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Original Article

Clustering out-of-hospital cardiac arrest patients with non-shockable rhythm by machine learning latent class analysis

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Aim: We aimed to identify subphenotypes among patients with out-of-hospital cardiac arrest (OHCA) with initial non-shockable rhythm by applying machine learning latent class analysis and examining the associations between subphenotypes and neurological outcomes.

Methods: This study was a retrospective analysis within a multi-institutional prospective observational cohort study of OHCA patients in Osaka, Japan (the CRITICAL study). The data of adult OHCA patients with medical causes and initial non-shockable rhythm

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presenting with OHCA between 2012 and 2016 were included in machine learning latent class analysis models, which identified subphenotypes, and patients who presented in 2017 were included in a dataset validating the subphenotypes. We investigated associations between subphenotypes and 30-day neurological outcomes.

Results: Among the 12,594 patients in the CRITICAL study database, 4,849 were included in the dataset used to classify subphenotypes (median age: 75 years, 60.2% male), and 1,465 were included in the validation dataset (median age: 76 years, 59.0% male). Latent class analysis identified four subphenotypes. Odds ratios and 95% confidence intervals for a favorable 30-day neurological outcome among patients with these subphenotypes, using group 4 for comparison, were as follows; group 1, 0.01 (0.001–0.046); group 2, 0.097 (0.051–0.171); and group 3, 0.175 (0.073–0.358). Associations between subphenotypes and 30-day neurological outcomes were validated using the validation dataset.

Conclusion: We identified four subphenotypes of OHCA patients with initial non-shockable rhythm. These patient subgroups presented with different characteristics associated with 30-day survival and neurological outcomes.

Key words: Asystole, cardiac arrest, clustering, latent class analysis, pulseless electrical activity, subphenotype

INTRODUCTION

OUT-OF-HOSPITAL CARDIAC ARREST (OHCA) with non-shockable rhythm (pulseless electrical activity [PEA] and asystole) is a life-threatening medical situation with a very low survival possibility.[1–3] To select the optimal resuscitation strategy for patients with OHCA, including implementation or withdrawal of advanced resuscitation, understanding the pathogenesis of OHCA with non-shockable rhythm and predicting the prognosis during resuscitation are essential.[2,3] The prognosis of OHCA with non-shockable rhythm is affected by various clinical features, including patient characteristics, bystander cardiopulmonary resuscitation (CPR), quality of CPR, pre-hospital care, and cardiac arrest etiology, making it difficult to predict prognoses and make effective clinical decisions.[2,3]

Recently, some studies have focused on identifying subphenotypes through unsupervised machine learning techniques, including latent class analysis conducted among patients with sepsis or acute respiratory distress syndrome, to overcome patient heterogeneity before selecting appropriate treatment strategies.[4–10] A phenotype is defined through patient groups with common clinical features, including specific syndromes (e.g., sepsis or acute respiratory distress syndrome), whereas a subphenotype is defined as a subgroup within a given phenotype with distinct clinical features and response to treatment compared to other subgroups of the same phenotype.[11] Subphenotype identification likely plays a valuable role in understanding pathophysiology and the prediction of prognoses and may be used to implement precision treatments that could reduce mortality or avoid undesirable invasive treatment.[12] However, few clinical studies have investigated clinical subphenotypes associated with OHCA using machine learning latent class analysis. We aimed to identify the subphenotypes based on the physiological features using a machine learning-based unsupervised clustering technique and to evaluate associations between subphenotypes and clinical outcomes.

METHODS

THE ETHICS COMMITTEE of Kyoto University and each participating institution approved this study protocol and retrospective analysis (approval ID: R1045); the requirement for written informed consent was waived. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Study design and settings

This study was a retrospective analysis conducted within a multi-center prospective observational cohort study using the CRITICAL study database, consisting of pre-hospital and in-hospital data among OHCA patients in Osaka, Japan. Details of this database and prehospital emergency care system in Japan have been published previously[13–16] and are described in Appendix S1 in the Supporting Information. Pre-hospital data were obtained from the All-Japan Utstein Registry (from the Fire and Disaster Management Agency), and in-hospital data were obtained from 16 tertiary critical care medical centers and one other community hospital.[13,17–19]

