Factors influencing time to death after withdrawal of life support in neurocritical patients

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ABSTRACT

Objective: Improving our ability to predict the time of death after withdrawal of life-sustaining measures (WLSM) could have a significant impact on rates of organ donation after cardiac death and allocation of appropriate medical resources. We sought to determine which pre-WLSM clinical factors were associated with earlier time to death in patients with catastrophic neurologic disease.

Methods: We retrospectively analyzed all patients who underwent WLSM from 2002 to 2008 in a neurologic intensive care unit. Individuals who died within 60 minutes were compared to those who died beyond this time from the point of WLSM. Patients declared brain dead or not intubated and cases with insufficient data were excluded. Demographic, clinical, laboratory, and radiographic data were reviewed. Statistical analysis was based on multivariate logistic regression.

Results: A total of 149 comatose patients satisfied our inclusion criteria. A total of 75 patients had cardiac arrest in <60 minutes; 57% were male and 52% were older than 66 years. Ischemic stroke (30%) and intraparenchymal hemorrhage (52%) were the most frequent diagnoses. Absent corneal (odds ratio [OR] = 4.24, 95% confidence interval [CI] 1.57–11.5, $p = 0.005$) and cough reflexes (OR = 4.46, 95% CI 1.93–10.3, $p = 0.0005$), extensor or absent motor response (OR = 2.83, 95% CI 1.01–7.91, $p = 0.048$), and an oxygenation index greater than 4.2 (OR = 3.36, 95% CI 1.33–8.5, $p = 0.011$) were associated with earlier death.

Conclusions: Specific neurologic signs and respiratory measurements are associated with earlier death after withdrawal of life-sustaining measures in the neurologic intensive care unit. This subset of comatose patients with irreversible neurologic injury may be suitable for organ donation after cardiac death protocols. These attributes need validation in a prospective data set.
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GLOSSARY

A-a = alveolar-arterial; **ABG** = arterial blood gas; **CI** = confidence interval; **DCD** = organ donation after cardiac death; **FOUR** = Full Outline of Unresponsive Score; **NICU** = neurologic intensive care units; **OI** = oxygenation index; **OR** = odds ratio; **SAH** = subarachnoid hemorrhage; **WLSM** = withdrawal of life-sustaining measures.

Patients cared for in neurologic intensive care units (NICU) are often admitted with devastating neurologic conditions. NICU patients are frequently candidates for donation after cardiac death (DCD) protocols because withdrawal of life-sustaining measures (WLSM) is prevalent[1] and other organs can be healthy. However, after WLSM, the time to death is often uncertain.

Algorithms exist for predicting time to death after WLSM; however, these models either require temporary disconnection of ventilatory support[2] or include minimal neurologic and cranial imaging findings,[3] limiting their applicability among critically ill neurologic patients being considered for DCD protocols. Sixty minutes is the time used for consideration of non-heart-beating organ donation.[4] Death beyond 1 hour often leads to donor ineligibility because of potential organ compromise, occurring in up to 20% of cases.[4,5] To date, no study has been published including comprehensive neurologic clinical data in a pre-WLSM model without temporarily halting supportive care.

Supplemental data at www.neurology.org

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The aim of the current study was to perform an exploratory analysis to determine which pre-WLSM clinical factors are associated with earlier time of death in patients with catastrophic neurologic disease. Providing an accurate, reliable, and simplified prediction tool before WLSM could increase the organ donation rate by DCD protocol and optimize medical resource allocation.

METHODS We retrospectively analyzed all patients admitted to our NICU who underwent WLMS over a 6-year period (2002–2008). Time to death was recorded from the time of WLSM (i.e., extubation). Patients who were declared brain dead, had insufficient available data (e.g., absent arterial blood gas), or had not been intubated were excluded.

Our 2 study groups consisted of those who died within the first 60 minutes compared with those who died beyond this time after WLSM. Patient demographic, clinical, radiographic, and laboratory data were obtained. Disease of any organ system was considered recent if diagnosed within 4 weeks of WLSM.

Standard protocol approvals, registrations, and patient consent policies were reviewed and approved by the Institutional Review Board.

Demographics. Age, gender, and race were recorded (table e-1 on the *Neurology*® Web site at www.neurology.org).

