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Original Research

CRITICAL CARE MEDICINE

Predictors of Time to Death After Terminal Withdrawal of Mechanical Ventilation in the ICU

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Background: **Little information exists about the expected time to death after terminal withdrawal of mechanical ventilation. We sought to determine the independent predictors of time to death after withdrawal of mechanical ventilation.**

Methods: **We conducted a secondary analysis from a cluster randomized trial of an end-of-life care intervention. We studied 1,505 adult patients in 14 hospitals in Washington State who died within or shortly after discharge from an ICU following terminal withdrawal of mechanical ventilation (August 2003 to February 2008). Time to death and its predictors were abstracted from the patients' charts and death certificates. Predictors included demographics, proxies of severity of illness, life-sustaining therapies, and *International Classification of Diseases, 9th ed., Clinical Modification* codes.**

Results: **The median (interquartile range [IQR]) age of the cohort was 71 years (58-80 years), and 44% were women. The median (IQR) time to death after withdrawal of ventilation was 0.93 hours (0.25-5.5 hours). Using Cox regression, the independent predictors of a shorter time to death were nonwhite race (hazard ratio [HR], 1.17; 95% CI, 1.01-1.35), number of organ failures (per-organ HR, 1.11; 95% CI, 1.04-1.19), vasopressors (HR, 1.67; 95% CI, 1.49-1.88), IV fluids (HR, 1.16; 95% CI, 1.01-1.32), and surgical vs medical service (HR, 1.29; 95% CI, 1.06-1.56). Predictors of longer time to death were older age (per-decade HR, 0.95; 95% CI, 0.90-0.99) and female sex (HR, 0.86; 95% CI, 0.77-0.97).**

Conclusions: **Time to death after withdrawal of mechanical ventilation varies widely, yet the majority of patients die within 24 hours. Subsequent validation of these predictors may help to inform family counseling at the end of life.** ***CHEST 2010; 138(2):289–297***

Abbreviations: HR = hazard ratio; ICD-9-CM = *International Classification of Diseases, 9th ed., Clinical Modification*; IQR = interquartile range; OR = odds ratio

Approximately 20% of all American patients die during or shortly after a stay in the ICU,[1] the majority of whom do so in the context of a decision to forego life-sustaining therapy.[2-4] Once families and caregivers decide to withdraw life support, experts in end-of-life communication advocate for clinicians to inform families of what they should expect during their loved one's dying process.[5,6] This communication might include details about the expected myoclonus of dying patients, the potential for agonal respirations after discontinuation of mechanical ventilation, and the timing of death after withdrawal of life support.[6]

Despite frequent family requests as well as expert recommendations for discussion of the postwithdrawal course, few data exist to guide clinicians in accurately conveying the anticipated course.[7-9] The majority of studies that examine the timing of death after withdrawal focus on patients with severe neurologic injury in the context of organ donation after cardiac death[10] or on whether the use of analgesics and sedatives during the dying process hasten death in patients who are critically ill.[7,11] These studies, among others,[12,13] dedicate little attention to other factors that may influence the timing of death after withdrawal of life support, such as age, severity of illness, or underlying diagnosis. Characterization of the factors that predict time to death may inform family-caregiver communication at the end of life and alleviate some of the anxiety and frustration resulting

from excessive uncertainty regarding the anticipated time course to death.[14]

Withdrawal of life support is a complex and active process involving the cessation of numerous life-sustaining therapies. Although the sequence of interventions that are stopped during withdrawal can vary, mechanical ventilation is the last aggressive therapy stopped in the majority of patients[15,16] because it tends to be more determinant of immediate death.[16] We sought to determine the patient characteristics and care processes that predict time to death after terminal withdrawal of mechanical ventilation in a cohort of patients dying in or shortly after a stay in the hospital ICU.

Materials and Methods

Participants and Setting

We performed a secondary analysis of data collected during a cluster randomized trial aimed at improving end-of-life care for hospital ICU patients in Seattle and Tacoma, Washington. Pre- and postintervention data collected from 14 hospitals (two university-affiliated teaching hospitals, three community-based teaching hospitals, and nine community-based nonteaching hospitals) were included in the analysis. The study protocol was approved by institutional review boards at the University of Washington (Seattle, WA) and each participating hospital. Details about the randomized trial intervention have been described previously.[17] Briefly, the intervention involved five components: (1) clinician education about the principles and practice of palliative care in the ICU; (2) identifying end-of-life critical care clinician local champions; (3) academic detailing of nurse and physician ICU directors to identify and address local barriers to improving end-of-life care; (4) feedback of local quality improvement data; and (5) implementation of other system supports, such as palliative care order forms, for providing palliative care in the ICU. Overall, the intervention was not associated with changes in the outcomes, which allowed us to pool the pre- and postintervention data for these analyses.[18,19]

All patients dying in the hospital ICU or within 30 hours of discharge from the ICU were identified by examining hospital admission and discharge logs between August 2003 and February 2008. Patients who died in the setting of full support or who were not mechanically ventilated prior to withdrawal of support were excluded from these analyses.