Study participants

This study included adult OHCA patients (≥18 years of age) from the CRITICAL database presenting with medical causes and an initial non-shockable rhythm and transferred to the hospitals between July 1, 2012 and December 31, 2017. Medical causes are defined as cases in which the cause of the cardiac arrest is presumed to be cardiac arrest because of cardiac etiology, other internal medical causes (e.g., asthma, gastrointestinal bleed), or in cases with no obvious

cause of cardiac arrest based on the standardized recording format.[20] Initial non-shockable rhythm was defined as either PEA or asystole and was confirmed by paramedics at the scene because current guidelines regarding advanced life support propose different resuscitation algorithms based on specific initial rhythms.[1] The exclusion criteria were as follows: no resuscitation or treatment at the hospital, unavailable pre-hospital records, <18 years of age (or unknown age), external mechanism of cardiac arrest, or return of spontaneous circulation on contact with paramedics, with no resuscitation attempts performed by paramedics.

Derivation and validation datasets

Patient data were placed in a derivation dataset to identify subphenotypes and a validation dataset to evaluate the validity of subphenotype identification. The derivation and validation datasets were based on patient data from OHCA incidents occurring between 2012 and 2016 and in 2017, respectively. Generally, external validation requires different patient profiles in the same target population. Therefore, we split the dataset based on temporal conditions, and each cohort was expected to be heterogeneous and consist of different patient profiles.[12,21]

Latent class analysis

Latent class analysis is an unsupervised machine learning method used to cluster groups of people with similar characteristics, such as demographic and clinical characteristics. It is different from the k-means clustering method, which is not compatible with categorical variables; therefore, we selected latent class analysis because it can handle specific combinations of observed categorical and continuous variables.[12,22] The term "latent" is derived from the concept that the subgroups potentially exist, but it cannot be directly observed.[12,22] The concept of latent class analysis is shown in Appendix S1. We consider that latent class analysis is more suitable for exploring subphenotypes of OHCA patients because OHCA patients have some clinically important categorical variables, such as witnesses, the existence of bystander CPR, or cardiac rhythm. We performed latent class analysis with variable selection to classify subphenotypes according to previously suggested key steps.[12] Details of variable selection and methodology are described in Appendices S1 and S3.

Selected variables

We selected clinically relevant variables that were measurable at hospital admission and registered in the database because identifying subphenotypes using readily available emergency department variables can be expected to contribute to determining resuscitation strategy. Fifteen clinically important variables were selected for analysis. Variables included demographic information (age and sex), pre-hospital data (e.g., bystander CPR, initial cardiac rhythm, and witness of collapse), and in-hospital data (e.g., cardiac rhythm on hospital arrival, blood gas analysis, and laboratory data obtained on hospital arrival). Details of the variables are described in Appendix S3. The outcomes described below were not included in the clustering. Prehospital adrenaline administration and advanced airway management were not included in the analysis because these were not patients' physiological features and it is influenced by the policy of local medical control committee, the treating paramedics' intentions or skill, by the physicians supervising the paramedics or clinical context at the scene.

Data setup

Implausible data and outliers were verified and treated as missing in the data cleaning process, similar to that described in previous studies.[13] Because of the advantages of random forest imputation for mixture data, missing data were imputed using the "missForest" package before variable selection (Table S1).[7,23,24] Variables with a correlation coefficient >0.5 were filtered, and only the most clinically relevant variable among correlated variables was selected (Appendices S2 and S3, Table S2).[7,12] For sample size, although there is no standard method to estimate adequate sample size in latent class analysis, and it is data-driven, some simulation studies indicate that sample sizes >500 are adequate to obtain consistently high accuracy.[12,25]

Fitting the model

In the model derivation, we explored the optimal number of clusters between two and determined optimal clustering based on the "Elbow method" for the Bayesian information criterion value suggested in a previous study[12] because we aimed to identify novel subphenotypes that have potential value in clinical decision-making or further research. The discriminative power of each variable was calculated, as the logarithm of the ratio of the probability that the variable is relevant for clustering to the probability that it is not. Discriminative power was scaled such that the sum value was 100%. A higher variable index indicated a higher relevance to clustering. For model fitting, we used the "VarSelLCM" package in R (R Foundation for Statistical Computing, Vienna, Austria).

Evaluating the model

Once subphenotypes were identified, we described differences in demographics, pre-hospital data, and in-hospital data. Continuous variables were summarized as boxplots indicating medians and interquartile ranges (IQRs), whereas categorical variables were summarized as frequencies and percentages.

