hospital cardiac arrest (OHCA) is one of the major challenges of healthcare. The number of annual OHCA cases has been reported to be approximately 420,000, 275,000, and 100,000 in the United States,[1] Europe,[2] and Japan,[3] respectively. Although the most common aetiology of adult OHCA is a cardiac cause such as acute myocardial infarction and ventricular arrhythmia,[4–6] and medical resuscitation has been developed, there is still a need for improvement in survival rates and neurological outcomes of OHCA.[7] To address this issue, accurate outcome prediction models of OHCA with presumed cardiac aetiology are useful because prediction models can retrospectively detect a patient group that could have been potentially saved. Having the ability to detect these patients may help identify problems within a medical facility or specific area of treatment and may help progress new ideas for treatment within the field of resuscitation medicine. In other words, accurate outcome prediction models of OHCA can help identify preventable resuscitation failures, as has been used to define preventable traumatic death in the

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field of traumatic management.[8] To date, many studies have been developed to determine factors that predict the outcome of OHCA.[9–12] Additionally, the outcome prediction ability of several factors during OHCA management has been revealed, such as initial rhythm, prehospital defibrillation, bystander-initiated CPR, prehospital return of spontaneous circulation (ROSC), and renal function,[13–15] but the independent predictability of each factor is limited. To generate an accurate prediction model, a combination of multiple factors should be considered. Additionally, to establish a highly accurate prognostic prediction model of OHCA with presumed cardiac aetiology, regional

