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Original Research Article

Predict cardiac death after withdrawal of life-supporting treatment in the neurocritical patients: a neurological score

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ABSTRACT

Background: Accurate prediction the time of death after withdrawal of life-supporting treatment (WLST) in the neurocritical patients is important for donation after cardiac death. We aimed to establish a new neurological scoring system to predict the probability of death within 60 minutes after WLST.

Methods: We retrospectively reviewed the clinical data from a cohort of 231 neurocritical patients from June 2016 to July 2018. The patients were divided into training and external validation sets. In the training set, we used univariate and multivariable logistic regression analyses to assess associations between death within 60 minutes after WLST and these variables. Points attributed to each variable were summed to create a predictive score for cardiac death. We assessed performance of the score using ROC analysis. Finally, we validated the predictive ability of the score in an external validation set.

Results: Multivariable logistic regression analysis showed that absent corneal reflexes, absent cough reflexes, extensor or absent motor response and anisocoric or bilaterally dilated pupil were associated with death within 60 minutes in training set (all $p<0.05$). The area under curve for the score was 0.839 (95% CI 0.763-0.916) for prediction of death within 60 minutes. A score of 4-6 had a sensitivity of 95.88% and a specificity of 69.05% to predict death within 60 minutes after WSLT. In external validation set, the prevalence of these predictors was similar with training sample.

Conclusions: The neurological score may be useful to predict time of death after WLST in neurocritical patients.

Keywords: Neurocritical patients, Cardiac death, Prediction, Score system

INTRODUCTION

Common neurocritical patients are traumatic brain injury (TBI), intracranial hemorrhage, and ischemic stroke.[1] With mortality rates ranging from 30% to 45%, severe traumatic brain injury (Glasgow coma scale≤5) is a leading cause of death.[2] The ability to predict outcome accurately is important for early clinical decision, but is also of specific interest for organ donation after cardiac death (DCD) since these patients are the most common candidates for DCD.[3,4] Successful DCD requires identification of patients who will die within 60 minutes after withdrawal of life-supporting treatment (WLST).[5-7] Available scores used by organ-procurement organizations to estimate the time of death after WLST, such as the University of Wisconsin (UW) criteria, and the United Network for Organ Sharing (UNOS) criteria, are lacking of predictive accuracy because they include little information about the neurological status of the patient before WLST and do not present results in a user friendly fashion.[4,8]

Several studies concerning severe TBI had suggested that, after WLST, some clinical variables, such as corneal reflex, cough reflex and oxygenation index, were associated with death within 60 minutes after extubation.

However, these associations were only confirmed in a small independent cohort.[5,8,9] In this study, we further validated these findings and established a novel model to predict death within 60 minutes after WLST in patients with neurocritical state.

METHODS

Study population and inclusion criteria

In this study, we retrospectively obtained data from neurocritical patients who underwent WLST and died in the Department of Neurosurgery of the First Affiliated Hospital of Sun Yat-sen University between June 2016 and July 2018. The study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. Informed consent was waived by the committee because of the retrospective nature of the study. We enrolled patients in the study if anticipated death was attributable directly to severe TBI. We excluded patients without tracheal intubation or who fulfilled criteria for brain death. Our selected variables are derived from our own findings and the study by Yee et al, Rabinstein et al and Hoffmann et al.[5,9,10] Variables obtained for this study included age, sex, pupil reflexes, pupil size, corneal reflex, cough reflex, motor response to pain and cisterna ambiens in head CT or MRI. Severe TBI was defined as a GCS score of 3.[11,12] We assessed these variables at the last examination before WLST, which occurred after discontinuation of sedation and opiate analgesia. The endpoint for the analysis was death within 60 min of WLST. Coding of all variables was based on the study by Yee et al and Hoffmann et al.[5,10] Our score is a neurologic assessment tool that combines six neurologic parameters to calculate a score from 0 to 10.

