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Donors After Cardiac Death: Validation of Identification Criteria (DVIC) Study for Predictors of Rapid Death

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Donation after cardiac death (DCD) is uncommon in part because clinicians cannot prospectively identify patients who are likely to die within 60 min of withdrawal of life-sustaining treatments (LST). UNOS criteria exist but have not been validated. Consecutive patients electively withdrawn from LST at five university-affiliated hospitals were prospectively enrolled. Demographic and treatment characteristics were collected. Chi-square was used to determine risk for death within 60 min and validate the UNOS criteria. A total of 533 patients were enrolled. A total of 28 were excluded from this report due to age $<$18 years or failure to include time of death. Of 505 (95%) patients, 227 (45%) died within 60 min, 134 (27%) in 1–6 h and 144 (29%) $>$6 h after withdrawal of LST. A total of 29%, 52%, 65% and 82% of patients with 0,1,2 and 3 UNOS DCD criteria, respectively, died within 60 min of withdrawal of LST. The data validate the UNOS criteria. Patients with no criteria might be excluded from consideration for DCD. Those with more than one criterion are reasonable candidates, while those with a single criterion should be considered if a 50% failure rate for DCD is acceptable.

Key words: Donation after cardiac death, non-heartbeating organ donation, organ donation, withdrawal of life-sustaining treatment

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Introduction

Even though 98% of deaths are determined using cardiac criteria (1), organ donation following cardiac determination of death remains uncommon. In 2002, only 169 (0.0069% of all cardiac deaths) were donors after cardiac death (DCD) (2). Because warm ischemia impairs organ function (3), patients who die more than 60 min after forgoing life-sustaining treatment (LST) are regularly deemed unsuitable for DCD. Organs from DCD generally function nearly as well as those from brain-dead donors, and so are worth the effort and expenditure (4,5). One difficulty in 'identifying' the DCD candidate has been the lack of reliable criteria for predicting death within 60 min of withdrawal of LST. A United Network for Organ Sharing (UNOS) DCD consensus committee developed such criteria (Table 5) based on expert opinion and scant data. The criteria have not been validated as yet, and their utility is therefore suspect.

The objective of this study was to obtain key clinical observational data from patients having LST withdrawn in intensive care units (ICU). We tested the hypothesis that the UNOS criteria predict death within 60 min after withdrawal of LST. We also intended to identify other candidate criteria that may be better predictors. This information will be helpful for clinicians at the bedside and researchers in determining an individual's potential for DCD as well as making national estimates for the process.

Methods

Design and setting

The Donors after Cardiac Death: validating identification criteria (DVIC) study is a prospective cohort study of consecutive patients electively withdrawn from LST at five academic medical centers: The University of Pittsburgh Medical Center (UPMC) Presbyterian Hospital; UPMC Shadyside Hospital; Children's Hospital of Pittsburgh; Case Western Reserve University Hospital in Cleveland, Ohio and University of Cincinnati Hospital. The Epidemiology Data Center (EDC) at the University of Pittsburgh was responsible for assisting with study design, database management and statistical analysis.

Data collection

Data extractors collected clinical data from consecutive patients who had withdrawal of LST in the ICU. The vast majority of data was collected concurrently. For cases that occurred without a data collector present, the data was collected retrospectively within 24 h from the medical record and from personal contact with the individuals who had cared for the patient during the withdrawal process. The physiologic variables collected were those present immediately before withdrawal of LST began. Data forms were de-identified at each institution prior to transmission to an EDC database to ensure patient confidentiality. 'We defined circulatory failure as the requirement for pressor or inotropic medications, hepatic failure from physician diagnoses, and renal failure as anuria or requirement for dialysis'.

Outcome measures

The primary outcome for this analysis is death within 60 min of removal of LST.

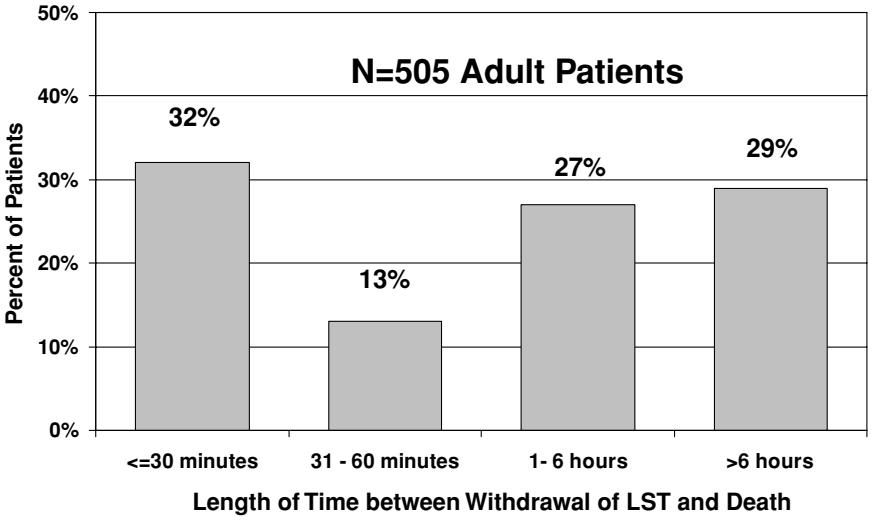

Figure 1: The distribution of time between the initiation of withdrawal of life-sustaining treatment and death. The percent of patients in each time category is shown.