Associations between subphenotypes and outcomes

The primary outcome was defined as 30-day survival with a favorable neurological outcome (Cerebral Performance Category 1 or 2).[26] Based on the All-Japan Utstein Registry from the Fire and Disaster Management Agency, all survivors were followed up to confirm the outcome at 30-day after OHCA. The secondary outcome was 30-day survival. The outcomes were assessed by the supervising physician in charge of patient care through a follow-up interview. To identify associations between groups and outcomes, we performed logistic regression analysis to generate odds ratios (ORs) with 95% confidence intervals (CIs) for each group. We did not adjust for confounders because the potential confounders were used as variables to identify subphenotypes, and these were conditioned in each group.

Regarding the discriminatory ability for groups and outcomes, we calculated the area under the curve (AUC) of the receiver-operating curve (ROC) and presented the 95% CI of the AUC.

External validation of the derived subphenotypes

The model for clustering was applied to the validation dataset from 2017 using the "predict" function of the "VarSelLCM" package to evaluate external validation and reliability. The characteristics and outcomes of each subphenotype in the validation data were described. Further, we calculated the OR and 95% CI for each group regarding the outcomes, along with the AUC of the ROC (with 95% CI) as mentioned above, to confirm the replicability of our findings.

RESULTS

AMONG THE 12,594 patients in the CRITICAL database, 6,314 OHCA patients with initial non-shockable rhythm were included in the analysis: 4,849 in the derivation dataset (median [IQR] age, 75 [65–83]; men, 2,920 [60.2%]) and 1,465 in the validation dataset (median [IQR] age, 76 [66–84]; men, 2,874 [59%]). The study flowchart is included in Figure S1. Patient characteristics and in-hospital data are described in Table 1 and Table S3. Regarding the outcomes in the datasets, the rates of 30-day-survival and 30-day survival with favorable neurological outcomes were 4.4% (n = 211) and 1.8% (n = 87) in the derivation dataset and 4.2% (n = 62) and 1.5% (n = 22) in the validation dataset, respectively.

Clustering subphenotypes in the derivation dataset

After removing variables with high degrees of correlation in the derivation dataset, 15 variables were used to cluster subphenotypes (Appendices S1 and S3, Table S2). The optimal number of clusters was four, based on Bayesian information criterion values (Figs. S2 and S3). To identify these 4 clusters, 14 of 15 variables were selected to the model, and variables with the highest discriminative power were partial pressure of oxygen (PO_2), age, serum potassium, and estimated glomerular filtration rate (eGFR; Fig. 1). The characteristics and distribution of variables with high discriminative power among the patients were modeled by the groups in the derivation dataset (Table 1, Fig. 2).

Association between subphenotypes and outcome in derivation dataset

For the primary outcome, the 30-day neurological favorable outcomes were group 1, 0.1% (1/1,386); group 2, 0.7% (13/1,896); group 3, 1.2% (7/571); and group 4, 6.6% (66/996) (Fig. 3). The ORs (95% CI) of each group for the 30-day neurological favorable outcome were group 1, 0.01 (0.001–0.046); group 2, 0.097 (0.051–0.171); and group 3, 0.175 (0.073–0.358) compared to group 4. The AUC of ROC (95% CI) of groups was 0.819 (0.784–0.855).

For the secondary outcome, the 30-day survival outcomes in each group were group 1, 0.4% (5/1,386); group 2, 2.2% (42/1,896); group 3, 2.6% (15/571); and group 4, 15% (149/996) (Fig. 2). The ORs (95% CI) of each group for the 30-day survival outcome were group 1, 0.021 (0.007–0.045); group 2, 0.129 (0.09–0.181); and group 3, 0.153 (0.086–0.255) compared to group 4. The AUC of ROC (95% CI) of groups was 0.798 (0.771–0.825).

Subphenotype and outcome in validation dataset

The clustering model was fitted and identified the subphenotypes in the validation dataset. The characteristics of the four