Data Collection and Definitions

Trained chart abstractors reviewed patient medical records using a standardized chart abstraction protocol. Details regarding the training of chart abstractors and maintenance of data quality have been published.[16] Data collected from the medical record included information about the interventions during the last 5 days of life as well as patient demographics, clinical variables, *International Classification of Diseases, 9th ed., Clinical Modification* (ICD-9-CM) codes, and end-of-life care processes. Race/ethnicity and education were not consistently available from the charts, so we used data from each patient's death certificate. Because of the low numbers of racial and ethnic minorities in the sample, all nonwhite patients and patients of Hispanic ethnicity (regardless of race) were grouped as a single category and were labeled as nonwhite for the study.

We calculated time to death from the recorded time of discontinuation of mechanical ventilation to death in hours and minutes. Mechanical ventilation included both noninvasive positive pressure ventilation and traditional invasive ventilation. Terminal withdrawal was defined as the episode of withdrawal of ventilatory support most proximal to death, with documentation in the medical record endorsing the expectation that the patient would die without ventilation.

We hypothesized that severity of underlying disease would be a predictor of a short time to death. Because laboratory and physiology data were not collected during the parent study, we used proxies of severity of illness to evaluate this hypothesis. Variables we considered were patient age; primary insurance status; race/ethnicity; education; underlying diagnosis; number of organ failures during the hospital stay; use of IV fluids, renal replacement therapy, or vasopressors prior to terminal withdrawal; ICU length of stay prior to withdrawal; admission source to the ICU; and comorbidities.

We used the first recorded ICD-9-CM code to determine each patient's diagnosis group during the hospital stay (e-Table 1). All 18 ICD-9-CM code fields were used to calculate the total number of nonpulmonary organ system dysfunctions according to Angus et al[20] (e-Table 2) and the Charlson/Deyo comorbidity index for each patient.[21]

Statistical Analysis

We plotted Kaplan-Meier curves to describe the time to death and used the log-rank test to compare differences in time to death between groups in bivariate analysis and one-way analysis of variance, Fisher exact test, or Wilcoxon rank-sum test as appropriate. To determine the independent predictors of death, we used Cox proportional hazards regression. The relationship between time to death and each covariate in the model are presented as hazard ratios (HRs). An HR >1.0 indicates that the covariate is associated with a more rapid death, whereas an HR <1.0 indicates a longer time to death. All variables that a priori were thought to be associated with time to death were included in the regression model without attention to their statistical significance.[22-27] Two covariates, Charlson/Deyo comorbidity score and hospital, violated the proportional hazards assumption; all subsequent models were stratified by these two covariates. As a result, the coefficients

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for these two variables could not be reported. We elected not to explore any multiplicative or additive interactions in the Cox model because we had no prespecified hypothesis that effect modification would be expected. Finally, all models included a covariate representing whether the patient received the parent study intervention. We use logistic regression to determine the predictors of death occurring at or beyond 24 hours after terminal withdrawal in a post hoc analysis. Details of the logistic regression analysis are presented in e-Appendix 1.

Handling of Missing Data

A total of 46 (3.1%) patients had missing data for at least one covariate of interest, including education (n = 32); use of vasopressors, renal replacement therapy, and IV fluids (n = 5); admission source to the hospital ICU (n = 3); age (n = 3); ICU length of stay (n = 2); and service at time of death (n = 1). In general, patients with missing data were healthier than those without missing data at the time of withdrawal, as illustrated by their lower mean Charlson/Deyo comorbidity score (1.0 vs 1.9, respectively; $P < .01$). We performed multiple imputation of these missing values. This approach improves the efficiency of the final regression through incorporating additional patients and reduces the bias in the regression coefficients resulting from exclusion of patients with missing data.[28-32] Further details of the imputation procedure are presented in the e-Appendix 1.

Results

During the observation period, 3,400 consecutive patients who died in the hospital ICU or within 30 hours of discharge from the ICU were screened for eligibility. Of these, we excluded 262 patients for whom charts were not available. We excluded an additional 1,633 (48%) patients because they were not ventilated or died in the setting of full support, mechanical ventilation was not withdrawn prior to death, data for the outcome was missing, or withdrawal was not expected to result in death (Fig 1). A total of 1,505 patients were available for analysis.