Neurologic examination, disease type, and cranial imaging. The neurologic examination was detailed by all major components of the Full Outline of Unresponsive Score (FOUR)[6] (table e-1), presence of an abnormal vestibulo-ocular reflex, and eye skew deviation. When available, intracranial pressure measurements were recorded. Levels greater than 20 cm H_2O were considered abnormal.

The 2 major disease types were intracranial infarction or hemorrhage. Table e-1 outlines the lesion locations, hemorrhage classification, imaging abnormalities, and neurologic conditions other than intracranial stroke or hemorrhage. Patients with varying combinations of hemorrhage were noted (e.g., traumatic subdural and subarachnoid hemorrhage) (SAH). The extent of SAH present was categorized by using the modified Fisher Scale (grades 0–4)[7] based on the latest available head CT or MRI closest to the time of WLSM.

Cardiovascular, gastrointestinal, renal, and pulmonary data. Definitions and categorization of organ-related diseases are outlined in table e-1.

Respiratory physiologic calculations. Specific respiratory physiologic data were calculated (table e-2) from the immediate last measurements before WLSM. These include partial pressure of arterial oxygenation/fraction of inspired oxygen (PaO_2/FiO_2 or PF ratio), arterial blood gas (ABG) abnormalities (table e-1), alveolar-arterial (A-a) oxygenation gradient, and oxygenation index (OI).

Metabolic/abnormal sodium concentration. Conditions included diabetes mellitus, drug intoxication or overdose, and an abnormal serum sodium concentration (table e-1).

Coagulopathy/hematologic. Coagulopathy is defined in table e-1. Neutropenia (fewer than 3,000 white blood cell count per microliter of blood) and hematologic cell line dyscrasias from any cause were documented. Marrow cell lineage dyscrasias included any form of leukemia, lymphoma, myeloma, or myelodysplastic syndrome.

Physiologic data. Specific vital signs were evaluated and are outlined in table e-1.

Other. Recent sepsis was defined by clinical features consistent with the systemic inflammatory response syndrome secondary to a defined bloodstream infection. Patients admitted to the NICU secondary to trauma (e.g., head or spine injury), cardiac or respiratory arrest, and malignancy were recorded.

Statistical analysis. Descriptive summaries were presented as frequencies and percentages or median and ranges as appropriate. Organ-specific diseases (e.g., myocardial infarction and congestive heart failure) were grouped into single systems categories (e.g., cardiovascular disease) applied to the univariate analysis. Table e-1 outlines the organ-specific categorization applied toward univariate analysis.

Univariate assessment of risk factors and multivariate analysis were performed using logistic regression, where death within 1 hour (yes/no) was used as an outcome. Variables having a p value of ≤ 0.15 in univariate analysis were considered candidates in the multivariate logistic regression model building.[8] A sample size of 149 (75 deaths within 1 hour and 74 beyond 1 hour) allowed us to consider up to 6 variables in multivariate models. This conservative statistical approach allowed us to increase statistical power and estimate precision during model building. In the event more than one possible multivariate predictive model was identified, subsequent analyses were performed to determine which combination would provide the most accurate predictive model by 1) estimating the area under the curve (when variables were not common between the 2 models) and 2) comparing 2 nested models using partial likelihood tests. All the tests were 2-sided and a p value <0.05 was considered significant. Analysis was performed using SAS version 9 (SAS Inc., Cary, NC).

RESULTS A total of 149 patients satisfied the inclusion criteria. Seventy-five patients died within the first 60 minutes of WLSM. Of these 75 patients, 57% were male and 52% were older than 66 years. Eighty-four percent of the total patient population was Caucasian. Of those who died within the first hour, 84% died within the first 30 minutes.

Neurologic. ***Stroke and intracranial hemorrhage.*** The neurologic diseases most frequently encountered in our cohort were ischemic stroke in 30% and intraparenchymal hemorrhage in 52%. The majority (55%) had subcortical lesions. Twenty-nine percent of patients had localized cortical disease. A cerebellar process was less frequently encountered; however, of the 23 patients that developed a cerebellar infarct or hemorrhage, over half died in less than 1 hour after WLSM. Similarly, 15 of the 29 patients with brainstem stroke or hemorrhage also died within this time period. Of the 39 patients with posterior fossa lesions, 87% of the 23 patients who died within 60 minutes of WLSM did so 30 minutes after extubation.