Table 1. Characteristics in derivation cohort

Characteristics	Subphenotypes				
	Overall (*N* = 4,849)	Group 1 (*N* = 1,386)	Group 2 (*N* = 1,896)	Group 3 (*N* = 571)	Group 4 (*N* = 996)
Sex (men)	2,920 (60%)	781 (56%)	1,159 (61%)	406 (71%)	574 (58%)
Age (years)	75.0 (65.0, 83.0)	78.0 (71.0, 85.0)	77.0 (68.0, 83.0)	46.0 (39.0, 52.0)	75.0 (66.8, 82.0)
Initial cardiac rhythm					
Asystole (%)	2,027 (42)	306 (22)	936 (49)	177 (31)	608 (61)
PEA (%)	2,822 (58)	1,080 (78)	960 (51)	394 (69)	388 (39)
Witness (%)	2,129 (44)	231 (17)	1,064 (56)	193 (34)	641 (64)
Bystander CPR (%)	1,861 (38)	586 (42)	693 (37)	238 (42)	344 (35)
Time from call to hospital (min)	32 (27, 40)	33 (27, 39)	32 (26, 40)	33 (28, 41)	33 (27, 41)
Cardiac rhythm at hospital arrival					
VF/VT (%)	87 (1.8)	12 (0.9)	37 (2.0)	11 (1.9)	27 (2.7)
PEA (%)	1,110 (23)	97 (7.0)	556 (29)	88 (15)	369 (37)
Asystole (%)	3,382 (70)	1,276 (92)	1,277 (67)	458 (80)	371 (37)
ROSC (%)	270 (5.6)	1 (<0.1)	26 (1.4)	14 (2.5)	229 (23)
BT (°C)	35.4 (34.7, 36.1)	35.2 (34.1, 35.9)	35.6 (35.0, 36.1)	35.3 (34.4, 36.0)	35.4 (34.6, 36.1)
PCO_2 (mm Hg)	84 (64, 106)	100 (72, 131)	84 (71, 98)	97 (77, 126)	59 (40, 80)
PO_2 (mm Hg)	38 (19, 73)	32 (17, 61)	30 (16, 47)	31 (17, 56)	127 (81, 234)
BE (mEq/L)	−17.6 (−22.6, −13.2)	−21.8 (−25.5, −17.2)	−15.7 (−18.2, −11.4)	−20.8 (−25.6, −16.8)	−16.5 (−21.6, −10.9)
Glu (mg/dL)	226 (139, 304)	166 (90, 256)	242 (172, 297)	271 (154, 368)	250 (160, 344)
Alb (g/dL)	3.1 (2.8, 3.3)	3.0 (2.6, 3.2)	3.1 (2.9, 3.3)	3.4 (3.1, 3.6)	2.9 (2.5, 3.3)
Na^+ (mEq/L)	140 (138, 142)	140 (136, 143)	140 (139, 142)	140 (137, 143)	139 (136, 142)
K^+ (mEq/L)	6.3 (5.1, 7.7)	8.3 (7.2, 9.7)	5.7 (5.0, 6.5)	6.8 (5.3, 9.2)	5.2 (4.2, 6.2)
eGFR (mL/min/1.73 m^2)	37 (25, 49)	30 (18, 43)	37 (29, 45)	48 (34, 61)	43 (28, 60)

Continuous variables were summarized as median and interquartile range (IQR), whereas categorical variables were summarized as frequencies and percentages (%).
Alb, albumin (g/dL); BT, body temperature (°C); CPR, cardio-pulmonary resuscitation; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); Glu, glucose (mg/dL); K^+, serum potassium (mEq/L); Na^+, serum sodium (mEq/L); PCO_2, partial pressure of CO_2 (mm Hg); PEA, pulseless electrical activity; PO_2, partial pressure of O_2 (mm Hg); ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, pulseless ventricular tachycardia.

groups were similar to that of derivation dataset (Table S3, Fig. S4).

For the primary outcome, the 30-day neurological favorable outcomes were group 1, 0% (0/408); group 2, 0.5% (3/569); group 3, 1.2% (2/163); and group 4, 5.2% (17/325; Fig. 3). The ORs (95% CI) of each group for the 30-day neurological favorable outcome were group 1, not available because of zero value; group 2, 0.096 (0.022–0.289); and group 3, 0.225 (0.035–0.798) compared to group 4. The AUC of ROC (95% CI) of groups was 0.822 (0.759–0.885).

For the secondary outcome, the 30-day survival outcomes in each group were group 1, 0% (0/408); group 2, 2.3% (13/569); group 3, 2.5% (4/163); and group 4, 13.8% (45/325). The ORs (95% CI) of each group for the 30-day survival outcome were group 1, not available because of zero value; group 2, 0.145 (0.074–0.266); and group 3, 0.157 (0.047–0.394) compared to group 4. The AUC of ROC (95% CI) of groups was 0.804 (0.76–0.847).

