Early Prediction Model of Brain Death in Out-of-hospital Cardiac Arrest Patients: a Single-centre Retrospective and Internal Validation Analysis

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Abstract

Background

A shortage of donor organs amid a high demand for transplantable organs is a worldwide problem, and an increase in organ donation would be welcomed by the global healthcare system. Patients with brain death (BD) are potential organ donors, and early prediction of BD patients may facilitate the process of organ procurement. Therefore, we developed a model for early prediction of BD in patients who survived the initial phase of out-of-hospital cardiac arrest (OHCA).

Methods

We retrospectively analysed data of patients aged, who were aged < 80 years, experienced OHCA with return of spontaneous circulation (ROSC), and were admitted to our hospital between 2006 and 2018. We categorised the patients into either a non-BD or BD group. Demographic and laboratory data on emergency department admission were used for stepwise logistic regression. Prediction scores of BD after OHCA were based on β -coefficients of prognostic factors identified in the multivariable logistic model.

Results

Overall, 419 OHCA patients with ROSC were admitted to our hospital during the study period. Seventy-seven patients showed BD (18.3%). Age and OHCA aetiology were significantly different between the groups. Logistic regression analysis confirmed that age, low-flow time, pH, and aetiology were independent predictors of BD. The area under the receiver operating characteristic curve for this model was 0.831 (95% CI, 0.786–0.876).

Conclusion

We developed and internally validated a new prediction model for BD after OHCA, which could aid in early identification of potential organ donors for early donor organ procurement.

Background

A shortage of donor organs amid a high demand for transplantable organs is a worldwide problem [1–5], and an increase in organ donation would be welcomed by the global healthcare system [6]. Patients with brain death (BD) are potential organ donors. Thus, early prediction of BD patients may facilitate the process of organ procurement. Few studies have established predictive models for BD [7]. In spontaneous intracerebral haemorrhage, poor corneal reflexes and swirl signs on an initial computed tomography scan are good predictors of BD (sensitivity: 0.89, specificity: 0.68) [7].

Despite recent progress in resuscitative and critical care medicine, mortality after out-of-hospital cardiac arrest (OHCA) remains high. Approximately 300,000 cardiac arrests occur in the United States and

100,000 occur in Japan annually [8]. Since the brain is the organ most susceptible to hypoxia and inadequate organ perfusion [9], some OHCA patients unfortunately develop total loss of brain function (i.e., BD) in the first several days after the return of spontaneous circulation (ROSC) [10]. A futility score (NULL-PLEASE) predicting poor outcomes in OHCA patients was developed [11] and externally validated by a group in the United Kingdom [12]. However, its predictive ability for fatal outcomes was not strong enough [11, 12]. The bispectral index during extracorporeal cardiopulmonary resuscitation (E-CPR) for cardiac arrest is also useful in predicting BD [13]. A bispectral index below 30 is associated with a sensitivity of 96% and a specificity of 82% for BD occurrence in patients treated with E-CPR.

As OHCA is associated with complicated patient characteristics, situations and environments, detailed information gathered upon emergency department (ED) admission can be used to obtain a clear idea of the patient's health status and situation. Given these variables, certain clinical factors contributing to BD can be detected. However, few prediction models have been developed for BD in OHCA patients. Therefore, we aimed to identify significant predictive variables to develop and validate a discriminative model for the early prediction of BD in patients who survived the initial phase of an OHCA.

Methods

Patients

We performed a retrospective analysis using data from the electronic medical records of patients who experienced OHCA with ROSC and were admitted to Hokkaido University Hospital between 2006 and 2018.

Patients who were under 80 years of age were eligible for this study, as patients aged over 80 years are unlikely to be donor candidates. The records of eligible patients were searched to collect laboratory test results from ED arrival along with data on clinical characteristics, treatments, and patient outcomes.

Definition

BD is defined as deep coma, electrocerebral inactivity, loss of brainstem reflexes, dilation (≥ 4 mm) and fixing of the pupils, and apnoea. A diagnosis of BD was made based on the attending physician's judgement. We categorised patients into two groups: a non-BD group and a BD group. Low-flow time was defined as the time from the initiation of chest compressions to ROSC and was included as a continuous variable. Bystander CPR was defined as the initiation of CPR by a witness of the cardiopulmonary arrest (Utstein style).