Target populations

Consecutive patients who had LST withdrawn in ICU at the five institutions were included. We report only the results of patients >18 years because the UNOS criteria are for adults. The study subjects did not have to meet OPO criteria for potential organ donation because OPO's criteria for 'viable and transplantable' organs vary between sites, and change over time. A posthoc analysis was performed on subgroup of 'desirable donor candidates' (age <60, creatinine <2 and no overwhelming sepsis).

Human subjects requirements

IRB approval was obtained at each participating institution.

Statistical methods

For descriptive data, we determined proportions for categorical variables, and medians and interquartile ranges for continuous variables. The relative risk (RR) of death in <60 min for each variable was computed. For categorical variables, the risk of the death within 60 min is assessed for patients with the specified characteristic relative to those without the specified characteristic. Chi-square statistics were used to test the significance of the association for categorical variables; continuous variables are categorized by accepted clinical thresholds, and Mantel-Haenszel chi-square statistics were used to test the trend between each ordered categorical variable and death outcome.

Nonparametric Classification and Regression Tree analyses (CART® Salford systems, version 5) were used to define potential decision rules for predicting death within 60 min. (Positive predictive value indicates death will occur within 60 min.) Two models were created. One model includes only predictor variables that depend on patient characteristics at the time of withdrawal of LST (for example, Glasgow coma score [GCS]), while the other model includes both patient characteristics at the time of withdrawal of LST as well as variables that describe the withdrawal process (for example 'all interventions withdrawn simultaneously'). 'Trees' were constructed and were restricted to a positive predictive value of $\geq$0.60. The CART models were evaluated with respect to sensitivity, specificity, positive predictive value and negative predictive value.

Logistic regression was used to parametrically estimate the probability of death within 60 min using factors identified by the CART analysis and factors identified by stepwise regression using an entry threshold of p-value <0.05. Estimated odds ratios and 95% confidence intervals for each factor are reported. For all of the logistic regression models, goodness of fit was assessed with the Pearson chi-square statistic or the Hosmer-Lemeshow statistic depending on the number of covariate patterns in the model, and model discrimination was assessed by the area under the ROC curve (c-statistic).

Results

Between September 1, 2003, and February 28, 2005, we enrolled 533 consecutive patients[i] who underwent withdrawal of LST in the ICU. Time of death was not available for 9 patients and another 19 patients were under the age of 18. These 28 (5.3%) were excluded. A total of 505 adult patients comprise the sample analyzed and reported herein.

Death occurred within 60 min of withdrawal of LST in 227 (45%) patients. Six (1.2%) patients were discharged from the hospital alive. The median time to death is 75.5 min (inter-quartile range 23–412 min). The distribution of time between withdrawal of LST and death is presented in Figure 1. A total of 95 patients were 'desirable donor candidates', and 43 (45%) of these died within 60 min.

Patient demographic characteristics are not predictive of death within 60 min (Table 1). Among the disease process variables, only central nervous system failure, circulatory failure and overwhelming infection are significantly associated with increased risk of death within 60 min. Four physiologic measures (Respiratory rate $\leq$10, heart rate <60, systolic blood pressure (BP) <85 and GCS = 3) and three ventilatory characteristics (FiO_2 >0.80, peak inspiratory pressure (PIP) >35 and SaO_2/FiO_2 <196) at the time of

[i] Patient enrollment was briefly interrupted at UPMC P, UPMC S, and CHP from November 14, 2003, to January 20, 2004, due to IRB renewal delay. Deaths during that time frame were excluded. Consecutive patient enrollment resumed on January 20, 2004.

Table 1: Demographic and disease process characteristics for patients withdrawn from life-sustaining treatments

Characteristics at time of withdrawal of life-sustaining treatments	N (%) or median (25th and 75th percentile) n = 505 patients	Association with death ≤60 min	
		Rel. risk+	p-Value
Demographics			
Male	261 (52%)	0.95	NS
Age (years)	67 (54, 77)		
<60 years	171 (34%)	1.00	NS
60–70 years	117 (23%)	1.03	
>70 years	217 (43%)	0.87	
Race			
White	389 (77%)	1.00	NS
Black	107 (21%)	1.08*	
Other race	6 (1%)		
Disease processes			
Central nervous system failure	279 (55%)	1.43	0.001
Status postcardiac arrest	116 (23%)	1.15	NS
Circulatory failure	244 (49%)	1.72	0.001
Respiratory failure	486 (96%)	1.64	NS
Renal failure	152 (30%)	1.01	NS
Hepatic failure	56 (11%)	0.99	NS
Overwhelming infection	107 (21%)	1.28	0.028
Hemorrhage and shock	42 (8%)	0.83	NS

+Rate of death within 60 min for the entire sample of n = 505 patients is 45%.
*RR of death within 60 min for Black or other race versus White race.

withdrawal are strongly associated with death within 60 min (Tables 2 and 3). Finally, the use of life-sustaining medications including vasopressors, and neuromuscular blockers are powerfully associated with higher rates of death within 60 min, while use of comfort medications such as opioids and benzodiazepines prior to withdrawal of LST is not (Table 4).