DISCUSSION

Key observations

WE IDENTIFIED FOUR subphenotypes of OHCA patients with initial non-shockable rhythm. These patient subgroups presented with different characteristics associated with 30-day survival and neurological outcomes. The replicability of these subphenotypes was confirmed using the validation dataset.

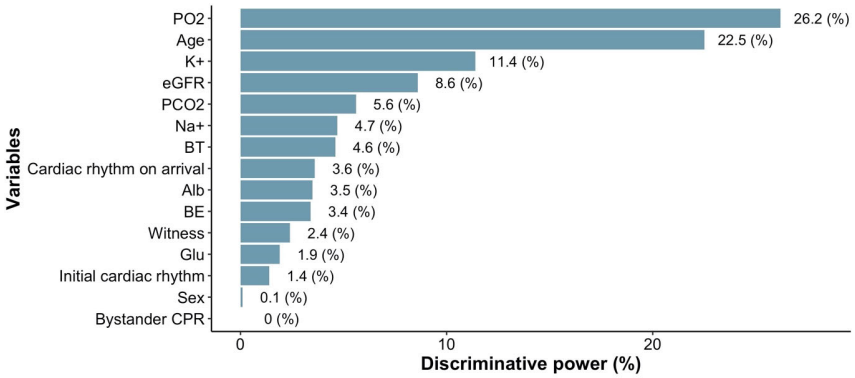

Fig. 1. Discriminative power. Alb, albumin; BE, base excess, BT, body temperature; CPR, cardio-pulmonary resuscitation; eGFR, estimated glomerular filtration rate; Glu, glucose; K^+, Serum potassium; Na^+, serum sodium; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen. The discriminative power of each variable was calculated as the logarithm of the ratio between the probability that the variable is relevant for clustering and the variable is irrelevant for clustering. It is scaled as the sum value is 100%.

Strengths

This study had several strengths compared with previous studies. First, to the best of our knowledge, this was the first study to investigate subphenotypes of OHCA patients with initial non-shockable rhythm. Previous studies used traditional methods, including logistic analysis, to identify factors associated with survival and clinical outcomes (including age, presence of witnesses, bystander CPR, a shorter ambulance response time, initial PEA, cardiac rhythm conversion to shockable rhythm, early administration of adrenaline, and biomarker levels).[3,27–30] However, analysis by logistic model is intended to investigate the independent association between the factors and outcomes, and these individual factors are generally not suitable for distinguishing heterogenic patients when other factors are not considered.[22] However, this study is focused on the distribution of variables for capturing the features of the data and suggests the novel concept of subgroups among OHCA patients with non-shockable rhythm, which have not been realized using traditional analyses. This concept is likely to help promote understanding of the underlying pathogenesis, prompt hypotheses, contribute to developing a prediction model, and aid in investigating the heterogeneity of treatment, which may further enhance precision medicine. Second, the latent class analysis in this study includes clinically relevant categorical variables, including cardiac rhythm on hospital arrival or the presence of witnesses at the event. In contrast, only continuous variables were included in the analysis in previous studies implementing other clustering methods, including k-means.[4,8–10] Therefore, our study characterizes subphenotypes more comprehensively by considering categorical variables. Third, in this clustering approach, there is some concern regarding validation and replicability.[22] However, this study confirmed that the identified subphenotypes were replicable using the validation dataset; therefore, these results may be generalizable to similar settings.

Interpretation

The results of this study can be reasonably explained by the following potential mechanisms. First, PO_2 in arterial blood indicates alveolar oxygenation and oxygen delivery in the systemic circulation. During resuscitation, a high PO_2 value may indicate good CPR quality, return of spontaneous circulation, or a situation in which spontaneous circulation is slightly maintained, but the carotid pulse is not detectable because of hypotension, and this parameter was reportedly associated with the return of spontaneous circulation and survival discharge.[31,32] Similarly, in our previous study investigating the subphenotypes among patients with OHCA and a shockable rhythm, PO_2 in blood gas assessment is also the variable with the highest discriminative power. Accordingly, we suggest that the PO_2 value may play an important role in identifying subphenotypes among patients with OHCA. Second, age is one of the most relevant factors influencing the prognosis for patients with cardiac arrest,[33,34] and we consider that age has high discriminative power. However, in a previous study involving patients with OHCA and an initial shockable rhythm, age was reported to have minimal discriminative power for the subphenotypes.[35] This may have been because patients in this study were older than those in the previous study (median age, 65 [IQR: 53–75] years), and age becomes more relevant among older populations, as in our study. Third, increased serum