Study design

First, univariate and multivariable logistic regression analyses with death within 60 min as a binary outcome variable were used to assess the predictor variables in our training set. The area under the receiver operating characteristic (ROC) curve was estimated as a measure of the ability of the model to discriminate between individuals who died within 60 min of WLST versus those who died after 60 min. Second, the model containing identified predictor variables was refitted in the validation sample. We assessed the performance of the model in terms of discrimination and calibration when applied to our validation data.

Statistical analysis

Statistical analyses were performed using SPSS 22.0 statistical software (SPSS Inc., Chicago, U.S.A.). First, a univariable logistic regression analysis was performed to assess the association between the different predictors and death within 60 minutes after WLST. A multivariable logistic regression analysis was performed, including the variables under investigation. Coefficients of the final model are presented, together with the respective odds ratio (OR) and their corresponding 95% confidence intervals (CI).

The ability of variables to predict death was evaluated using ROC analysis and expressed as the areas under the ROC curve (AUC) with 95% CI. The ROC curve is based on sensitivity and specificity for various cutoff points, and the corresponding AUC varies from 0.5 to 1.0. Non overlapping or only marginally overlapping 95% CIs correspond to statistical significance ($p<0.05$). Presentation of multiple p values from pairwise comparisons was avoided, and statistical significance was mentioned only in selected situations. All tests were two-tailed p values and values of $p<0.05$ were considered statistically significant.

RESULTS

Patient and clinical manifestations

After review of the medical records of all neurocritical patients in our department, 231 patients were included in our study. The baseline characteristics of these patients were summarized in Table 1. In the last neurological examination before WLST, no patient showed brisk pupil reactivity, 194 (84.0%) patients presented anisocoric or bilaterally dilated pupil, 191 (82.7%) patients presented an extensor or no motor response to pain, 181 (78.4%) patients presented an absent corneal reflex, 186 (80.5%) patients presented an absent cough reflex, and 211 (91.3%) patients presented narrowed or absent cisterna ambiens in the last head CT or MRI (Table 1).

Table 1: Baseline characteristics.

Variables	Patients (n=231) N (%)	OR (95%CI)	P value
Age (years) (Mean±SD)	45.21±17.63	0.99 (0.98-1.01)	0.55
Sex (male)	163 (70.6)	0.67 (0.28-1.59)	0.36
Primary diagnosis			
Traumatic head trauma	116 (50.2)	1.24 (0.46-3.39)	0.67
Intracranial haemorrhage	94 (40.7)	1.01 (0.99-1.02)	0.89
Ischemic stroke	8 (3.5)	2.25 (0.25-20.28)	0.47
Active introcrinal tumor	13 (5.6)	2.25 (0.25-20.28)	0.47

Continued.

Variables	Patients (n=231) N (%)	OR (95%CI)	P value
Death			
Sluggish or fixed pupil reflexes	100 (100)		
Anisocoric or bilaterally dilated pupil	194 (83.9)		
Extensor or absent motor response to pain	191 (82.7)		
Absent corneal reflex	181 (78.4)		
Absent cough reflex	186 (80.5)		
Narrowed or absent cisterna ambiens	211 (91.3)		

Data are mean (SD, range) or n (%).

Table 2: Comparison of multivariable associations between predictions and time to death within 60mins from withdrawal of life-sustaining measures.

Predictors		The training set			The validation set		
		Death within 60 minutes N (%)	Odds ratio (95%CI)	P value	Death within 60 minutes N (%)	Odds ratio (95%CI)	P value
Pupil size	Anisocoric pupil	17 (12.2)	3.13 (1.63-15.54)	0.035	14 (15.2)	3.25 (1.12-12.96)	0.034
	Bilaterally dilated pupil	93 (66.9)	4.87 (1.36-17.35)	0.015	60 (65.2)	4.13 (1.51-17.34)	0.022
Absent corneal reflexes		118 (84.8)	4.86 (1.75-33.92)	0.016	80 (86.9)	4.93 (1.53-33.52)	0.012
Absent cough reflex		111 (79.8)	4.43 (1.97-20.21)	0.024	70 (76.1)	4.48 (1.48-20.65)	0.020
Extensor reflexes to pain		69 (49.6)	4.12 (1.01-1.55)	0.026	47 (51.1)	4.64 (1.02-1.56)	0.029
Absent motor reflexes		62 (44.6)	3.82 (1.05-12.32)	0.030	38 (41.3)	3.42 (1.02-12.52)	0.031

Data are n (%) unless otherwise stated.