Baseline characteristics of the cohort are displayed in Table 1. In general, the cohort was elderly (median age, 71 years; interquartile range [IQR], 58-81 years); white, non-Hispanic (81%); and insured by Medicare (60%).

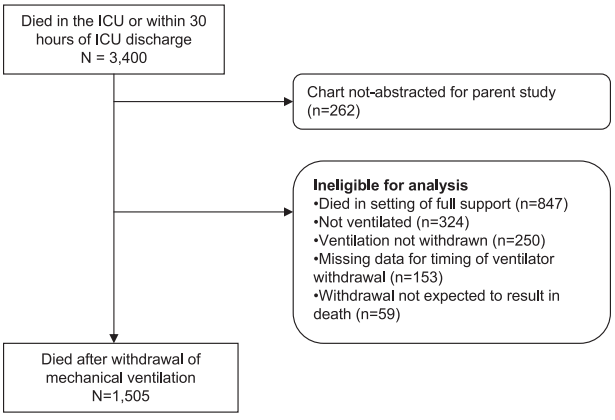

Figure 1. Cohort flow diagram.

Bivariate Comparisons

The median (IQR) time to death for the entire cohort was 0.93 hours (0.25-5.5 hours) after withdrawal of mechanical ventilation, with a range of 0 to 6.9 days (Fig 2). The proportion of patients who died within 24 hours of terminal withdrawal of mechanical ventilation was 93.2% (95% CI, 92% to 94%). A minority (9.3%) of patients were discharged from the hospital ICU prior to death. Median (IQR) time to death from ICU discharge for this subgroup was 8.8 hours (4-17 hours) with a range of 17 minutes to 28.8 hours. Of these patients discharged from the ICU, 61% died within 12 hours of discharge, and 83% died within 20 hours of discharge. The distribution of time to death from ICU discharge for patients dying outside the ICU is presented in e-Figure 1. Unadjusted associations between predictors and time to death are presented in Table 2. Age was a strong predictor of time to death; however, it was older patients who had significantly longer times to death than younger patients (Fig 3). On average, women had longer median times to death than their male counterparts (1.17 vs 0.75 hours, respectively; $P = .003$). With the exception of the presence of chronic respiratory disease, nonmetastatic cancer, and dementia, most individual comorbidities were not associated with differences in time to death. However, when combined in the Charlson/Deyo score, greater comorbidity score was associated with a longer time to death. Time to death for patients grouped by discharge diagnosis, number of organ failures, and therapy received showed that greater severity of illness predicted shorter times to death (Table 3).

Multivariable Analysis

In the multivariable model, greater age remained significantly associated with longer times to death (Table 4). Female sex also was associated with a longer time to death. Patients of nonwhite race/ethnicity had shorter time to death than white patients (HR, 1.17; 95% CI, 1.01-1.35). Other variables independently associated with a shorter time to death included the number of nonpulmonary organ failures, surgical service, use of vasopressors prior to withdrawal, and use of IV fluids prior to withdrawal. Other characteristics were not associated with time to death. We imputed data for 46 patients prior to fitting the multivariable Cox model. No substantive differences were noted between the complete case analysis and the imputed analysis. Results of the complete case analysis can be found in e-Table 3.

Table 1—*Characteristics of Study Patients*

Patient Characteristic	Value
Total sample, N	1,505
Age, median y (IQR)	71 (58-81)
Female, %	44
Race, %[a]	
White, non-Hispanic	81
Other race/ethnicity	19
Primary insurance status	
Medicare	60
Private/commercial	19
Other government (VA, Medicaid)	15
Other, unknown, none	6
Comorbidities	
Chronic respiratory disease	31
Diabetes	30
Congestive heart failure	20
Nonmetastatic solid organ cancer	16
Dementia	10
Metastatic solid organ cancer	8
Chronic renal disease	7
Cirrhosis	6
Immunocompromised state	6
Leukemia/multiple myeloma	1.8
Liver failure	1.7
Non-Hodgkin's lymphoma	1.3
HIV or AIDS	0.8
ICU admission source, %	
ED	57
Hospital floor/observation unit	27
Operating room/procedure recovery	10
Direct admission	6
Primary ICD-9-CM diagnosis, %	
Respiratory	23
Neurologic	16
Cardiovascular	15
Infectious	13
Trauma/burn	10
Gastrointestinal and hepatic	7
Cancer	5
Miscellaneous	11
Number of nonpulmonary organ failures (ICD-9-CM based), median (IQR)	1 (0-2)
Hospital LOS, median d (IQR)	6 (3-11)
ICU LOS, median d (IQR)	3.4 (1.5-7.7)

Race/ethnicity was collected from patient death certificates and collapsed into two categories. ICD-9-CM = *International Classification of Diseases, 9th ed., Clinical Modification*; IQR = interquartile range; LOS = length of stay; VA = Veterans Administration.