Statistical analyses

The Mann–Whitney U and chi-squared tests were used for comparisons between the two groups. Classification and regression tree models were applied to categorise continuous variables. We input the following demographic and laboratory data regarding ED admission for the stepwise logistic regression model: age, sex, witnessed status, initial rhythm, presence of a shockable rhythm, lactate level, low-flow

time, pH, and the presence or absence of end-stage renal failure requiring dialysis. A stepwise logistic regression analysis was performed to confirm the variables that were both readily available at admission and predictive of BD. The prediction scores for BD after OHCA were based on the β -coefficients of prognostic factors identified from a multivariable logistic model. The calculated β coefficients were rounded to the nearest integer to reflect the weight of each variable. A binary logarithmic function model was developed according to the score. We estimated the predictability of the score using the area under the receiver operating characteristic curve (AUROC). Youden's index was used to determine cut-off value of the OHCA-BD score for predicting BD. Internal validation was performed by bootstrapping using a bias-corrected and accelerated method based on 1000 bootstrapped samples, and we assessed the discrimination by determining the AUROC for each original dataset and the 1000 computed samples. Optimism was estimated by calculating the AUROC using 1000 bootstrapped resamples of the dataset and calculating the differences between the AUROCs of all bootstrapped resamples and the original dataset. The Hosmer–Lemeshow test was performed to confirm score calibration. All statistical analyses were performed with R (version 3.5.1). All tests were two-tailed, and p-values of 0.05 or less were considered statistically significant.

Results

A total of 419 OHCA patients with ROSC were admitted to our hospital during the study period. Their demographic and clinical characteristics are shown in Table 1. The overall BD rate was 18.3% (n = 77). The values for age, lactate levels, and low-flow time were significantly higher in the BD group. The male-to-female ratio and proportions of witnessed status and defibrillation were lower in BD patients than in non-BD patients. OHCA due to cerebrovascular disease were much more likely to lead to BD. pH was significantly lower in the BD group. Although lactate levels, low-flow time, pH, and sex were not significantly different between groups, age and OHCA aetiology were significantly different.

Classification and regression tree models were applied to convert continuous variables to categorical variables. The thresholds for each continuous value were as follows: age (< 43 years, 43–67 years, > 67 years), pH (< 6.62, 6.62–7.06, $\geq$ 7.06), low-flow time (< 20 min, $\geq$ 20 min), and lactate (< 8.75 mmol/L, 8.75–12.65 mmol/L, $\geq$ 12.65 mmol/L). After categorising the continuous variables, stepwise logistic regression was performed. Stepwise logistic regression analysis confirmed that age, low-flow time, pH, and aetiology were independent predictors of BD (Table 2). The developed prediction score (OHCA-BD score) is shown in Table 3.

Consequently, we created a linearised logarithmic function model using this score. In Fig. 1, the predictive probability of BD according to this score is shown by a line graph, and the actual rate of BD is shown by a bar graph. The AUROC for this model was 0.831 (95% CI, 0.786–0.876) (Fig. 2). The cut-off point was 20/41 (sensitivity 67.5%, specificity 81.8%).

Internal validation of the score using bootstrapping yielded an average optimism of 0.0015. The Hosmer–Lemeshow chi-squared value was 4.3674 (degrees of freedom = 6), and the non-significant p-

value of 0.6271 indicated a good model fit.

We also calculated the AUROC of the NULL-PLEASE score to determine its ability to predict BD. However, its prediction ability for BD was not high enough (AUROC 0.596; 95% CI 0.53–0.66) and was significantly different compared with the OHCA-BD score ($p < 0.01$) (Fig. 2).

Discussion

We developed a model to predict BD based on a relatively large population of OHCA patients admitted to our hospital between 2006 and 2018. This was done through creating a logistic regression model based on variables that were easily available after ED arrival. The predictability of BD was accurate, and internal validation yielded an appropriate optimism value. We successfully predicted BD using the OHCA-BD score.

Since the brain is the organ that is most susceptible to hypoxia and inadequate perfusion, OHCA contributes enormously to BD. The rate of organ donation from BD patients following OHCA was reported to be 5.4% in a single-centre study from the United Kingdom [14], which is not high. Certainly, coordination of organ donation through the decedent's family is essential for organ donation from BD patients because the refusal rate for organ donation remains high. However, in many cases of OHCA, circulation is refractory, and the patient dies without confirmation of BD or fails to be diagnosed with BD. Furthermore, withdrawing life-sustaining therapy because of perceived poor neurological prognosis is the main cause of hospital death after OHCA [15, 16]. It should be noted that our hospital does not make early decisions to withdraw mechanical, ventilated or organ-perfusion support. Therefore, among patients with a poor neurological prognosis in our retrospective cohort, we could distinguish between patients who developed BD and those who died without developing BD, as in the study by Galbois et al. [7]. We have the same concepts and rules, which leads to lengths of stay in which patients proceed towards BD. Therefore, our intensive care practice did not introduce bias by preventing BD development.