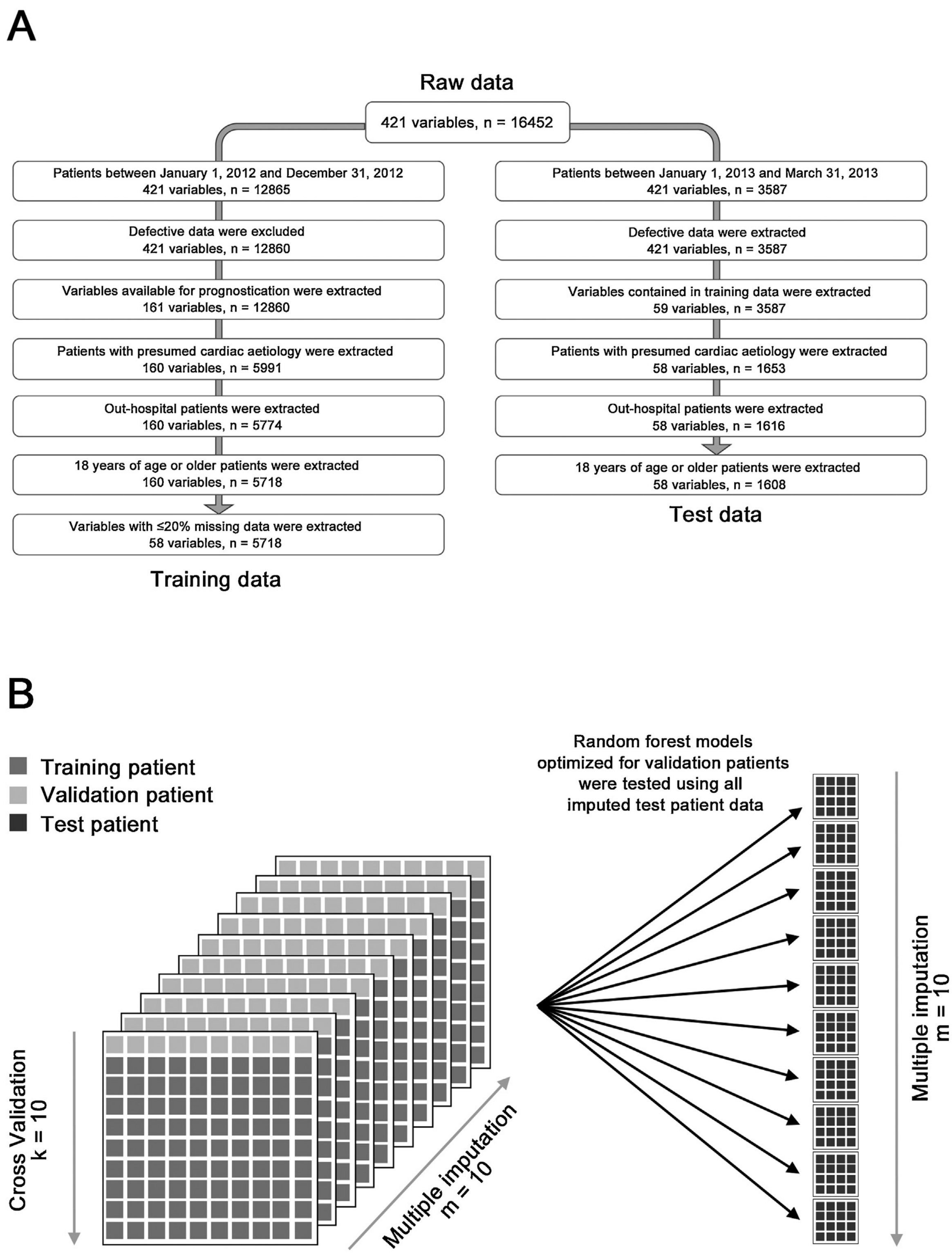


Fig. 1 – (A) Patient selection and data preprocessing. (B) Scheme of multiple imputation, cross-validation, model training and model test. Cross-validation was performed in the k- (=10) fold condition. The missing data are filled with multiple imputation in m (=10) times to generate m (=10) complete data sets.

differences in the emergency medical service (EMS) systems should be considered. Therefore, to make accurate outcome predictions of OHCA with presumed cardiac aetiology in specific regions, patient data with multiple factors that were collected in a target region is desirable.

In the course of treatment of OHCA, patient status is highly dynamic, and many observed variables can occur, one after another, in a short period of time. Prediction ability of specific factors during OHCA managements has been already shown.[9–12] Recently, advanced machine learning techniques have been applied for diagnosis and prognostication in the clinic.[16] For the prediction of outcome of OHCA, the survival of OHCA discharged after ROSC using deep learning methods have been reported.[17] However, the development of long-term outcome predictions of OHCA using multiple factors with a non-linear method is currently limited. Recent developments in computing power and machine learning techniques enable non-linear mechanical prediction, using a large number of variables.[18] Supervised machine learning is a category of machine learning that has been applied for predicting a known output or target in the clinical area, and uses an algorithm that extract features from a training dataset with a known output or target.[19] This type of machine learning has been effective when clear outputs or targets were previously obtained in the training dataset. Therefore, in this study, we applied an advanced supervised machine learning technique to establish a prognostication model for 1-year survival of OHCA with presumed cardiac aetiology.

Methods

Data availability

Data from the SOS-KANTO 2012 study (Survey of Survivors after Out-of-Hospital Cardiac Arrest in Kanto Area)[20] were analysed in this study. These data are maintained by the Kanto Chapter of Japanese Association for Acute Medicine. The study was approved by the relevant institutional review boards or ethics committee of medical institutions.[20] The data can be requested from the website (http://jaam-kanto.umin.ne.jp/index.html) by following the prescribed procedure.

Study population and data sources

The SOS-KANTO 2012 study was a prospective multi-centre cohort study of OHCA patients transported by an ambulance to one of 67 medical institutions in the Kanto area of Japan between January 2012 and March 2013.[20] In this study, 421 variables were recorded, which consisted of age and sex of patients, time at which ambulance transport occurred, location and circumstance of OHCA occurrence, prehospital evaluation, prehospital treatments, initial in-hospital evaluation, initial in-hospital treatments and prognosis of up to one year. Data preprocessing is shown in Fig. 1A. The total number of registered OHCA patients in this study was 16,452. Prognostic information is recorded according to Cerebral Performance Category (CPC) score and survival. The 16,452 patients in the registry were divided into a training set and a test set, according to the time of calls for ambulances (training set: n = 12,865, between January 1, 2012 and December 12, 2012; test set: n = 3587, between January 1, 2013 and March 31, 2013). Patient data with transcription errors (training set: n = 5, test set: n = 0) were excluded. In these five cases with transcription errors, 3-digit integers were written in the column of pupil diameter and therefore correct values for pupil diameter were unknown. Although this registry is termed as a multi-centre cohort study of OHCA patients, it did contain a small number of in-hospital cases that could be identified with the site of incidence variable. These in-hospital cases were excluded during data preprocessing. Presumed cardiac OHCA patients (i.e. no other known cause) of 18 years of age or above were retrieved from the training set and the test set.