Forty-four (56%) of the 78 cases with intraparenchymal hemorrhage died in less than 1 hour after WLSM; 86% died within 30 minutes. Forty-one

percent of these patients who died within the first 60 minutes had a coagulopathic disorder. Subdural hematomas were seen in 24 patients and half died in less than 1 hour. Fifty-eight percent of subdural hematoma cases were related to trauma. The majority of patients diagnosed with primary intraventricular hemorrhage (4/5) died within 60 minutes.

Neurologic examination. Patients who died in less than 60 minutes after WLSM had more frequent and severe brainstem deficits. Eighty-three percent had absent pupillary light responses compared with only 47% of those who died beyond 1 hour. Corresponding percentages were 87% vs 43% for absent corneal response and 64% vs 22% for absent cough reflex. Seventy-six percent were apneic compared with only 42% in the group that died beyond 60 minutes. Eighty-five percent of patients dying within 1 hour had either extensor posturing or an absent motor response to painful stimuli, a finding only present in 46% of patients who died later. Very low FOUR scores (i.e., $\leq$4) were seen in 85% of those who died early vs 45% in the comparative group. There were insufficient data regarding the presence or absence of abnormal eye positioning or intracranial pressure to include these variables in the final analysis.

Cranial imaging. A total of 148 patients had brain imaging available for review (1 patient died secondary to complications related to spinal cord abscess). The presence of midline shift was seen in 77 patients and intraparenchymal hemorrhage was the predominant etiology (73% of cases). Fifty-one percent of patients with midline shift died within the first 60 minutes after WLSM. The average degree of shift present was 13 mm (3 mm to 129 mm) among all cases. Fifty-seven patients had basilar cisternal effacement and 68% of these patients died under 1 hour. In patients who had 2 consecutive brain scans available for review, 63 cases showed progression of disease (e.g., hemorrhage); less than half (44%) of patients with progression died within 60 minutes.

Cardiovascular. Eight patients were successfully resuscitated from a cardiopulmonary arrest. The majority of these patients (6 of 8) died beyond 60 minutes after WLSM.

Pulmonary. Forty-seven percent of 19 patients with a pulmonary infection, 47% of 15 patients with chronic pulmonary obstructive disease, 50% of 6 patients with pulmonary embolism, and 60% of 5 patients with acute respiratory distress syndrome died in less than 60 minutes after WLSM. Two patients developed alveolar hemorrhage and died within 30 minutes of WLSM.

The OI was calculated for all patients (OI range = 1–41; median = 3.3). The index was dichotomized such that patients with values greater than 4.2 (upper tercile) were considered high risk for early death after WLSM. The average OI for those who died in less than 60 minutes after WLSM was 6.1 vs 4 in those dying beyond this time.

The mean PF ratio for all subjects was 269. Forty patients had evidence of acute respiratory distress syndrome (PF ratio $\leq$200). Thirty-nine percent of the 75 individuals who died within 60 minutes had ratios lower than 200. The average PF value in this group was 250. Of the 74 individuals who died beyond 60 minutes, only 15% had a PF ratio under 200. The average ratio for all patients dying more than 1 hour after WLSM was 287. The distribution of PF ratios and corresponding OI is shown in figure e-1.

Abnormal ABG variables were evaluated for all patients. Few (7 patients) had a pH less than 7.30; however, 5 of these 7 died under 60 minutes after WLSM. Nearly 20% of all patients (29 of 149) had a pH greater than 7.50 and 69% of these alkalotic patients died within 60 minutes. Eight of the 14 hypercapnic patients (Pa_{CO_2} >45 mm Hg) and 11 of the 16 hypoxemic patients (Pa_{O_2} <80 mm Hg) died within 60 minutes of WLSM.

The majority of patients (121 of 149; 81%) had an A-a gradient greater than 100 mm Hg. Sixty-five patients with an abnormal gradient died within 60 minutes of WLSM; 86% died within the first 30 minutes.

Gastrointestinal. Seven of the 8 patients who developed recent hepatic failure died in less than 60 minutes.

Renal and metabolic. Eighty-one percent of patients (25 of 31) who developed acute renal failure died in less than 1 hour of WLSM. Sixty-two percent of patients (26 of 42) found to have serum sodium concentration abnormalities died within 1 hour.

Other clinical conditions. Six of the 7 patients diagnosed with sepsis within 4 weeks of WLSM died in less than 60 minutes after extubation.