According to the demographic data, there are specific tendencies in BD patients. Younger age is an independent predictor of BD. This may be because the brain of a younger person occupies less space in the cranium than those of older individuals. Hematomas and multiple hemispheric lesions with oedema contribute to brain herniation, which leads to BD due to compression of the brainstem. Furthermore, older patients tend to die by circulatory collapse, which avoids progression towards BD. OHCA due to cerebrovascular disease corresponded most strongly with BD in terms of aetiology. However, other parameters of tissue hypoperfusion, such as lactate, pH, and low-flow time, were indicators of poor outcomes but not specific indicators of BD.

Ahmad et al. introduced the NULL-PLEASE score, which predicts poor neurological outcomes in OHCA patients [11]. However, the NULL-PLEASE score could not predict the development of BD in the present study. Patients with poor neurological outcomes predicted by the NULL-PLEASE score include patients in a vegetative state and those who died without developing BD. Therefore, to predict progression to BD, a specific prediction scoring model is needed.

Organ donation is a stressful and difficult end-of-life decision causing anxiety, depression, and decreased quality of life among family members of the deceased donor [17]. The family needs to fully understand that BD means the death of their loved one and that we need consent from the family for organ donation [18]. This process is also ethically and emotionally challenging for the physicians involved [19]. We may reduce this burden by objective assessment using a predictive score. Taking these concerns into account, the early detection of BD is merely one step aimed toward respecting the patient's and family's decisions.

Limitations of this study include the single-centre design, possible selection bias, and confounding by unknown or unmeasured variables. We may also have bias in treatment for OHCA patients. Although bootstrapping is a strong tool for statistical internal validation, it cannot avoid overlapping of patients selected for each dataset. Furthermore, we did not perform external validation with the present score. Prospective observational studies are needed for external validation.

Conclusion

In conclusion, a new predictive model for BD after OHCA was developed and internally validated. By using this scoring model, patients at high risk of BD after OHCA may be identified early.

Abbreviations

Out-of-hospital cardiac arrest, OHCA; Return of spontaneous circulation, ROSC; Extracorporeal cardiopulmonary resuscitation, E-CPR; Emergency department, ED; Brain death, BD; Area under the receiver operating characteristic curve, AUROC

Declarations

Ethics and consent:

The study was approved by the institutional review board of the Hokkaido University Hospital, and the requirement for informed consent was waived because of the retrospective design.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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This study did not receive any funding.

Author contributions:

YI collected, analysed, and interpreted the data and drafted the manuscript. MH conceived the study, interpreted the data, and drafted the manuscript. KM conceived the study and analysed and collected the data. AK, KM, YT, and HS read the manuscript and revised it for important intellectual content. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic and clinical characteristics of the patients after out-of-hospital cardiac arrest