The variables based on the information available at the time of ambulance transport, or based on the objective information available immediately after arrival, were retrieved as candidates for model training. Variables with >20% missing data in the training set were excluded from the analysis, and the remaining 58 variables (35 prehospital variables listed in Supplemental Table 1, 18 initial in-hospital variables listed in Supplemental Table 2, and survival recorded at five time-points listed in Supplemental Table 3) were defined as eligible variables for the analysis.

Imputation of missing data

Missing data within the training set (4319 of 5718 records had missing data) and the test set (1112 of 1608 records had missing data) were imputed with probability-based multiple imputation. Missing data were calculated and filled 10 times using the micemd package (version 1.2.0)[21, 22] with R (version 3.3.2) as shown in Fig. 1B, considering the computing power of our machine (Mac pro Late 2013 with 2.7 GHz 12-Core Intel Xeon E5) and acceptable calculation time of repeated examination. To impute missing data, the selection of the imputation method for each variable was performed by an internal algorithm of the micemd package according to the structure of the incomplete dataset following recommended guidelines.[23] During multiple imputation procedures for our study, the outcome variables were included among the predictors. Obtained data sets (10 different training sets and 10 different test sets) were used for analysis.

Random Forest machine learning

Random forest is an advanced machine learning method for supervised learning involving a process of aggregating a series of decision trees for classification and regression.[24] This algorithm creates multiple different decision trees from the training dataset and takes the majority vote in the case of classification as shown in Supplemental Fig. 1. The random forest method has advantages of being applicable to data of mixed variable types, reduced susceptibility to over-fitting, and is practical for estimation of variable importance.[24,25] In the random forest process, decision trees are generated using a random subset of the data, and final results of the random forest process are calculated by combining these decision trees. Before testing the random forest model for prognostication, 10-fold cross-validation using all training sets and hyper parameter optimization of the random forest model were performed using scikit-learn (version 0.19.1) with Python (version 3.5.2, in Anaconda 4.2.0) in order to avoid overfitting of the model. After the training stage, 10 trained models were generated from 10-fold cross validation. In the training stage, validation was performed using 10% of each imputed training data (90% of each imputed training data was used to train the model). After parameter optimization with 10-fold cross validation, these 10 trained models were tested using all imputed test data. All predicted results of random forests were converted to probabilities and mean probabilities obtained from 10 trained models used to calculate the final area under the receiver operating characteristics curve (AUC) as combined results. To determine the importance of each variable, the Gini impurity index during random forest model training was used.

Results

Baseline characteristics

From the 16,452 cases, the training set (n = 5718) and the test set (n = 1608) were obtained, respectively, after data preprocessing, as shown in Fig. 1A. After the removal of variables unsuitable for prognostication and the ones with >20% missing data in the training set, the residual 58 variables consisted of 35 prehospital variables listed in Supplemental Table 1, 18 initial in-hospital variables listed in Supplemental Table 2, and survival recorded at five time-points listed in Supplemental Table 3. Detailed baseline characteristics calculated from the 10 different imputed training sets and test sets are shown in Supplemental Table 1–3. The percentage of OHCA cases that are presumed cardiac was 46.5%. In the pre-processed data, 1-year survival rates were 6.35% and 4.27%, respectively, as shown in Supplemental Table 3. These imputed training sets and test sets were applied to subsequent machine learning.

Prediction of 1-year survival using prehospital variables

To generate a model to evaluate whether a patient can be saved, the model should be trained with variables that can be obtained without the physician's medical decision. Therefore, we generated prediction models trained with 35 prehospital variables for 1-year survival and tested the prognostic performance of the model. The random forest model was trained and optimized using training data, and showed an AUC value of 0.943 (95% CI [0.930, 0.955]) when it was tested using independent test data, as shown in Fig. 2A. Defibrillation by emergency medical service (EMS), age, electrocardiography (ECG) waveform on EMS contact, ROSC on EMS contact, and ROSC during transport were determined to be the top five most important variables, evaluated by reverse rank sum of Gini importance, as shown in Fig. 2B. Although survival rates increased as predicted probability increased, the range of low probability of survival (0.1% ≤probability <0.25%) contained one survivor as shown in Fig. 4A.