Mortality and outcomes

In training set, 139 patients were included. In unvariable test, 97 (69.8%) patients died within 60 minutes after WLST. Regarding each component alone, a worsening of the pupil reactivity (5.54, 95%CI 2.24-13.69, p=0.0002) and size (2.62, 95%CI 1.09-6.29, p=0.03), absent corneal reflex (11.32, 95%CI 3.79-33.83, p=0.000), absent cough reflex (12.86, 95%CI 4.83-34.21, p=0.000), narrowed or absent cisterna ambiens (23.33, 95%CI 5.72-95.15, p=0.000) and absent motor response to pain (15.56, 95%CI 2.96-81.86, p=0.001) were associated with death within 60 minutes after WLST. In a multivariable logistic regression, only anisocoric or bilaterally dilated pupil ($p<0.05$), extensor or absent motor response to pain ($p<0.05$), absent cough reflex ($p<0.05$) and absent corneal reflexes ($p<0.05$) were associated with death within 60 minutes after WLST (Table 2).

We created a score to predict the chance of death within 60 minutes of WLST based on the odds ratios for every related variable (the neurological score, Table 3). The probability of death within 60 minutes of WLST increased as the score increased. The ROC was generated to evaluate the performance of the neurological score (N-score) as a predictor for patient death within 60 minutes after WLST. The AUC for the score was 0.83(95% CI 0.763-0.916) for prediction of death within 60 minutes (Figure 1). Compared with a score of 0-3, a score of 4-6 had a sensitivity of 95.9%, a specificity of 69.1%, a positive predictive value of 85.6% and a negative predictive value of 64.3% to predict death within 60 minutes after WSLT. In other words, 93 of 97 (95.9%) patients who died within 60 min had a score of 4 or more (sensitivity) and 29 of 42 (69.1%) of patients who did not die within this interval had a score of 0-3 (specificity) (Table 4). Taking into account the prevalence of death within 60 min in this population, a score of 4 or more translates into a 85.6% probability of death within 60 min (positive predictive value) whereas a score of 0-3 translates into a 64.3% probability of survival beyond 60 min (negative predictive value).

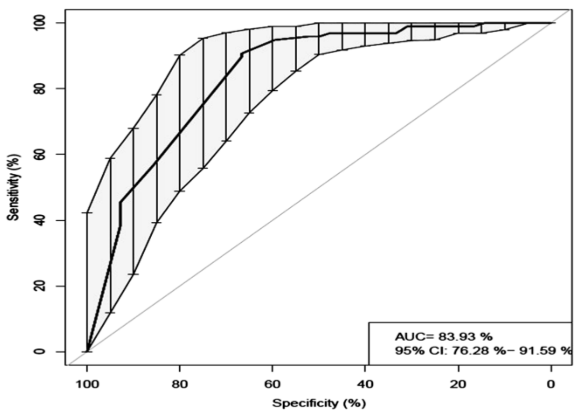

Figure 1: Receiver operating characteristic curve based on a multivariable model for prediction of death within 60 minutes after WLST.

Dashed line shows equivalent sensitivity and 1–specificity.

The performance of the score was validated with set of 92 patients, univariable and multivariable odds ratios of the predictors were very similar between the straining and validation sample (Table 2). In this validation sample, the strongest univariable predictors of death within 60 mins after WLSM were an absent corneal reflex (OR=4.93, 95%CI 1.53-33.52, p=0.012) (Table 2). The prediction of our model showed better discrimination than Yee model with an AUC of 0.75(95% CI 0.63-0.87) (Table 5). The predictors included in the final multivariable model were anisocoric or bilaterally dilated pupil, extensor or absent motor response to pain, absent cough reflex and absent corneal reflexes. The prevalence of these predictors was similar between the training and validation sample (0.811, 95% CI 0.804-0.818). In this cohort, a cut-off score of 4 (scores 4-6 versus 0-3) had a sensitivity of 94.4%, a specificity of 62.1%, a positive predictive value of 88.1%, and a negative predictive value of 79.2% to predict death within 60 min of WSLT (Table 4).