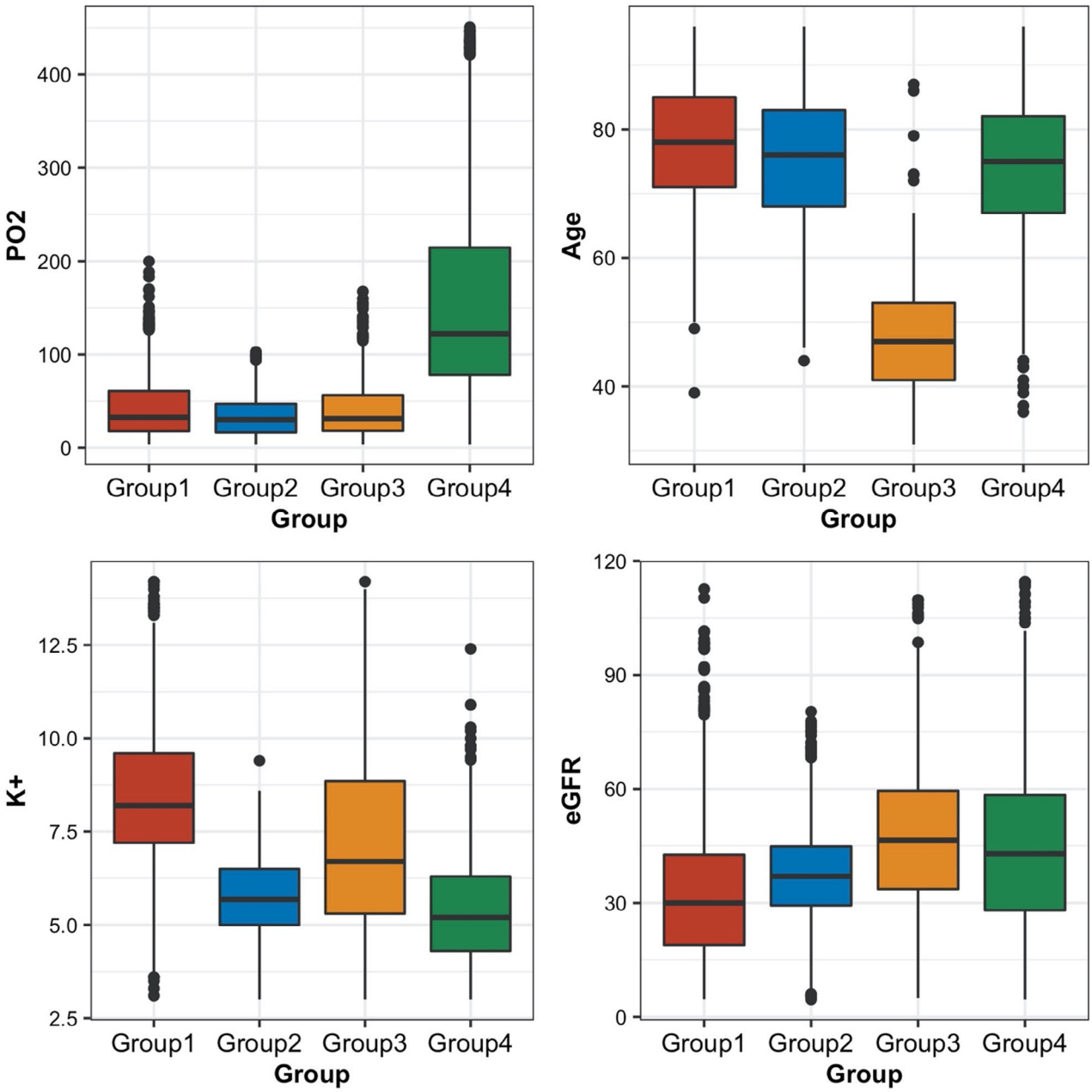

Fig. 2. Distributions of variables with the highest discriminative power in the derivation dataset. The box plot indicates median and interquartile range. Age, year; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); PO_2, partial pressure of oxygen (mm Hg).

potassium levels may be representative of organ injury. Because increases in serum potassium are associated with cell lysis after cell death, indicating the futility of resuscitation attempts.[16,36] Fourth, chronic kidney disease (defined as low eGFR) is a well-known major risk factor for cardiovascular events or sudden death and is associated with mortality and unfavorable neurological outcomes in OHCA patients.[37–39] Based on these findings, these parameters may be relevant when identifying the subphenotypes of OHCA patients with non-shockable rhythm.