The prevalence of each UNOS criterion is presented in Table 5. Unadjusted RRs of death within 60 min of withdrawal of LST are provided for the individual UNOS criterion and for the number of UNOS criteria fulfilled. Only one or two patients fulfill four of the UNOS criteria (LVAD, right ventricular assist device [RVAD], veno-arterial extracorporeal membrane oxygenator [VA ECMO] and IABP). Consequently the RRs for these criteria are undefined. Figure 2 shows the proportion of patients who died within 60 min based on the number of UNOS criteria fulfilled. The more UNOS criteria met, the more likely death occurred within 60 min ($p < 0.001$). A total of 29% of patients with no UNOS criteria, 52% of patients with one, 65% with two and 80% with three or more criteria died within 60 min. This relationship existed among 'desirable donor candidates': for no, one, two or at least three criteria fulfilled, 33%, 41%, 67% and 88%, respectively died within 60 min ($p = 0.0012$).

Potential predictors of death within 60 min: CART analysis

The characteristics of the technique of support withdrawal and the unadjusted RR of death within 60 min for the withdrawal process variables are presented in Table 6. The simultaneous withdrawal of all treatments (defined as within 10 min) is strongly related to an increased risk of death within 60 min. The use of comfort medications during the first hour after withdrawal begins is significantly associated with decreased risk of death within 60 min.

The best CART models reflecting patient characteristics and predict death within 60 min are: (i) GCS equal to 3 and (ii) the combination of GCS >3, the ratio of SaO_2/FiO_2 <230 and PIP ≥35 (Figure 3). This CART model classifies 282 (56%) patients in the nodes that predict death within 60 min. The model has 79% sensitivity (179/227), 63% specificity (175/278), a 63% positive predicted value (PPV) (179/282) and a 78% negative predicted value (NPV) (175/223). Among 'desirable donor candidates' the CART model classifies 56 (59%) patients in the death within 60 min nodes, and this model has 91% sensitivity (39/43), 67% specificity (35/52), a 70% PPV (39/56) and a 90% NPV (35/39).

When the withdrawal process variables are added to the patient status variables as candidates for the CART model, the first terminal node is modified such that death within 60 min is predicted if the GCS is equal to 3 *and* all treatments are withdrawn within 10 min; the second terminal node predicting death within 60 min remains the same as before (the combination of GCS >3, the ratio of SaO_2/FiO_2 <230 and PIP ≥35). This CART model classifies 245 (49%) patients in the nodes that predict death within 60 min with 75% sensitivity (170/227), 73% specificity (203/278), 69% PPV (170/245) and 78% NPV (203/260). In the subgroup of 'desirable donor candidates', this CART model classifies 53 (56%) patients in the death within 60 min nodes, with 91% sensitivity (39/43), 73% specificity (38/52), a 74% PPV (39/53) and 90% NPV (38/42).

Table 2: Physiologic measures for patients withdrawn from life-sustaining treatments

Characteristics at time of withdrawal of life-sustaining treatments	N (%) or median (25th and 75th percentile) n = 505 patients	Association with death ≤60 min	
		Rel. risk+	p-Value
Physiologic measures			
Respiratory rate off ventilator (n = 125)	20 (11,28)		0.001
≤10	30 (24%)	8.48	
11–24	53 (42%)	1.00	
≥25	42 (34%)	1.52	
Heart rate (beats/min)	92 (78,110)		0.008
<60	26 (5%)	1.56	
60–≤100	301 (60%)	1.00	
>100	178 (35%)	1.31	
Systolic blood pressure	105 (85,131)		0.001
<85	121 (24%)	1.85	
85–<105	124 (25%)	1.57	
≥105	260 (51%)	1.00	
Diastolic blood pressure	51 (40,63)		0.001
<40	98 (19%)	1.77	
40–<60	248 (49%)	1.26	
≥60	159 (31%)	1.00	
Glasgow coma scale	4 (3,7)		0.001
3	234 (47%)	2.34	
4–6	122 (24%)	1.19	
≥7	145 (29%)	1.00	
PaO_2/FiO_2 (n = 312)	185 (100,309)		0.001
<100	76 (24%)	1.91	
100–<185	79 (25%)	1.38	
≥185	157 (50%)	1.00	
SaO_2/FiO_2 (n = 461)	196 (110,248)		0.001
<196	115 (25%)	1.98	
196–<248	109 (24%)	1.49	
≥248	237 (51%)	1.00	

+Rate of death within 60 min for the entire sample of n = 505 patients is 45%.