Parameters	All patients (n = 419)					
	Non-BD			BD n=77	p value	
	All n=342	Survived n=198	Death n=144		All non-BD vs. BD	Non-BD Death vs. BD
Age (IQR)	66 (56, 74)	64 (55, 74)	67 (58, 75)	56 (42, 64)	<0.001	<0.001
Male (%)	232(67.8)	136 (68.7)	96 (66.7)	41 (53.2)	0.017	0.059
Etiology (%)						
Cardiac	215 (62.9)	137 (69.2)	78 (54.2)	24 (31.2)	<0.001	0.004
Respiratory	25 (7.3)	13 (6.6)	12 (8.8)	9 (11.7)		
Cerebrovascular	20 (5.8)	7 (3.5)	13 (9.0)	18 (23.4)		
External	58 (17.0)	31 (15.7)	27 (18.8)	20 (26.0)		
Other	24 (7.0)	10 (5.1)	14 (9.7)	6 (7.8)		
Witness (%)	227 (66.4)	156 (78.8)	73 (50.7)	40 (51.9)	0.025	0.778
Bystander CPR (%)	195 (57.0)	104 (52.5)	91(63.2)	41(53.2)	0.611	0.154
Initial rhythm upon EMS arrival (%)						
ROSC	11 (3.2)	9 (4.5)	2 (1.4)	2 (2.6)	0.036	0.399
VF/pulseless VT	137 (40.1)	98 (49.5)	39 (27.1)	18 (23.4)		
PEA	64 (18.7)	38 (19.2)	26 (18.1)	21 (27.3)		
Asystole	119 (34.8)	48 (24.2)	71 (49.3)	35 (45.5)		
Unknown	11 (3.2)	5 (2.5)	9 (6.2)	1 (1.3)		
Defibrillation (%)	162 (47.4)	110 (47.5)	52 (36.1)	21 (27.3)	0.001	0.230
Low-flow time, min (IQR)	25.5 (15.0, 40.8)	20.0 (11.25, 34.8)	31.5 (21.0, 43.0)	35.0 (25.0, 46.0)	<0.001	0.192
Blood gas analysis on arrival at ED						
pH (IQR)	7.08 (6.89, 7.30)	7.21 (7.00, 7.33)	6.97 (6.80, 7.14)	6.91 (6.82, 7.03)	<0.001	0.167
Base deficit, mmol/L (IQR)	13.55 (6.72, 21.08)	10.2 (4.4, 16.5)	18.8 (12.10, 23.7)	20.10 (14.10, 23.50)	<0.001	0.526
Lactate, mmol/L (IQR)	9.80 (6.23, 13.17)	7.9 (4.4, 11.6)	11.6 (9.1, 14.9)	12.70 (9.20, 14.60)	0.001	0.906
End-stage renal failure on dialysis (%)	14 (4.1)	5 (2.5)	9 (6.2)	1 (1.3)	0.324	0.170

IQR, interquartile range; BD, brain death; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; BE, base deficit; ED, emergency department

Table 2. Results of the stepwise multivariate logistic regression analysis					
Coefficients		β coefficient	Odds ratio	95% CI	p-value
Intercept		-2.7717	0.06	(0.02 - 0.19)	<0.01
Age	<43 years	0			reference
	43-67 years	-1.024	0.36	(0.17 - 0.78)	<0.01
	≥ 67 years	-2.4262	0.09	(0.04 - 0.22)	<0.01
Etiology	Cardiac	0			reference
	Respiratory	1.5243	4.59	(1.71 - 12.3)	<0.01
	Cerebrovascular	2.1272	8.39	(3.47 - 20.3)	<0.01
	External	1.2052	3.34	(1.57 - 7.1)	<0.01
	Other	0.7364	2.09	(0.71 - 6.19)	0.18
Low-flow time	<20 min	0			reference
	≥ 20 min	1.7976	6.03	(2.18 - 16.7)	<0.01
	< 6.62	0			reference
pH	6.62-7.06	0.6964	2.01	(0.74 - 5.44)	0.17
	≥ 7.06	-0.1774	0.84	(0.27 - 2.6)	0.76
Low-flow time means the time from the initiation of chest compressions to the return of spontaneous circulation					

Table 3. Categorical classification of each variable for brain death

Variables		β coefficient	corrected coefficient
Intercept		-2.7717	
Age	<43 years	0	14
	43-67 years	-1.024	6
	≥ 67 years	-2.4262	0
Etiology	Cardiac	0	0
	Respiratory	1.5243	9
	Cerebrovascular	2.1272	12
	External	1.2052	7
	Other	0.7364	4
Low-flow time	< 20 min	0	0
	≥ 20 min	1.7976	10
pH	< 6.62	0	1
	6.62 - 7.06	0.6964	5
	≥ 7.06	-0.1774	0

Low-flow time means the time from the initiation of chest compression to return of spontaneous circulation

Figures

Figure 1.

Figure 1

Relationship between the rate of brain death and OHCA-BD score Line graph shows the predicted probability of brain death according to the OHCA-BD score; bar graph shows the actual rate of brain death according to the OHCA-BD score.

Figure 2.

Figure 2

Areas under the receiver operator characteristic (ROC) curves of OHCA-BD and NULL-PLEASE scores for predicting brain death Cut-off point of OHCA-BD score to predict brain death was 20 points (sensitivity 67.5%, specificity 81.8%). Solid line, ROC curve of OHCA-BD score; dotted line, ROC curve of NULL-PLEASE score.