Table 3: The N-score components.

Variables	Findings	Score
Pupil size	Normal	0
	Anisocoric	1
	Bilaterally dilated	2
Corneal reflexes	Present	0
	Absent	1
Cough reflex	Present	0
	Absent	1
Motor response to pain	Normal	0
	Extensor	1
	Absent	2

The N-score is calculated by summing the value of each subscore. Scores are from a minimum of 0 (best neurologic score) for a patient showing brisk reactive normal-sized pupils, a normal motor response, a present cisterna ambiens, a present corneal reflexes and cough reflex to a maximum of 6 (worst neurologic score) for a patient presenting with fixed and bilaterally dilated pupils, no motor response, an absent corneal reflexes and cough reflex.

Table 4: Frequency of death after withdrawal of life-sustaining measures according to donation after cardiac death in patients in a neurocritical state (DCD-N) score in the prospective cohort of 92 patients.

Score	The training set		The validation set	
	Deaths within 60 minutes	**Deaths after 60 minutes**	**Deaths within 60 minutes**	**Deaths after 60 minutes**
	N (%)	**N (%)**	**N (%)**	**N (%)**
0	2 (33.3)	4 (66.7)	0 (0)	1 (100)
1	0 (0)	7 (100)	0 (0)	8 (100)
2	2 (20)	8 (80)	0 (0)	8 (100)
3	0 (0)	10 (62.5)	3 (75)	1 (25)
4	17 (77.3)	5 (22.7)	10 (76.9)	3 (23.1)
5	39 (90.7)	4 (9.3)	31 (88.6)	4 (11.4)
6	37 (90.2)	4 (9.7)	19 (82.6)	4 (17.4)
Overall	97 (66.9)	42 (28.9)	63 (68.5)	29 (31.5)

Data are n (%) unless otherwise stated.

Table 5: Area under the curve and 95% confidence intervals.

	Training set	Validation set
Yee model	0.76 (95% CI 0.64-0.88)	0.73 (95% CI 0.61-0.85)
Our model	0.839 (95% CI 0.763-0.916)	0.811 (95% CI 0.804-0.818)

We adjusted the weight of the variables on the basis of the strength of the associations identified in our study, which was basic on a previously described linear predictor by de Groot et al.[13] The resulting model used the following formula.

Linear predictor=-1.523+1.140 pupil size (anisocoric=1, others=0)+1.582 pupil size (bilaterally dilated=1, others=0)+1.582 cornal reflex (absent=1, normal=0) +1.488 cough reflex (absent=1, normal=0) -2.080 motor response (extensor=1, absent=0) -0.204 motor response (absent=1, other=0).

Probability of death within 60 mins after WLST

Exp (*linear predictor*)/1 + Exp (*linear predictor*). This model equation can be used to calculate the probability of death within 60 mins for individual patients, e.g., for a patient with a present corneal reflex, absent cough reflex, absent motor response, and bilaterally dilated pupil, the linear predictor is 58%.

DISCUSSION

One way to expand the donor pool is by the use of organs from DCD donors for transplantation.[6] Patients with catastrophic, irreversible brain injury who do not meet criteria for brain death are the most frequent candidates for DCD.[4,6,8] The success of DCD relies on identification of patients who are most likely to die within 60 minutes after WLST. Prolongation of the withdrawal phase undoubtedly increases the warm ischemia time (WIT) of organs, which would compromise organ function.[7,14] Currently, donation after cardiac death protocols are sometimes underused because of concern that the potential donor will not die within the period of time compatible with an acceptable duration of warm ischaemia.[14] Our score might be useful to identify the best candidates for donation among patients in a neurocritical state, thus reducing the chances of unsuccessful activation of retrieval teams and improved allocation of resources.