Using the node definitions as variables in a logistic regression and allowing additional baseline status variables and ultimately withdrawal variables to enter the model, several independent predictors of death within 60 min are identified (Table 7). Most notably, respiratory rate <8 while off a ventilator, PaO_2 <72 and a total dose of epinephrine, norepinephrine and phenylephrine ≥0.2 μg/kg/min are all highly significantly associated with increased odds of death within 60 min, while comfort medications given during the first hour of the withdrawal process have a significant independent effect on decreasing the odds of death within 60 min. The Hosmer–Lemeshow goodness of fit statistic for the full model is 9.34 (p = 0.31) suggesting a good model fit, and the c-statistic is 0.86 indicating excellent discrimination. When these models were applied to the subset of 95 desirable donor candidates, the results were generally consistent. Due to the small number of desirable donor candidates with respiratory rate <8, this variable had to be dropped from the model; GCS = 3 and SaO_2/FiO_2 <230 were significantly associated with death within 60 min; low diastolic BP, PaO_2 <72, use of epinephrine, norepinephrine and phenylephrine and absence of hepatic failure were all positively related with the death outcome; only PIP ≥35 showed little or no association with death within 60 min in this small subset of patients.

Discussion

The American Medical Association (AMA), the Institute of Medicine (IOM) (6) and the Society for Critical Care Medicine (SCCM) (7) have endorsed DCD yet there are relatively few DCD. The reasons for this are many, ranging from the ethical (is it ethical to remove life-sustaining treatments with the knowledge that organ procurement will ensue?), to the legal (are those who become DCD really dead?), to educational (do caregivers understand what DCD is?) and to the emotional (how do caregivers feel about DCD?). Another barrier is logistic: are there process barriers? The Organ Procurement and Transplant Network (OPTN) and UNOS have attempted to improve DCD rates by developing a 'Critical Pathway for DCD', which includes suggested identification criteria (8). These criteria have not yet been validated.

There is in theory a large pool of DCD organ donors. One estimate predicts that DCD could add 1500 more donors per year in this country (9). The obvious question is, 'Why are there so few DCD donors?' Two potential factors include (i) the inability of clinicians to identify patients who might die rapidly enough to allow DCD to be feasible; and (ii) the potential donor pool is vastly overestimated.

Table 3: Mechanical treatments for patients withdrawn from life-sustaining treatments

Characteristics at time of withdrawal of life-sustaining treatments	N (%) or median (25th and 75th percentile) n = 505 patients	Association with death ≤60 min	
		Rel. risk+	p-Value
Ventilator treatments			
Ventilator	486 (96%)	2.18	0.033
Ventilator mode (n = 486 on ventilator)			
SIMV	114 (24%)	1.00	0.010
CMV	344 (71%)	1.42	
PC	10 (2%)	1.71	
CPAP	12 (2%)	0.71	
Other	3 (1%)		
FiO_2	0.50 (0.40,0.80)		
<0.50	235 (46%)	1.00	0.001
0.50–<0.80	125 (26%)	1.45	
≥0.80	136 (28%)	2.13	
Peak inspiratory pressure, cm H_2O	28 (22,36)		
<28	217 (47%)	1.00	0.001
28–<36	125 (27%)	1.35	
≥36	120 (26%)	1.88	
PEEP	5 (5,8)		
≥6	131 (27%)	1.72	0.001
Other mechanical support			
Endotracheal tube	426 (85%)	1.58*	0.013
Tracheostomy	56 (11%)		
Pacemaker	39 (8%)	1.35	NS
Circulatory support (LVAD, RVAD, ECMO)	8 (2%)	1.69	NS
Intra-aortic balloon pump	9 (2%)	1.24	NS
CVVHD	62 (12%)	0.96	NS
Hemodialysis	31 (6%)	1.16	NS

+Rate of death within 60 min for the entire sample of n = 505 patients is 45%.
*RR of death within 60 min for endotracheal tube versus tracheostomy.
SIMV = synchronous intermittent mandatory ventilation; CMV = continuous mandatory ventilation; PC = pressure control ventilation; CPAP = continuous positive airway pressure; PEEP = positive-end expiratory pressure; CVVHD = continuous veno-venous hemodiafiltration.

Table 4: Medications received by patients withdrawn from life-sustaining treatments

Characteristics at time of withdrawal of life-sustaining treatments	N (%) n = 505 patients	Association with death ≤60 min	
		Rel. risk+	p-Value
Life-sustaining medications			
Any 'life-sustaining medications' used†	275 (54%)	1.76	0.001
Number of vasopressors*			
0	272 (54%)	1.00	0.001
1	136 (27%)	1.57	
2	77 (15%)	1.98	
3–4	20 (4%)	2.75	
Total dose norepinephrine, epinephrine, phenylephrine ≥0.2 μg/kg/min	156 (31%)	2.03	0.001
Neuromuscular blockade within 24 h	35 (7%)	1.66	0.011
Medications 1 h prior to withdrawal of LST			
Any comfort medications** used prior	354 (70%)	0.80	0.030
Morphine	250 (50%)		
Fentanyl	95 (19%)		
Propofol	47 (9%)		
Lorazepam	54 (11%)		

†Life-sustaining medications include epinephrine, norepinephrine, dopamine at any dose, phenylephrine, vasopressin and dobutamine.
*Vasopressors include: epinephrine, norepinephrine, dopamine, phenylephrine and vasopressin.
**Comfort medications include: morphine, fentanyl, propopfol, lorazepam, midazolam and hydromorphone.
+Rate of death within 60 min for the entire sample of n = 505 patients is 45%.