Prediction of 1-year survival using pre- and in-hospital variables

To generate an outcome prediction model that achieves higher predictability, prediction models trained with 35 prehospital variables

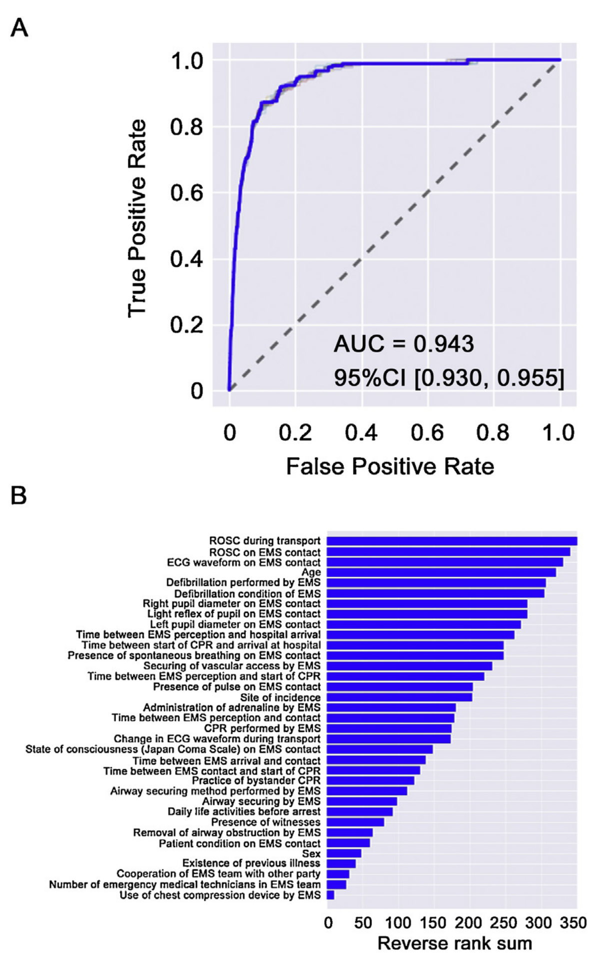


Fig. 2 – (A) The receiver operating characteristics curve (ROC) of prehospital model. The results of the predicting test data are shown. Each thin line shows the result of testing with the model generated at each cross-validation stage. Blue bold lines show the result of testing with the assembled model. Area under ROC (AUC) is shown with 95% confidence interval (CI). (B) Reverse rank sum of Gini importance of the prehospital model.

and 18 in-hospital variables for 1-year survival were tested. The in-hospital variables used in this model are obtainable at the early stage of OHCA management because all in-hospital variables used in this model can be collected between hospital arrival and obtaining initial blood test results, and can be collected without a physician's medical decision.

The random forest model, which was trained and optimized using training data, achieved AUC values of 0.958 (95% CI [0.948, 0.969]). ROSC during transport, light reflex of pupil on hospital arrival, presence of pulse on hospital arrival, presence of spontaneous breathing on hospital arrival, and ECG waveform on hospital arrival were determined to be the five variables with the most predictive values. These variables were evaluated using the reverse rank sum of Gini importance, as shown in Fig. 3B. In addition to these variables, almost all in-hospital variables ranked highly in the rank of reverse rank sum of Gini importance. Survival rates increased as predicted probability increased and the range of very low probability of survival (<1%) showed no survivors at 1 year as shown in Fig. 4A.

Discussion

In this study, we have successfully established a survival prediction model of OHCA with presumed cardiac aetiology using the combination of random forests machine learning and multiple clinical variables. Prediction models of OHCA with presumed cardiac aetiology using deep learning in a recent publication[17] showed AUC values that were nearly equivalent to our models. However, our models were fundamentally different from their models because the time-point of the prediction target of their models was at the time of discharge and that of our models was 1-year. Additionally, the variables used in the model contain none of the in-hospital treatments performed by physicians; these models can predict outcomes based on medical background without intervention by physicians. These models can be applied to evaluate treatment results between medical institutions or reveal the need for structure improvement in specific institutions with retrospective validation. These are also useful for retrospectively detecting patients who may have been potentially saved. Having the ability to detect these patients may help identify problems within a medical facility and may help progress new ideas for treatment within the field of resuscitation medicine. For further application, this type of model has the potential to evaluate intervention effects in specific populations without the need for a control group.