Twenty-four patients were admitted due to severe head trauma. Eleven (46%) of them died within 60 minutes of WLSM. Two-thirds of the patients had a FOUR score $\leq$4. Eighty-eight percent had intracranial hemorrhage and the majority of patients had evidence of poor oxygenation (16 of 24 had a PF ratio <300; 23 of 24 had an A-a gradient >100 mm Hg).

Physiologic measurements. ***Systemic hypotension.*** Twelve of 14 hypotensive patients not treated with vasopressor agents and 12 of 15 hypotensive patients

Table 1 Univariate analysis results of demographic, clinical, laboratory, and radiographic variables in patients dying less than 60 minutes from withdrawal of life support

Variable	Death under 60 minutes, odds ratio (95% CI)	*p* Value
Demographics		
Gender	1.34 (0.704–2.56)	0.37
Age (years; reference <46)	0.992 (0.678–1.45)	0.97
Age category 2 (46–65)		
Age category 3 (66–85)		
Age category 4 (>86)		
Race[a]	1.02 (0.424–2.43)	0.97
Neurologic examination		
Pupillary light reflex	5.32 (2.51–11.2)	<0.0001[b]
Corneal reflex	9.01 (4.02–20.4)	<0.0001[b]
Cough reflex	7.00 (3.34–14.7)	<0.0001[b]
Breaths at ventilatory set rate/apneic	4.08 (2.04–8.20)	<0.0001[b]
Motor response (extensor or absent)	6.67 (3.04–14.7)	<0.0001[b]
FOUR score <4 (reference value >4)	7.23 (3.29–15.9)	<0.0001[b]
Cranial imaging		
Intracranial disease (stroke/hemorrhage)	1.35 (0.47–3.82)	0.58
Stroke/hemorrhage location—supratentorial	1.05 (0.743–1.48)	0.79
Stroke/hemorrhage location—infratentorial	1.26 (0.491–3.22)	0.63
Greater than 2 lesion locations (stroke/hemorrhage)	2 (1.03–3.92)	0.039[b]
Effacement of basilar cisterns	3.37 (1.68–6.78)	0.0006[b]
Imaging evidence of progression of disease	1.03 (0.54–1.95)	0.94
Other neurologic disease	0.823 (0.423–1.60)	0.57
Cardiovascular disease	0.668 (0.35–1.27)	0.22
Pulmonary disease		
Presence of disease	0.823 (0.423–1.60)	0.57
PF ratio <200	1.82 (1.19–2.78)	0.006[b]
PF ratio 201–300	1.72 (0.879–3.38)	0.11
PF value	1.00 (1.00–1.01)	0.043[b]
Oxygenation index	1.10 (1.00–1.22)	0.041[b]
Abnormal blood gas pH	1.63 (0.807–3.29)	0.17
Abnormal arterial blood gas	2.09 (1.06–4.13)	0.033[b]
A-a gradient >100 mm Hg	2.09 (0.892–4.90)	0.09
Gastrointestinal disease	3.33 (1.02–10.9)	0.046[b]
Renal disease	3.49 (1.64–7.42)	0.0011[b]
Serum sodium abnormality (reference 135–145 mmol/L)	2.00 (1.05–3.81)	0.034[b]
Sodium (120–134 mmol/L)		
Sodium (>145 mmol/L)		
Coagulopathy	2.86 (1.29–6.37)	0.01[b]
Hypotension	6.49 (2.32–18.2)	0.0004[b]
Abnormal temperature	0.621 (0.32–1.21)	0.16

Abbreviations: A-a gradient = alveolar-arterial oxygenation gradient; CI = confidence interval; FOUR = full outline of unresponsiveness scale score[6]; PF = partial pressure of arterial oxygenation/fraction of inspired oxygen.
[a]Race was dichotomized as Caucasian and non-Caucasian.
[b]Significant.

treated with vasopressors died within 60 minutes of WLSM.

Heart rate. Twenty-nine patients had a heart rate greater than 100 beats per minute prior to WLSM. Fifteen of the 29 patients died within 60 minutes of WLSM. Seventy-two percent (21 of 29 patients) also had a PF ratio lower than 300 and 83% (24 of 29 patients) had an A-a gradient greater than 100 mm Hg.