Table 5: UNOS criteria presence among patients withdrawn from life-sustaining treatment

Characteristics at time of withdrawal of life-sustaining treatments	N (%) n = 505 patients	Percent with death ≤60 min	Association with death ≤60 min	
			Rel. risk+	p-Value
UNOS criteria				
Apnea	30 (6%)	77%	1.79	0.001
RR < 8 (i.e. RR 1–7)	12 (2%)	67%	1.50	0.13
RR > 30	45 (9%)	29%	0.62	0.023
LVAD	2 (0.4%)	100%	2.22	0.12
RVAD	1 (0.2%)	100%	2.22	0.27
V-A ECMO	1 (0.2%)	0%	0.00	0.37
Pacemaker-unassisted heart rate <30	5 (1%)	80%	1.79	0.11
PEEP≥ 10 and SaO_2≤ 92%	50 (10%)	78%	1.89	0.001
FiO_2≥ 0.5 and SaO_2≤ 92%	94 (19%)	67%	1.68	0.001
V-V ECMO	5 (1%)	80%	1.79	0.11
Norepinepherine or phenylephrine ≥0.2	151 (30%)	70%	2.05	0.001
Dopamine≥15	19 (4%)	79%	1.81	0.0024
IABP1:1 or (dobutamine or dopamine ≥10 and CI ≤ 2.2)	25 (5%)	68%	1.55	0.018
IABP1:1 and CI ≤ 1.5	1 (0.2%)	100%	2.22	0.27
Number of UNOS criteria present				
0	249 (49%)	29%	1.00	0.001
1	146 (29%)	52%	1.83	
2	54 (11%)	65%	2.27	
3	39 (8%)	82%	2.88	
4–5	17 (3%)	76%	2.68	

+Overall rate of death within 60 min for the entire sample of n = 505 patients is 45%.
RR = respiratory rate; VA ECMO = veno-arterial extracorporeal membrane oxygenator; CI = cardiac index in liters/minute/meter^2.

The objective of this study was to generate data that improve the ability of caregivers to identify potential DCD. The improved accuracy for predicting death within 60 min after withdrawal of LST might increase the efficiency of DCD (fewer failures to progress to donation), expand the potential donor pool (by identifying more potential donors) and enable others to more accurately estimate the potential donor pool size in a population. Inaccuracy in predicting rapid occurrence of death may lead OPOs to be reluctant to proceed with DCD because it requires a large logistic effort. Only one group has tried to validate rules and used a small sample size from a single institution and required a 10 min apnea trial (10). Our study attempted to validate simpler rules and a much larger sample population.

Our attempt required certain assumptions, which are controversial. The time from withdrawal of LST to the donor patient's death must be rapid if viable organs are to be transplanted. Some feel the kidney can withstand only

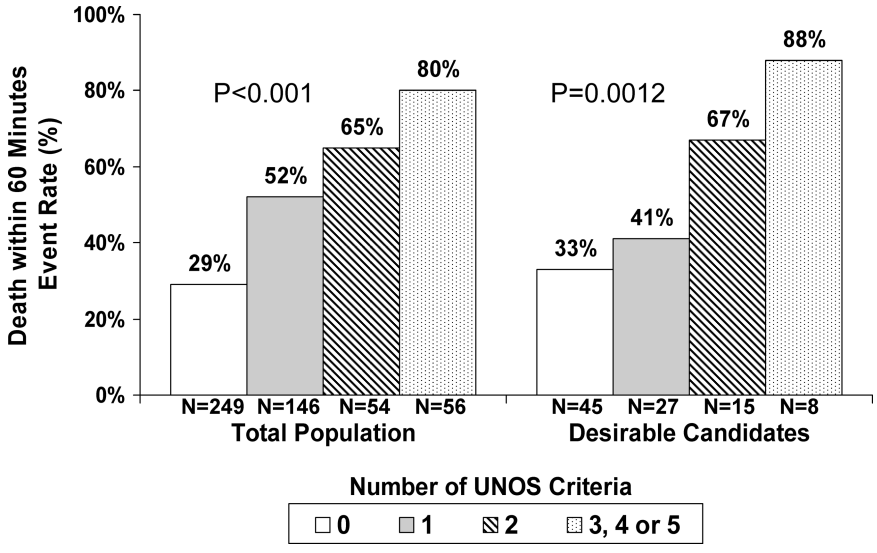

Figure 2: The percent of patients who died within 60 min of initiation of withdrawal of life-sustaining treatment based on the number of UNOS criteria fulfilled. The event rates for the entire study cohort are shown on the left and the event rates for the subgroup of desirable donor candidates are shown on the right. The p-value represents the significance of the tests for trend (Mantel-Haenszel chi-square test with one degree of freedom).