Post hoc analysis illustrated that older patients ($P = .04$) and women ($P = .01$) had fewer organ failures, whereas no relationship between race/ethnicity ($P = .91$) and organ failure was noted. There was a nonsignificantly greater median prewithdrawal hospital ICU length of stay among nonwhite patients than white patients (3.6 vs 3.0 days, respectively; $P = .06$). Men also had longer prewithdrawal ICU length of stay than women (3.4 vs 3.0 days, respectively; $P = .03$), and younger patients had longer prewithdrawal ICU length of stay prior to withdrawal than older patients ($P < .001$). Women were more likely to die beyond 24 hours after terminal withdrawal (odds ratio [OR], 1.83; 95% CI, 1.00-3.34), whereas patients on vasopressors (OR, 0.38; 95% CI, 0.26-0.57) or dialysis (OR, 0.31; 95% CI, 0.12-0.82) were more likely to die prior to 24 hours after terminal withdrawal (e-Table 4).

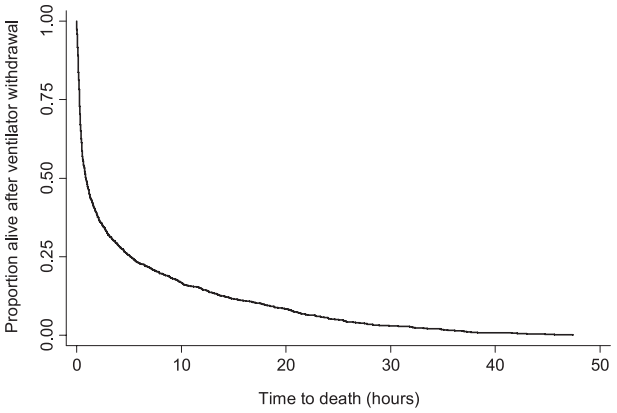

FIGURE 2. Kaplan-Meier estimate of survival after withdrawal of mechanical ventilation in the cohort. The plot is truncated at 48 h for ease of presentation and includes data for 1,484 (99%) of the patients.

DISCUSSION

We examined the timing of death and predictors of time to death after terminal withdrawal of mechanical ventilation among patients who died in or shortly after a stay in the hospital ICU. Our study showed that approximately 50% of patients die within 1 hour and >90% die within the first 24 hours after withdrawal of mechanical ventilation. The majority of the significant independent predictors that we identified explicitly capture aspects of acute severity of illness, with greater acute severity of illness predicting shorter time to death. These predictors include the number of organ failures, use of vasopressors, and use of IV fluids.

Other variables associated with time to death, including sex, age, and race/ethnicity, are more challenging to explain; however, we believe that they also reflect residual acute severity of illness not fully accounted for in our analysis. Older patients had longer times to death after withdrawal than younger patients. The fewer number of organ failures and shorter lengths of stay prior to withdrawal among older patients support the notion that differences in severity across age groups likely exist. To the best of our ability, we accounted for proxies of acute severity of illness with number of organ failures, use of life-sustaining interventions, diagnostic category, and admission source to the hospital ICU. However, we were unable to adjust for physiologic

Table 2—*Bivariate Associations Between Time to Death After Withdrawal of Mechanical Ventilation and Patient Demographics and Comorbidities*