The baseline characteristics of the cohort showed that the proportion of presumed cardiac cases was 46.5%, which appeared to be relatively low by international standards. In a previous systematic

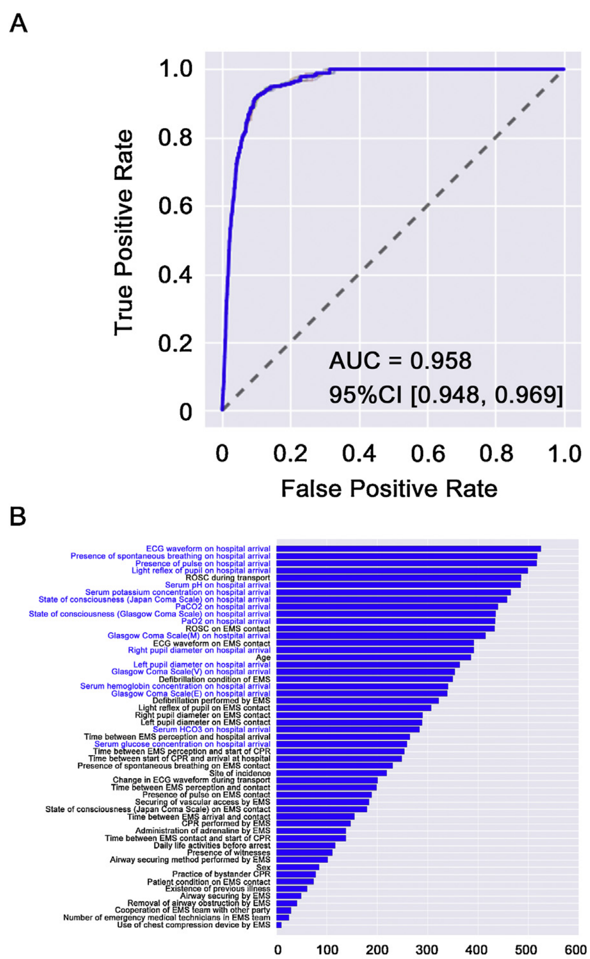
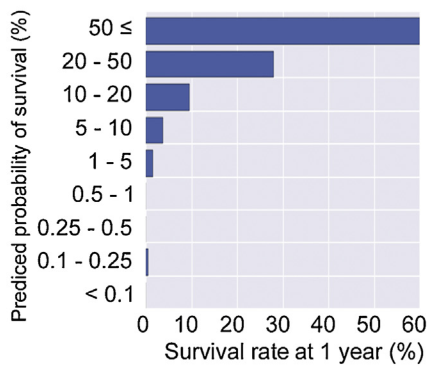


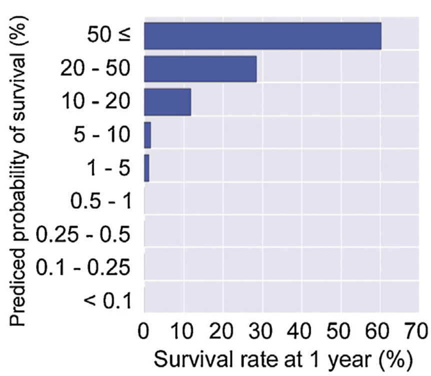
Fig. 3 – (A) ROC analysis of pre- and in-hospital model. Each thin line shows the result of testing with the model generated at each cross-validation stage. The blue bold line shows the result of testing with the assembled model. The results of predicting test data are shown (AUC with CI). (B) Reverse rank sum of Gini importance of the pre- and in-hospital model. In-hospital variables are shown in blue font.

A



Predicted probability of survival	Survival rate at 1 year (%)	Number of patients (total)	Number of patients (survived)
50% ≤ probability	60.00	50	30
20% ≤ probability < 50%	28.00	100	28
10% ≤ probability < 20%	9.43	106	10
5% ≤ probability < 10%	3.62	138	5
1% ≤ probability < 5%	1.44	278	4
0.5% ≤ probability < 1%	0	130	0
0.25% ≤ probability < 0.5%	0	143	0
0.1% ≤ probability < 0.25%	0.41	244	1
probability < 0.1%	0	419	0

B



Predicted probability of survival	Survival rate at 1 year (%)	Number of patients (total)	Number of patients (survived)
50% ≤ probability	60.27	73	44
20% ≤ probability < 50%	28.57	63	18
10% ≤ probability < 20%	11.76	85	10
5% ≤ probability < 10%	1.53	131	2
1% ≤ probability < 5%	1.08	370	4
0.5% ≤ probability < 1%	0	212	0
0.25% ≤ probability < 0.5%	0	223	0
0.1% ≤ probability < 0.25%	0	269	0
probability < 0.1%	0	182	0