Abnormal temperature. Fifty-three patients had fever (≥38.3°C). Forty percent died within 60 minutes of WLSM. Four of the 5 hypothermic patients died within the first hour. All patients with a temperature less than 35°C had large A-a gradients and FOUR sumscore ≤4.

Univariate analysis. Significant associations (p value <0.05) on univariate analysis are listed in table 1. Factors associated with death within 60 minutes of WLSM were components of the neurologic examination, cranial imaging abnormalities, abnormal respiratory measurements, renal disease, coagulopathy, gastrointestinal disease, abnormal serum sodium levels, and hypotension.

Multivariate analysis. The results of the multivariate logistic regression for patients dying in less than 60 minutes are shown in table 2. Absent corneal reflex (OR = 4.24, 95% CI 1.57–11.5; $p = 0.0045$), absent cough reflex (OR = 4.47, 95% CI 1.93–10.3; $p = 0.0005$), extensor or absent motor response (OR = 2.83, 95% CI 1.01–7.91; $p = 0.048$), and OI (OR = 3.36, 95% CI 1.33–8.50; $p = 0.011$) were independently associated with death within 60 minutes of WLSM. Based on the number and specific combination of variables present, the probability of death within 1 hour could be estimated (figure 1). For example, the probability of earlier death in the presence of a single variable ranged from 65% (e.g., abnormal motor response) to 76% (e.g., absent cough reflex) compared to 93% in patients when all 4 variables were present.

DISCUSSION Donation after cardiac death predictive models are available to assist in prognosticating timing of death after WLSM, but none of these models was designed for neurocritical patients or evaluated in this population. One of these tools—the University of Wisconsin DCD evaluation Tool—is used by UNOS.[3] Unfortunately, it is not certain whether these criteria assessed in this model are as relevant in critical neurologic patients. This tool has demonstrated good accuracy at predicting earlier death after WLSM[2]; however, cessation of mechanical ventilation for 10 minutes is required for its application. During this time period, respiratory measurements (respiratory rate, tidal volume, nega-

Table 2 Multivariate analysis of factors associated with time to death within 60 minutes from withdrawal of life-sustaining measures

Variable	Patients dying <60 minutes (total n = 75), n (%)	Patients dying >60 minutes (total n = 74), n (%)	Odds ratio (95% CI)	*p* Value[a]
Absent corneal reflex	65 (87)	32 (43)	4.24 (1.57–11.5)	0.0045
Absent cough reflex	48 (64)	15 (20)	4.47 (1.93–10.3)	0.0005
Extensor/absent motor response	64 (85)	34 (46)	2.83 (1.01–7.91)	0.048
Oxygenation index >4.2	34 (45)	17 (23)	3.36 (1.33–8.50)	0.0105

Abbreviation: CI = confidence interval.
[a]*p* Value was significant if <0.05.

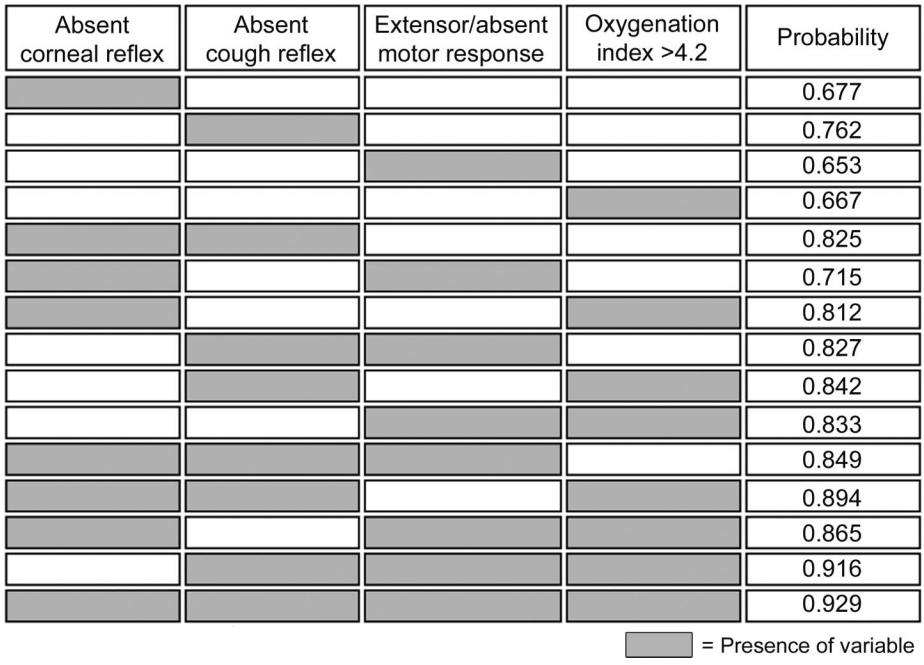
tive inspiratory force, oxygenation) are recorded and applied to a scoring system to predict timing of death after WLSM. The Wisconsin criteria do not include variables from neurologic examination.