Characteristic	No.	Time to Death, h		*P* Value
		Median	IQR	
Age, y				< .001
≤ 60	412	0.60	0.20-3.0	
61-70	293	0.73	0.25-5.3	
71-80	389	0.88	0.28-6.7	
81-90	355	1.6	0.35-8.3	
91+	53	4.25	0.50-17.2	
Sex				.003
Female	658	1.17	0.32-7.0	
Male	847	0.75	0.25-4.7	
Race				< .001
White, non-Hispanic	1,222	1.07	0.28-6.7	
Other race/ethnicity	283	0.53	0.25-3.1	
Education				.04
Less than high school	111	0.88	0.27-5.0	
Some high school	135	0.80	0.18-5.3	
High school graduate/equivalent	600	1.18	0.30-6.1	
Some college	358	0.92	0.28-7.8	
Four-year college degree	187	0.65	0.25-2.8	
Postcollege study	82	0.73	0.20-3.9	
Primary insurance status				< .001
Medicare	908	1.22	0.30-8.3	
Private/commercial	279	0.58	0.20-3.5	
Other government (VA, Medicaid)	233	0.80	0.25-3.7	
Other, unknown, none	85	0.83	0.30-2.2	
Comorbidity				
Chronic respiratory disease				.03
Yes	471	1.18	0.33-6.7	
No	1,034	0.78	0.25-6.8	
Diabetes				.96
Yes	449	0.83	0.27-5.5	
No	1,056	1.0	0.25-5.5	
Congestive heart failure				.24
Yes	301	1.23	0.33-7.5	
No	1203	0.87	0.25-5.1	
Nonmetastatic solid organ cancer				.02
Yes	380	1.35	0.33-7.4	
No	1,125	0.83	0.25-5.1	
Dementia				.003
Yes	146	2.47	0.50-10.0	
No	1,359	0.82	0.25-5.2	
Metastatic solid organ cancer				.09
Yes	113	1.62	0.33-7.9	
No	1,392	0.88	0.25-5.4	
Chronic renal disease				.51
Yes	109	1.21	0.25-8.3	
No	1,396	0.92	0.27-5.5	
Cirrhosis				.08
Yes	92	0.42	0.17-1.9	
No	1,413	1.10	0.27-5.6	
Immunocompromised state				.30
Yes	96	0.65	0.23-3.5	
No	1,409	0.97	0.28-5.7	
Liver failure				.84
Yes	25	0.83	0.25-1.3	
No	1,480	0.93	0.25-5.6	
Leukemia				.11
Yes	27	0.50	0.1-2.8	
No	1,478	0.95	0.27-5.6	
Non-Hodgkin's lymphoma				.19
Yes	19	0.37	0.25-1.6	
No	1,486	0.95	0.27-5.6	
HIV or AIDS				.06
Yes	19	0.38	0.12-0.83	
No	1,486	0.95	0.27-5.6	
Charlson/Deyo comorbidity score (ICD-9-CM)				.03
0	363	0.58	0.20-3.6	
1	460	0.95	0.30-5.1	
2	264	1.02	0.28-7.5	
3	187	1.17	0.28-7.9	
4+	231	1.23	0.27-7.9	

See Table 1 legend for expansion of abbreviations.

or laboratory perturbation, which explain a portion of acute illness severity. Differences in severity of illness across age groups at the time of withdrawal would suggest that a combination of age and acute severity of illness were factored into the decision to withdraw mechanical ventilation, a finding that we[16] and others[33,34] have described previously but that has not been consistently confirmed.[3] Providers may be more willing to withdraw mechanical ventilation earlier in older patients who have poor long-term prognosis with less attention to their short-term severity of illness; on the other hand, uncertainty in the long-term prognosis for younger patients may delay withdrawal until outcome of death is more certain and immediate.[16]

A similar argument can be made for the longer times to death observed for women. A number of studies have suggested that women prefer less invasive or heroic measures to sustain life than do men.[35-37] In concordance with their preferences, women and their surrogate decision-makers may be more likely to withdraw ventilatory support earlier in the course of illness. However, another plausible hypothesis is that providers are more likely to recommend earlier

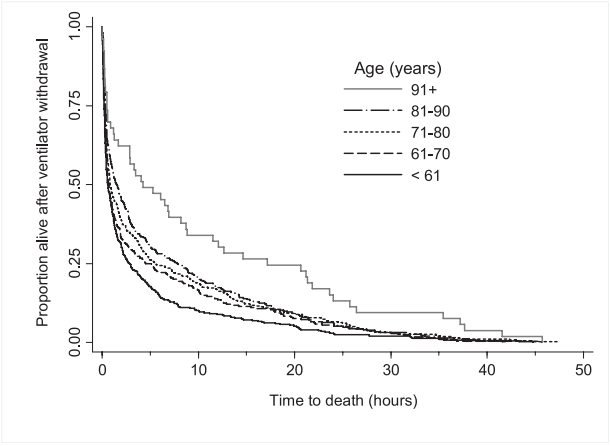

FIGURE 3. Kaplan-Meier estimate of survival after withdrawal of mechanical ventilation stratified by age category. The plot is truncated at 48 hours for ease of presentation and includes data for 1,484 (99%) of the patients.

withdrawal in women. A study by Johnson and colleagues[38] demonstrated that hospitalized women or their surrogates are twice as likely to receive a comfort care recommendation from a physician than are men. This finding was independent of age and comorbidities, raising the possibility of gender bias for recommendations at the end of life. Further studies characterizing the relationship among gender, severity of illness, and the timing of withdrawal are needed to test such hypotheses.

The shorter time to death noted between white and nonwhite patients also may be a result of differences in unmeasured severity of illness. Black patients often have greater severity of illness at the time of hospital ICU admission.[39] In addition, prior studies illustrate that black and Hispanic patients are more likely to prefer more aggressive life-sustaining treatments at the end of life,[40,41] and this may result in these patients having greater severity of illness at the time of terminal withdrawal of mechanical ventilation. Although we did not identify greater levels of organ dysfunction among nonwhite patients, post hoc analyses showed that prewithdrawal ICU lengths of stay were longer among nonwhite patients. The combination of longer lengths of stay prior to withdrawal, the likely greater illness severity at ICU admission, and the likely longer time to decisions to withdraw life support would suggest that nonwhite patients were sicker at the time of withdrawal. Although these hypotheses are plausible, we are cautious not to overinterpret our findings given our crude definition of race/ethnicity and the general lack of racial/ethnic diversity in this cohort.