Table 6: Withdrawal process of life-sustaining treatments

Withdrawal of life-sustaining treatments	N (%) n = 505 patients	Association with death ≤60 minutes	
		Rel. risk+	p-Value
Medications within first hour after withdrawal of LST			
Any comfort medication* within first hour	366 (72%)	0.53	.001
Morphine	287 (57%)		
Fentanyl	73 (14%)		
Propofol	33 (7%)		
Lorazepam	45 (9%)		
Withdrawal of support			
All treatments withdrawn simultaneously	321 (65%)	1.32	0.012
All treatments withdrawn within 10 min	404 (80%)	2.90	0.001
Endotracheal tube withdrawn			
Yes	345 (69%)	0.99	0.19
No	98 (20%)	1.00	
N/A‡	58 (12%)	0.62	

+Overall rate of death within 60 min for the entire sample of n = 505 patients is 45%.
*Comfort medications include: morphine, fentanyl, propopfol, lorazepam, midazolam and hydromorphone.
‡Tracheostomy, noninvasive mechanical ventilation or no ventilatory support.

30–45 min of warm ischemic time, while other centers now extend warm ischemic time for kidneys to 2 h (11–13). There are those that limit the warm ischemic time for livers to 20–30 min to yield acceptable results (14,15). In this report we describe the predictors for death within 60 min because the majority of authors cite this as the acceptable limit of warm ischemic time for organs to be considered suitable for transplantation.

There are few studies on death following withdrawal of life-sustaining treatment as it pertains to the probability of death within a specific time frame and its relationship to underlying disease, physiology and types of support withdrawn. DeVita et al. reported the clinical course of 15 patients who became DCD, then called non-heartbeating organ donation (NHBOD) (16). They found a 22-min mean time to death following withdrawal of LST. Of course this represents a highly selected population—the successes—and their data are not useful to accurately describe all potential candidates: the characteristics of those patients are highly specific, but insensitive. Lewis et al. reported a tool to assess probability of death within 60 min, with accuracy over 80%. The tool is limited by the requirement for an apnea trial off mechanical ventilation, and so does not consider patients on LST other than ventilators or patients who do not have severe neurologic defects. In addition it may be too complex to use to predict the size of the potential donor pool because some values required by the tool are not available on many ICU patient records. Daly et al. observed 42 patients withdrawn from mechanical ventilation, and only 5 of those expired in <30 min (17). Kaufman et al. examined withdrawal of LST among 32 adult patients (18). Prolonged prior mechanical ventilation (133 vs. 285 h), more organ failures (1.94 vs. 2.94) and lower spontaneous

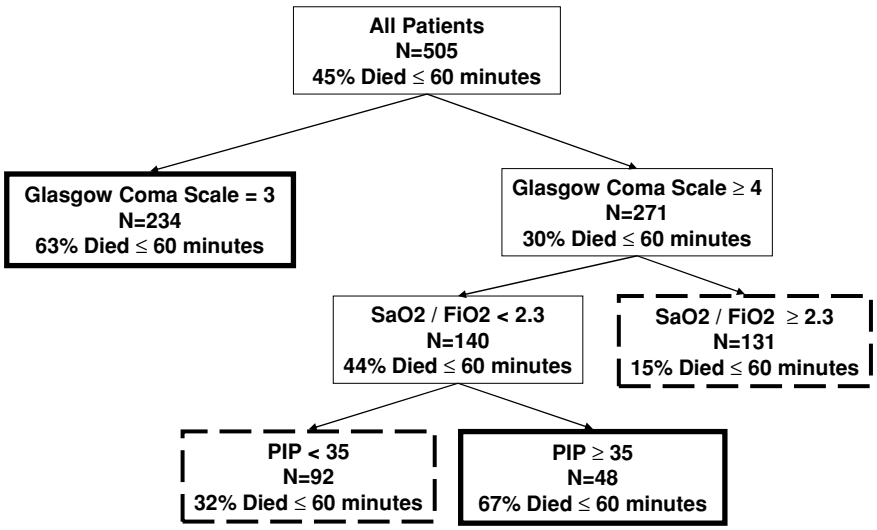

Figure 3: The prediction model for death within 60 min of initiation of withdrawal of life-sustaining treatment using only variables reflecting patient status at the time of initiation of withdrawal. Terminal nodes that predict death within 60 min are surrounded by heavy solid lines; terminal nodes that predict no death within 60 min are surrounded by heavy dashed lines.

respiratory rates (15 vs. 29 breaths/min) were all associated with death within 60 min. Zawistowski and DeVita have studied death following withdrawal of LST among 50 pediatric patients (19). All these studies' cohorts are all too small to permit a basis for national estimates.

We studied all patients who underwent withdrawal of LST for two reasons. First, the criteria for DCD are different between OPOs and even within the same OPO acceptable candidates change over time. Validating the UNOS criteria for all patients enables OPOs to use the UNOS criteria even if the candidate population changes. Secondly, the inclusive database enables validation of the criteria for specific subsets of patients. To this end, we also validated the UNOS criteria for 'desirable donor candidates'.