Our goal was to identify which pre-WLSM clinical factors were associated with earlier death in the NICU population. We analyzed detailed neurologic data germane to severely injured neurologic patients. We also collected extensive respiratory data and included the use of several simple calculations to evaluate oxygenation and ventilatory status: 1) A-a gradient, 2) PF ratio, and 3) oxygenation index.

We identified 4 clinical variables that were independently associated with death within 60 minutes of WLSM: absent corneal or cough reflex, presence of an extensor motor response or absence of motor response, and OI greater than 4.2. The association with earlier death increased with the presence of each additional variable. The presence of these abnormal neurologic signs suggests potentially severe irreversible brainstem dysfunction regardless of etiology. Combining these variables into a predictive model may allow accurate identification of potential candidates for DCD in the NICU without requiring temporary cessation of ventilatory support with its potential risk for acute irreversible organ compromise.

Neurologically devastated individuals frequently have compromised respiratory function. The OI is useful as both a continuous[9] and static variable when assessing the cost of oxygenation at the expense of lung function (e.g., mean airway pressure). Others have demonstrated that an elevated OI is an independent risk factor for mortality in patients with ARDS.[10] The PF ratio and A-a gradient are simple bedside tools that quickly allow estimates of oxygen exchange.[11] The PF ratio value is frequently used to determine the severity of acute lung injury and by definition aids in differentiating acute lung injury from ARDS.[12] In our study, both a PF ratio less than 200 and abnormal ABG, but not abnormal A-a gradient, were

Figure 1 Probability of death within 60 minutes after cessation of life-sustaining therapy



associated with death within 1 hour of WLSM. However, neither reached significance in the multivariate analyses. Although the PF ratio can compare arterial oxygenation across varying Fio_2 levels and is simple to obtain, it does not take into account dynamic changes in lung function related to varying grades of end airway pressure (i.e., PEEP). This may explain why the OI was more strongly associated with time to death after WLSM in our population.

Basilar cistern effacement and 2 or more intracranial lesions on imaging were associated with earlier death after WLSM; however, these variables failed to reach significance in the multivariate analysis. Radiologic data in isolation may be less reliable at predicting outcome than clinical signs; neurologic examination abnormalities directly reflect nervous system dysfunction. The presence of an abnormal pupillary light response and apnea were also associated with earlier time to death only in the univariate analyses. Dysfunction localized to structures at or above the mesencephalon may still leave a fully functioning brainstem caudally and allow for spontaneous breathing to occur. Alternatively, destruction of specific respiratory nuclei within the medulla may still allow intact neurologic functioning rostrally in a mechanically ventilated patient.

Our study has several limitations. As is the case with all retrospective studies, an inherent bias exists when reviewing medical records. Subjectivity when documenting clinical examination features may also lead to inaccuracy; however, there may be some reliable consistency as all patients were cared for in a single NICU. Collected clinical data from the time nearest to WLSM varied from minutes to hours (e.g., neurologic examination may have changed prior to WLSM). Moreover, there may have been imprecise timing of extubation (time zero) between 0 and 15 minutes due to the nature of the respiratory measurement recording software. We included patients with malignancies and systemic infections in our cohort; however, these factors often serve as exclusion criteria for organ donor candidacy. Finally, analyzing A-a gradients as a continuous rather than a dichotomized variable could have increased its predictive value.

Improving our ability to predict the time of death after WLSM may have a significant impact on improving rates of organ donation after cardiac death and optimizing appropriate allocation of medical resources. Having a simple predictive tool pertinent to patients with critical brain disease would be valuable to consulting neurologists and neurointensivists who are frequently asked to prognosticate the time to death after WLSM in potential candidates for DCD. The simple variables reported in this study may constitute the basis to develop such a predictive model that would need to be validated prospectively.

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DISCLOSURE

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