Our results have important implications for practicing critical care clinicians. Providers who care for patients in the hospital ICU often are confronted with dying patients and inevitably are called upon to counsel patients and their families through end-of-life care. Although the majority of time spent communicating with the families of dying patients involves discussions leading up to a decision about whether to forego life-sustaining therapy,[42] high-quality end-of-life communication requires informing patients and families about the typical events that occur after support is withdrawn,[6,43,44] yet many families report receiving limited information about what to expect during the dying process or are not informed about the uncertainty in the timing of death after withdrawal.[14,45] Lack of information about

Table 3—*Bivariate Associations Between Time to Death After Withdrawal of Mechanical Ventilation and Patient Diagnosis, Severity of Illness, and Interventions*

Characteristic	No.	Time to Death, h		*P* Value
		Median	IQR	
Nonpulmonary organ failure (ICD-9-CM)				< .001
0	625	1.02	0.32-6.0	
1	468	1.50	0.32-9.4	
2	281	0.65	0.25-4.1	
3	111	0.42	0.17-1.5	
4	17	0.25	0.08-1.0	
5	3	0.20	0.18-0.47	
First diagnosis (ICD-9-CM)				.06
Respiratory	340	1.43	0.33-7.2	
Neurologic	234	0.60	0.28-4.3	
Cardiovascular	233	1.32	0.25-8.3	
Infectious	197	1.02	0.25-7.2	
Trauma/burn	149	0.85	0.17-3.6	
GI and hepatic	108	0.45	0.23-3.7	
Cancer	80	1.02	0.33-4.5	
Miscellaneous	164	0.73	0.22-4.5	
Primary service at time of death				< .001
Medicine	1,127	1.05	0.30-7.2	
Surgery	182	0.48	0.18-2.4	
Neurology/ neurosurgery	194	0.75	0.25-4.3	
ICU LOS prior to withdrawal, d				.06
<2	549	0.75	0.25-6.0	
2-4	307	0.88	0.25-5.2	
5-8	306	1.03	0.32-6.1	
9+	341	0.98	0.27-4.8	
Use of life-sustaining interventions during 4 d prior to withdrawal				
Vasopressors				< .001
Yes	760	0.50	0.20-2.7	
No	740	1.85	0.40-9.5	
Dialysis				.13
Yes	152	1.00	0.20-4.6	
No	1,348	0.90	0.27-5.5	
IV fluids				.02
Yes	1,124	0.82	0.25-4.9	
No	376	1.50	0.32-7.3	

See Table 1 legend for expansion of abbreviations.

Table 4—*Multivariable Cox Model of the Predictors of Time to Death After Mechanical Ventilator Withdrawal*

Predictor[a]	All Patients (N = 1,505)	
	Hazard Ratio	95% CI
Age, per 10 y	0.95	0.90-0.99
Female	0.86	0.77-0.97
Race		
White, non-Hispanic	1.00	Referent
Other race/ethnicity	1.17	1.01-1.35
Education		
Less than high school	1.05	0.84-1.30
Some high school	0.96	0.79-1.17
High school graduate/ equivalent	1.00	Referent
Some college	0.88	0.76-1.01
Four-year college degree	1.21	1.01-1.44
Postcollege study	1.12	0.88-1.42
Primary insurance		
Medicare	1.00	Referent
Private/Commercial	1.12	0.94-1.33
Other government (VA, Medicaid)	1.11	0.91-1.36
Other, unknown, none	1.02	0.81-1.27
Primary diagnostic category		
Respiratory	1.00	Referent
Neurologic	1.22	0.97-1.52
Cardiovascular	0.90	0.75-1.08
Infectious	0.90	0.75-1.09
Trauma/burn	1.07	0.84-1.35
GI and hepatic	0.98	0.76-1.26
Cancer	1.04	0.80-1.35
Miscellaneous	0.99	0.82-1.21
Admission source to hospital ICU		
ED	1.00	Referent
OR, recovery room, procedure	1.00	0.82-1.21
Hospital floor or observation	1.10	0.96-1.26
Direct admission	0.92	0.71-1.20
ICU LOS prior to withdrawal, d		
< 2	1.00	Referent
2-4	1.00	0.86-1.16
5-8	0.88	0.75-1.02
> 8	0.95	0.81-1.12
Number of nonpulmonary organ failures, per organ	1.11	1.04-1.19
Service at time of death		
Medical	1.00	Referent
Surgical	1.29	1.06-1.56
Neurology/neurosurgical	0.88	0.69-1.13
Use of life-sustaining interventions during 4 d prior to withdrawal		
Vasopressors	1.67	1.49-1.88
Dialysis	1.02	0.85-1.22
IV fluids	1.16	1.01-1.32

OR = operating room. See Table 1 legend for expansion of other abbreviations.