The main conclusion from our study is that the UNOS criteria identify patients who are likely to die within 60 min of withdrawal of LST (Table 5). We also assessed whether an increase in the number of criteria met increases the odds of rapid death. The number of UNOS identification criteria has a 'dose-response curve'. The odds ratio death for death within 60 min of forgoing LST is 2.72,4.62 and 10.6 for patients with one, two and three or more criteria, respectively. This curve exists as well for 'desirable donor candidates'. A total of 72.7% (80/110) of the patients with two or more criteria died within 60 min making this a strong candidate for an organizational policy.

Because the data validate the UNOS criteria, we suggest that they are a simple method to assess patients for being eligible for DCD. While organizations that wish to have higher specificity might prefer two or more criteria, one criterion is sufficient for those who prefer better sensitivity: one criteria identified 156 (68.7%) of the 227 patients who died within 60 min. We recognize that the UNOS criteria may exclude about 25% of potential DCD, however, that 25% is in a group that has less than a one in three chance of becoming a DCD (thus two failures for each success). Programs with resources to support this effort may want to ignore prognostic factors for all medically appropriate DCD candidates. We observed a 63% PPV for the UNOS criteria. While a 63% PPV is relatively low, the stepwise increment in probability of death as number of criteria increases allows OPOs and hospitals to choose their own requirements. Our data helps them calculate accurately a priori their probable yield.

Other predictors of death within 60 min

There are few studies that identify predictors of death within 60 min, and none this large, so we sought other criteria that might identify this patient population. Several of the UNOS criteria by themselves have poor predictive value (RR <8, LVAD, RVAD, V-A or V-V ECMO, heart rate <30 and IABP 1:1 with a cardiac index <1.5) but this is because of the very few patients who had these characteristics. Despite the poor predictive value, these criteria indicate quite high severity of illness and it may still be reasonable to include these criteria as most patients did die quickly. Additional investigation including larger numbers of these patients is needed to clarify their relationships with rapid death.

Patient demographic characteristics are poorly predictive of rapid death following LST. We analyzed patients in each of three age groups determined a priori: under 60, 60–70 and over 70 years old and found age does not predict rapid death. Many OPOs accept patients in the first group and reject patients in the third age range, while there is disparity of opinion regarding patients between 60 and 70. The implication is that should the age range for candidate organ donors change, the UNOS criteria still apply.

Similarly, abnormal neurologic function, ventilator dependence and mechanical hemodynamic support were not useful discriminators in either CART or logistic regression models. Most patients were sedated or severely brain injured, virtually all patients (96%) were on mechanical ventilation, and few were on mechanical hemodynamic support. Because these factors are so unbalanced in our population, the statistical significance for these factors as predictors of death within 60 min is limited. For example, since virtually all patients were on ventilation, using it as a discrimination tool for who will and will not die is impossible.

In contrast, a few physiologic and support variables had a significant association. The RR of death within 60 min was 1.43 for neurologic failure ($p = 0.001$), 1.72 for circulatory failure ($p = 0.001$) and 1.28 for overwhelming infection ($p < 0.03$). Although the RR for ventilatory failure was 1.64, this value did not reach significance because of the few patients who had no respiratory failure. Table 2 shows the quartiles for various physiologic variables. Respiratory rate on the ventilator does not predict death. For patients who have a trial off mechanical ventilation, respiratory rate <11 increases RR dramatically to 5.80, ($p = 0.001$). Severe lung injury, as indicated by, low PaO_2/FiO_2 ratio (Table 2), high PEEP or high peak airway pressure (Table 3), is associated with a significantly higher RR for death within 60 min ($p = 0.001$). Among supportive treatments, there is a significant increase in RR for patients with 2 or more vasopressors, as well as a total dose of vasopressor >0.2 μg/kg/min (RR = 1.98, 2.75 and 2.0, respectively, $p = 0.001$ for all). Our data support the notion that as neurologic, circulatory and respiratory derangements increase, the RR for death in <60 min increases. Incorporation of these data into potential prediction rules is considered in the CART analysis described below.

Surprisingly, use of comfort medications during the first 60 min of the withdrawal process was associated with a *lower* risk of death. This seems counter intuitive since these medicines reduce respiratory rate (and presumably oxygenation) as well as BP. Perhaps those patients with higher consciousness are more likely to receive comfort

Table 7: Adjusted odd ratios of death within 60 min of first withdrawn LST (n = 505)

	Patient status predictors only		Patient status and withdrawal process predictors	
Variable	Adjusted odds ratio	95% CI CI odds ratio	Adjusted odds ratio	95% CI odds ratio
Glasgow coma scale = 3	3.35‡	2.21,5.08	2.83‡	1.79,4.46
SaO_2/FiO_2 <230*	1.62§	1.03,2.55	1.78§	1.09,2.90
PIP ≥35**	1.85§	1.15,2.99	2.58‡	1.49,4.48
Respiratory rate off ventilator <8***	3.40†	1.49,7.79	6.01‡	2.29,15.76
Diastolic blood pressure (10 mmHg)	0.85§	0.75,0.97	0.80†	0.69,0.93
PaO_2 <72	3.08 ‡	1.59,5.96	3.10†	1.53,6.30
Epinephrine,norepinephrine or phenylephrine ≥0.2	2.60‡	1.63,4.15	3.02‡	1.75,5.21
Hepatic failure	0.41§	0.20,0.84		
All treatments withdrawn within 10 min			8.55‡	4.23,17.30
Endotracheal tube withdrawn			2.28†	1.33,3.90
Comfort medication given during first hour after withdrawal of LST****			0.35‡	0.21,0.59