Fig. 4 – (A) Bar graph showing the distribution of survival rates of test patients (n = 1608) and probabilities of survival obtained from the prehospital model (Left). Results based on the mean prediction of 10 trained models against all imputed test data are shown. For calculating survival rates and mean predicted probabilities, the modes of outcome variables of all imputed test data were used. Table showing survival rates and number of patients at each range of probabilities obtained from the prehospital model (Right). (B) Bar graph showing the distribution of survival rates of test patients (n = 1608) and probabilities of survival obtained from pre- and in-hospital models (Left). The results based on the mean prediction of 10 trained models against all imputed test data are shown. For calculating survival rates and mean predicted probabilities, the modes of outcome variables of all imputed test data were used. Table showing survival rates and detail number of patients at each range of probabilities obtained from pre- and in-hospital models (Right).

review, global incidence of EMS-treated OHCA with a known cardiac cause among adults was 58%[26]. Since the registry used in this study contained the variable which indicated presumed cardiac or not, we extracted the patients with presumed cardiac aetiology according to this variable. Since this variable might be filled after hospital arrival, after the initial screening in the hospital, or after stopping resuscitation in some cases, there is a possibility that a relatively low proportion of the presumed cardiac cases may occur due to the different timings of recording of this variable. Although, in the previous systematic review,[26] there was a relatively low proportion of cardiac cases in Japan, the timing of recording of the variable had the possibility of affecting a relatively low proportion of the presumed cardiac cases in Japan and of affecting the generalizability of the model.

In this study, many of the variables demonstrated interdependency. To generate a predictive model, the variables with information associated with survival of the patients were removed at the data preprocessing stage even if the information was partial. This was done to secure the validity of the prediction model. The variables without information associated with survival of the patients can be useful for prediction despite partial interdependency between the predictors. Therefore, we applied these variables into the model training to generate accurate prediction models. For patient's survival, 1-year survival of OHCA with presumed cardiac aetiology was used as the target for prediction with machine learning. Clinically, predicting neurological prognosis such as CPC score is more informative than predicting survival.[27] Unfortunately, in the registry used this study, variables associated with CPC score contained many missing data points; therefore, a neurological prognostication model with supervised machine learning could not be established in this study.

Although this study showed a high AUC value for the prognostication model, this study has its limitations. The first limitation is regarding the uncertainty of practical applicability within a clinical setting. The probability distribution and survival rate in Fig. 4 shows the existence of patients who were predicted to have a low probability of survival

(<5%); however, they survived after 1 year. These results should be considered in clinical applications. Additionally, as our models predicted 1-year survival of OHCA, whether the decision of stopping resuscitation should be made based on 1-year survival needs is open for further discussion from an ethical aspect. Therefore, the model predictions cannot realistically be used as a basis for stopping resuscitation at this time. A possible method to generate a more accurate model for clinical use is to increase the variety of information input for machine learning. Although information pertaining to genetics, precise past medical histories, and socio-economics may help lead to accurate predictions with machine learning, the data analysed in this study did not contain these types of data, hence, effectiveness could not be validated in this study. Additionally, even if models become more accurate, in the time course of OHCA management, patient status is highly dynamic, with variables changing within a short period of time. Furthermore, a diagnosis of “presumed cardiac” aetiology is only obtained after initial screening on hospital arrival. Although future progress in mobile devices and diagnostic equipment may resolve these problems,[28,29] applying the model to practical clinical decisions is not possible at this time.

The second limitation is the incompleteness of the generalisation ability of the model. As training data and test data were derived from the same registry, predictive performance for new cases was not assessed in this study.[30] Additionally, the registry used in this study consisted of patient data limited in a specific area in Japan, in which a national health insurance system[31] and public EMS system[32] have been provided. There is no guarantee that this model demonstrates preferable performance with cases in other countries, where patients have different social backgrounds and EMS is operated under a different system and rules. Further testing of the model using new a registry and a registry in another area should be performed to confirm the generalization ability of the model in the future.

Conclusions

Prognostic models trained with a random forest machine learning technique showed favourable prediction capability for 1-year survival of OHCA with presumed cardiac aetiology. These models can be useful for retrospective detection of patients who may have been potentially saved which can help resolve problems within the field and create ideas for progress in resuscitation medicine.

Disclosures

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.06.006.

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