[a]Cox proportional hazards model adjusted for parent study intervention and stratified by hospital and Charlson/Deyo comorbidity score.

the timing of death may worsen the anxiety of families or cause frustration during a loved one's dying process.[14,45] Our results provide some general guidance for clinicians and are consistent with prior estimates of the timing of death after withdrawal[12,13] but require further validation.

We recognize several important limitations to our analysis. First, arguably the strongest predictor of time to death is the severity of a patient's acute illness, which was not fully incorporated into our model as described. As such, it is unclear whether the predictors in our Cox model would remain significant if acute illness severity was more completely accounted for. Second, our cohort was predominantly white, and all minority groups were collapsed into a single category we labeled nonwhite. This procedure may limit the generalizability of our findings and prevent richer explanation for racial/ethnic differences. Third, the focus of chart abstraction was the period surrounding death, and as a result, we have limited information about care prior to withdrawal of mechanical ventilation, which may lead to residual confounding of our reported associations. Fourth, our sample was identified as patients who died in the hospital ICU or within 30 hours of discharge from the ICU. Therefore, we are unable to quantify the proportion of patients who died beyond 30 hours after ICU discharge, which may limit the generalizability of our study. Although this subgroup is likely a minority of patients undergoing terminal withdrawal of mechanical ventilation, it may be an important subset.[13] Fifth, we did not account for multiple comparisons, which may have led to spurious associations. We attempted to minimize the chance of false-positive associations by specifying the covariates of interest a priori. Sixth, we collected limited data on administered therapies, such as opiates or anxiolytics, which may influence the time to death. Finally, our intent was not to optimize the predictive performance of our model or to provide an equation for providers to use in the process of end-of-life decision making. We do not believe that such a model would be predictive enough to be clinically useful. Our interest was only in identifying the variables independently associated with time to death. These limitations illustrate the need for further validation of these results, with specific attention paid to the acute physiologic severity of illness.

Comprehensive end-of-life communication requires adequately preparing families for what to expect once life support is withdrawn. We determined that the majority of patients on mechanical ventilation die within 24 hours after withdrawal of life support. Variability in the timing of death can be partly explained by demographic variables and measures of the severity of underlying disease. These results may inform clinicians and families about the expected timing of death after withdrawal of mechanical ventilation.

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Dr Engelberg: contributed to the study concept and design, data acquisition, interpretation of the data, data analysis, drafting of the manuscript, and acquisition of funding for the parent study.
Dr Rubinson: contributed to the study concept and design, interpretation of the data, and drafting of the manuscript.
Dr Curtis: contributed to the study concept and design, data acquisition, interpretation of the data, drafting of the manuscript, and acquisition of funding for the parent study.
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CHEST Online Supplement

Predictors of Time to Death After Terminal Withdrawal of Mechanical Ventilation in the ICU

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e-Appendix 1.

Multiple imputation procedure

We assumed the mechanism for missing data was random conditional on all of the measured covariates – missing at random[1]. We used the multiple imputation algorithm ice implemented in Stata as it allows for simple imputation of categorical variables[2,3].

Dichotomous variables were imputed using logistic regression and categorical values were imputed using multinomial (education, admission source, service) or ordinal (pre withdrawal ICU length of stay) logistic regression, and age was imputed using linear regression. Independent variables for each model included all variables included in the final regression model plus 21 additional variables in the dataset with complete data. Inclusion of a greater number of predictors in the imputation step results in greater efficiency and reduced bias in the final regression model[4]. These additional variables captured information about the documented decision makers for each patient (parent, sibling, spouse, other), completeness of chart documentation (nursing death note, physician death note), additional therapies (tube feeding, parental nutrition), symptoms at the end of life (pain, agitation, confusion, anxiety, shortness of breath, ventilator asynchrony) and comorbidities not included in the Charlson/Deyo score (hypertension, smoking, drug use, depression, immunosuppression). Finally, time to death was included in all imputation regression models. Inclusion of the outcome in multiple imputation yields much more valid results than when the outcome is excluded[5].

After we specified the regression model for each variable with missing data the algorithm replaced missing data with plausible substitutes including an appropriate amount of randomness to reflect uncertainty in the estimate. To increase the robustness of our approach, we used the boot option which relaxes the assumptions about the

distribution of the predicted missing values. This process was repeated 20 times creating 20 data sets that were each analyzed separately but identically and combined using Stata's mi estimate command.