*Patients who have missing SaO_2 values but are on a ventilator are classified as SaO_2/FiO_2 <230.
**Patients who have missing SaO_2 values but have PIP≥35 (on a ventilator) are classified as PIP ≥35.
Patients who are missing FiO_2 or PIP values (not on a ventilator) are classified as not having PIP ≥35.
***RR <8 includes Apnea (RR =0) and RR between 1 and 7.
****Comfort medications include: morphine, fentanyl, propofol, lorazepam, midazolam and hydromorphone.
§$0.01 \leq p < 0.05$.
†$0.001 \leq p < 0.01$.
‡$p < 0.001$.

medications and be less likely to die due to higher level of consciousness. Other studies have shown comforting medications are paradoxically associated with longer time to death following withdrawal of ventilators (20) and in palliative care units (21). These studies did not discriminate whether more comforting medications caused or resulted from delayed death (because patients lived longer). Our findings show this association exists even in the first hour after withdrawal of LST. We conclude that comforting medications are not associated with shorter time to death. A prospective trial of comfort medications is needed to prove a causal relationship.

Finally, there was no difference between the risk for rapid death amongst extubated versus not extubated patients. The controversy regarding the propriety and impact of extubation can now be informed by this observation. Prospective randomized studies would be required to confirm this finding.

Are there better rules than the UNOS criteria for predicting death in less than 60 min?

We used CART analyses to define a several rules that predict rapid death with a predetermined positive predictive value. The CART methodology does not provide parametric estimates (e.g. odds ratios) for the outcome of interest. Instead, it offers a flexible approach to determine the best cut-point for each predictor variable and to explore the complex relationships between multiple predictor variables with respect to the outcome. Based on this population, the most simple and accurate rules are either a GCS of 3 or the combination of a SaO_2/FiO_2 ratio <230 and a PIP >35 cm H_2O. Both rules have high specificity and sensitivity for death within 60 min. This rule is enticing since only three data points are needed, and they are all values that are readily available on the ICU chart. This rule has even higher sensitivity and specificity if vasopressors >0.2 μg/kg/min, respiratory rate <9 off mechanical ventilation are included. This rule set is less attractive for determining the size of the potential DCD population because it requires a trial off mechanical ventilation, which is not available on many ICU patient charts. These rules have yet to be validated; though simple, they are not as easy to apply as the UNOS criteria.

Limitations

Our study has several limitations. First, we used an open enrollment methodology, which included patients who are not organ donation candidates (patients with advanced age, severe infection, organ dysfunction, or disseminated cancer). We chose this strategy because we wanted to create rules based on physiology, demographics or medical support. By not excluding large classes of patients, we allow the use of these data in the future, should classes of patients now excluded become potential organ donors because of advances in therapy. Our strategy has created rules that apply to all patients, as well as to 'desirable donor candidates'.

A second limitation is the study population is drawn from university-affiliated hospitals. It is possible that the data may not be generalizable to patients in hospitals that do not belong to this profile. Nevertheless, because patient demographics are not associated with death in <60 min,

we believe that our data are generalizable to community hospitals. A related limitation pertains to whether DCD occurs at the hospital. UPMC Presbyterian Hospital, Shadyside and Cincinnati have DCD programs (although Shadyside did no procurements during this observation period) and the remainders do not. There were few DCD events so the impact on our observations is expected to be minimal.

Another limitation may be that the withdrawal of LST may have biased the result. To address this concern, we have described the withdrawal process in the population carefully.

Because we have validated several rules ($\geq$1 UNOS criterion, $\geq$2 UNOS criteria and the two CART derived rules), one might argue that this may increase the ambiguity of rapid death prediction. However, we view our results as an opportunity to satisfy several purposes: those looking for 'easy' rules or 'most sensitive' rules or 'most specific' rules can select the approach that best meets their needs. The rules may provide guidance in caring for specific patients, for improving program efficiency or for estimating of the size of the potential donor pool. Perhaps improved death prediction will help reduce the reluctance to embark on a DCD program. There is a critical care impact as well: identifying patients unlikely to die rapidly enables planning for clinical care and psychosocial support of both staff and family. The OPOs that want to maximize donation might use a 'one UNOS criterion' rule, while those wanting to minimize failure would choose a 'two criteria' rule.

Conclusions

Our data validate the UNOS criteria for predicting death in less than 60 min following withdrawal of LST for all patients and 'desirable donor candidates'. The absence of any criterion is associated with low probability of death within 60 min. The more UNOS criteria that are satisfied, the more likely that death will occur within 60 min.

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