A large variation has been reported in the interval between WLST and death, from 1 minute to 3.8 days (our data is form 8 minutes to 2.3 days), and the majority of patients died within the first hour after WLST.[4,9,14] In a prospective multicenter study, of the 211 potential donors, 134 (63%) died within 30 minutes after WLST, 161 (76%) patients died within 60 minutes, and 175 (83%) died within 2 hours and became organ donors, the median time to death after WLST was 20 minutes.[14] The predictive quality of the existed models, such as UW criteria or UNOS criteria, for death within 60 minutes was higher than the predictive quality of the intensivist, but still too low to be used in clinical practice.[5] Because severe brain injury (neurocritical state) is the most common cause of death in potentially suitable DCD donors, a good model should be especially applicable to patients in neurocritical state.[4] In our study, we validated the predictive value of a small set of variables that can be used to identify such patients confidently. Furthermore, we present the N-score that can be used at the bedside to quantify the likelihood of death within the time required in most DCD protocols.

There are only several studies on the prediction of death after WLST in neurocritical patients. In a cohort of mixed intensive care patients, the use of pupil reactivity, size, and a modified Glasgow coma scale (GCS) motor component were associated with a shorter time to death.[10] A recent study identified absent corneal reflexes, absent cough reflex, extensor or absent motor responses as the most important variables associated with early death in potential DCD donors.[5] The variables included in our study were identified after a comprehensive analysis of various neurological and non-neurological parameters in several cohorts of patients in neurocritical state.[5,9] In our study, the multivariable analysis showed that absent cough reflexes, anisocoric or bilaterally dilated pupil, absent corneal reflexes and extensor or absent motor response to pain were independently associated with death within 60 minutes after WLST.

Prediction of time to death after WLST on the basis of clinical impression has proven inaccurate.[5] In a recent prospective, multicenter, observational study of potential DCD donors, the clinical judgment of the treating intensive-care doctors had a fairly high sensitivity (73%) but a low specificity (56%) to predict death within 60 minutes.[10] The present scoring systems to estimate early death after WLST (UNOS and UW criteria) incorporate neurological information only at the level of consciousness, which is not a reliable predictor of early death in patients in neurocritical state.[4,8] Moreover, these calculations require disconnection from mechanical ventilation for 10 minutes. Our scoring system has been specifically designed to be used in neurological patients with severe, irreversible brain injury and it can be fully assessed while the potential donor remains supported by mechanical ventilation. In our retrospective study, only a few cases concluded the information that needed in the University of Wisconsin criteria and the United Network for Organ Sharing criteria. And in the similar studies, few had made the comparison with the University of Wisconsin criteria and the United Network for Organ Sharing criteria. Although the population in Rabinstein and colleagues' study was small and heterogenous and their scoring system was not compared with the established Wisconsin criteria, their analysis provides an encouraging step in refining the prediction of cardiac arrest within 1-2 h of WLST and thus selection of patients for DCD.[5] In the meantime, reliance on the Wisconsin scoring system or that developed by Rabinstein and colleagues would be imprudent. Furthermore, the information used to calculate the N-score is usually available as part of the routine medical care of these patients. Importantly, our score has the advantage of simplicity and can be used at the bed-side.

The retrospective nature represents the limitations to our study. We retrospectively collected data for only those variables that have been identified predictive of death within 60 minutes of WLST in several previous studies.[1,5,9] We regarded this approach as sufficient because these studies consisted of a comprehensive exploratory analysis of neurological and systemic variables. Furthermore, the validity of the predictive value of these variables had been subsequently confirmed in a different cohort of patients with severe, irreversible brain injury.[13] Nevertheless, other variables not included in our predictive score might also influence the likelihood of early death after WLST, such as the residual effect from sedatives and opiates might have had a confounding role.[13,15] Although the proportion of the exact doses of the used sedation and analgesic drugs was not available for the current analysis, their use was not significantly associated with early death, which supports the opinion that their use does not interfere with the dead-donor rule perse.[15-17] Finally, due to insufficient data, the N-score has not been compared with other predictive criteria.

CONCLUSION

The N-score may be used to predict time of death after WLST in neurocritical patients. However, it needs to be further tested in a prospective study.

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