Some results are somewhat counterintuitive. For example, group 3 was younger than group 4; however, group 3 had

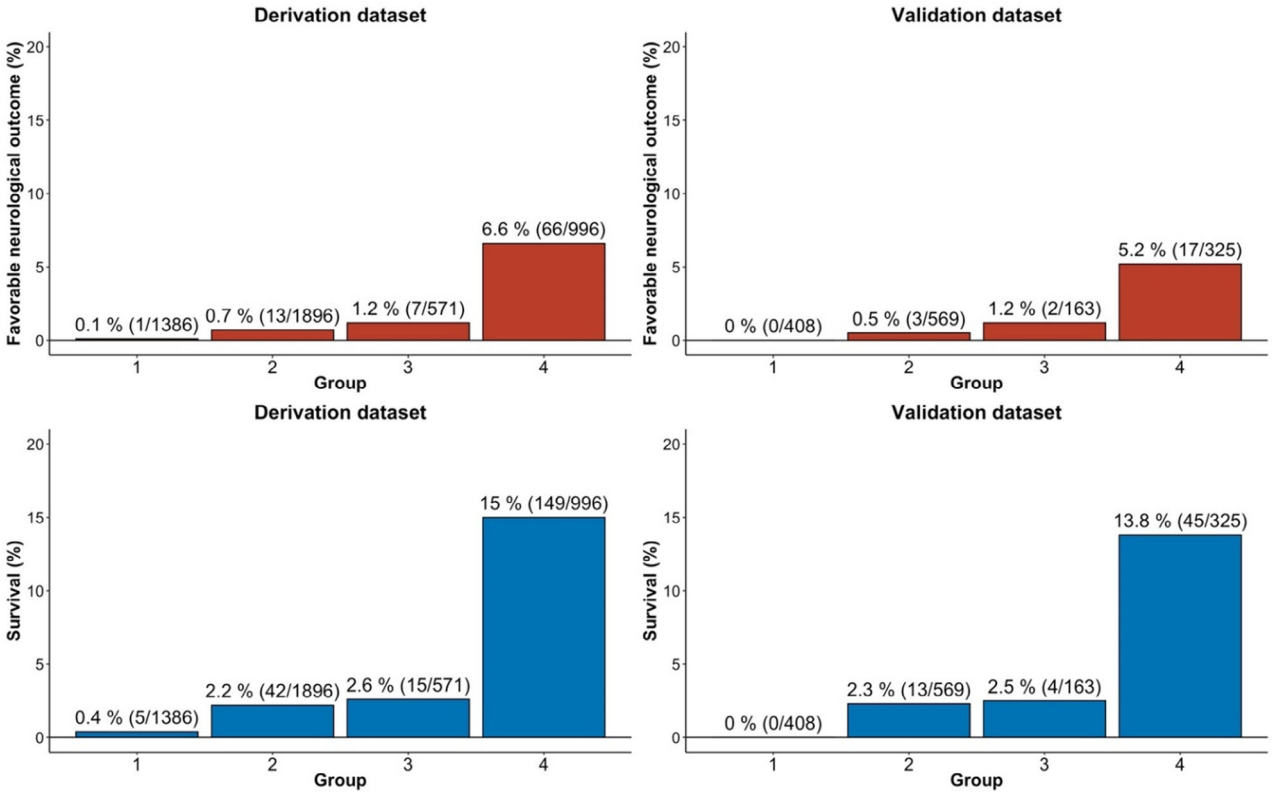

Fig. 3. Primary and secondary outcomes by dataset.

lower survival outcomes than group 4. Based on the results, although it appears that age is an important variable to differentiate the groups, age is not a single dominant variable to differentiate patient prognosis, and the combination of other variables, such as PO_2, should be considered. Clinically, it stands to reason that the OHCA patients who are young (e.g., 50 years old) with lower PO_2 values (e.g., 20 mm Hg) had lower survival probability than those who are elderly (e.g., 75 years), but had high PO_2 values (e.g., 140 mm Hg). This is because PO_2 of 20 mm Hg indicates a severe lack of oxygen delivery to vital organs, and this seems to lead to critical injury of the brain and other organs, even in young patients.

Clinical and research implications

Distinguishing subphenotypes may be helpful to understand the underlying pathogenesis of cardiac arrest, suggest a novel hypothesis, or contribute to developing a prediction model. Discriminatory abilities (i.e., the AUC of the ROC) for neurological outcomes were relatively high in both datasets for developing prediction models. Therefore, subphenotype features could be used to develop more accurate prediction models. Further, the fourth-highest discriminative power variable was eGFR, although differences in eGFR between the subphenotypes were relatively small. This result may suggest that even minor differences in eGFR may be relevant to patient outcomes. This finding may lead to further research to explore the role of eGFR in patient resuscitation.

Moreover, identifying these subphenotypes may be valuable when investigating the potential heterogeneity in the effect of resuscitation interventions. Previously, we reported that subphenotypes of patients with OHCA and an initial shockable rhythm might have potential heterogeneity in the effect of extracorporeal CPR on the outcomes,[35] and we consider that the results in that previous study may be of value in identifying an appropriate target population for extracorporeal CPR. In this study, the outcomes in groups 2 and 3 were equivalent; however, the characteristics differed, and there may have been some potential heterogeneity in terms of the effect of the intervention. In this study, although we did not explore the heterogeneity of the effect of intervention because there is no established intervention to

improve outcomes for patients with OHCA patients and a non-shockable rhythm, the concept of subphenotypes may be valuable for further research to investigate the potential heterogeneity of the treatment effect.

Limitations

This study had several limitations. First, although prehospital and in-hospital data were collected prospectively using the pre-specified data extraction sheet, some data may have been missed or measurement errors may have occurred. It is particularly concerning that blood test results were based on the blood sample collected on hospital arrival; however, the timing of blood collection may not have been uniform in all patients. Therefore, we should be cautious when interpreting the results because of the risk of bias. Second, the data available for this study were somewhat limited. We may have obtained different results with comprehensive, clinically significant data. For example, information on patient characteristics that include comorbidities or the situation in which the cardiac arrest occurred may have been valuable when developing subphenotype profiles. Further, the available outcome data is limited to only survival or Cerebral Performance Category status. If more clinically relevant outcome data, such as health-related quality of life, were available, the results of this study would have been more clinically valuable. Third, although there is no established standard to estimate the sample size required for sufficient statistical power, the small sample size in this study poses a risk of inaccurate estimation. Fourth, there is no gold standard to validate data clustering results. Therefore, the replicability and generalizability of these results to other settings is unclear. Further research is needed to address the risks of bias and concerns of applicability.

CONCLUSIONS

WE IDENTIFIED THE subphenotypes associated with favorable neurological outcomes using an unsupervised machine learning-based clustering technique. The replicability of these subphenotypes was confirmed with a validation dataset. Further research is necessary to validate these subphenotypes.

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DISCLOSURE

APPROVAL OF THE Research Protocol with approval number and committee name: the Ethics Committee of Kyoto University and each participating institution approved this study protocol and retrospective analysis (Approval ID: R1045). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent (if applicable): The requirement for written informed consent was waived.

Conflict of Interest: The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Y.O., S.K., AND T. Kitamura conceived and designed the study. T. Kitamura, T. Kiguchi, T. Ishibe, T.Y., K.Y., C.P., T.N., T.I., Y.Y., M.K., T Inoue, Y.H., Y.S., T.M., H.S., K.S., F.N., T.M., N.N., D.K., S.M., A.H., S.Y., SK., and T.S. acquired and managed data. Y.O., S.K., and T. Kitamura performed analyses. T. Iwami and T. Kitamura acquired funding. Y.O., S.K., T. Kitamura, T. Iwami, and S.O. were responsible for interpretation. Y.O., S.K., T. Kitamura, and S.O. drafted the manuscript. All authors provided feedback on the intellectual contents and approved the final manuscript.

DATA AVAILABILITY STATEMENT

THE DATASETS AND/OR analysis in this study are not publicly available because the ethics committee did not permit it.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Prehospital emergency service system in Japan and CRITICAL database.
Appendix S2. Methodology of latent class analysis.
Appendix S3. Detail of the variables.
Table S1. Variables with missing before imputation
Table S2. Excluded variables based on the correlation coefficients
Table S3. Characteristics in the validation dataset
Fig. S1. Study flowchart.
Fig. S2. BIC values in clusters.
Fig. S3. Probability of miss-classification.
Fig. S4. The distribution of variables with the four highest discriminative power in validation dataset.