Logistic regression analysis

Methods

We dichotomized the time to death after terminal withdrawal at 24 hours to determine the association between death occurring ≥ 24 hours after terminal withdrawal and each of the variables originally included in our proportional hazard regression (Table 4). This analysis included imputed data for the 46 patients missing data. Charlson-Deyo comorbidity score was included as an ordered categorical variable as described in Table 3. Standard errors for the logistic regression model were adjusted for clustering of patients within a study center. To allow for comparison with our primary time-to-death analysis, we report the OR (95% CI) for each variable in our multiple logistic regression model that was significant in our proportional hazard regression. We assessed model fit by describing the area under the receiver operating characteristic curve (AUC) and the Hosmer-Lemeshow goodness-of-fit statistic for each of the imputed data sets. The 20 estimates for the model coefficients and their standard errors were then combined into a single estimate using Rubin's rules[6]. We present the median (range) for the AUC in the 20 imputations as recommended by Marshall et al[7], but also combine AUC from the imputations using Rubin's to approximate the 95% confidence interval.

Results

Table A4 presents the results of the logistic regression model. Women were more likely to die beyond 24 hours after terminal withdrawal (OR 1.83; 95% CI 1.00, 3.34) while patients on vasopressors (OR 0.38; 95% CI 0.26-0.57) or dialysis (OR 0.31; 95% CI 0.12-0.82) were more likely to die prior to 24 hours after terminal withdrawal. Age, race, service, number of organ failures, and use of IV fluids were not significantly associated with death ≥ 24 hours, though point estimates were consistent with the reported associations in the primary analysis. The point estimate for age suggested older patients were more likely to die at ≥ 24 hours while estimates of non-white race, greater organ dysfunction, surgical service, and use of IV fluids indicated patients with these covariates were more likely to die < 24 hours after terminal withdrawal. The logistic model fit the data well. The median AUC (range) among the imputations was 0.75 (0.74-0.76). The approximate 95% CI for the AUC was 0.70 – 0.80. The Hosmer-Lemeshow χ^2 statistic was 8.07 ($p = 0.43$).

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e-Table 1. Diagnosis at hospital admission as defined by the first collected ICD-9 code

Disease	ICD-9 CM Code Definition
Cardiovascular	390* to 429*, 440* to 459*
Infectious	001* to139*
Respiratory	460* to 519*
Gastrointestinal/Hepatic	520* to 579*
Neurologic	320* to 389*, 430* to 438*
Trauma	800* to 959*, E800 to E848*, E880* to E929*, E950 to E999*
Cancer	140* to 239*

ICD-9, International Classification of Diseases, 9th Revision, Clinical Modification

* represents inclusion of all fourth and/or fifth digit of the respective ICD-9 CM codes

e-Table 2. Organ dysfunction definitions and coding using all 18 collected ICD-9 CM fields

Organ dysfunction	ICD-9 CM Code Definition
Cardiovascular	785.5* - *shock without trauma*, 458* - *hypotension*
Neurologic	348.3 – *encephalopathy*, 293* - *transient organic psychosis*, 348.1* - *anoxic brain injury*
Hematologic	287.4* - *secondary thrombocytopenia*, 287.5 - *thrombocytopenia, unspecified*, 286.9* - *other/unspecified coagulation defect*, 286.6* - *defibrination syndrome*
Hepatic	570* - *acute and subacute necrosis of the liver*, 573.4* - *hepatic infarction*
Renal	584 – *acute renal failure*

ICD-9, International Classification of Diseases, 9th Revision, Clinical Modification

* represents inclusion of all fourth and/or fifth digit of the respective ICD-9 CM codes

e-Table 3. Multivariable Cox proportional model of the predictors of time to death after ventilator withdrawal (excluding patients with missing values) – complete case analysis

	Complete case (n=1459)	
Predictor*	**Hazard Ratio**	**95% CI**
Age (per 10 years)	0.95	(0.90-0.99)
Female	0.84	(0.75-0.95)
Race		
White, non-Hispanic	1.00	Referent
Other race/ethnicity	1.16	(1.00-1.33)
Education		
Less than high school	1.07	(0.86-1.33)
Some high school	1.00	(0.83-1.21)
High school graduate / GED	1.00	Referent
Some college	0.91	(0.79-1.04)
Four year college degree	1.24	(1.04-1.48)
Post-college study	1.11	(0.87-1.42)
Insurance type		
Medicare	1.00	Referent
Private/Commercial	1.12	(0.94-1.33)
Other government (VA, Medicaid)	1.11	(0.90-1.36)
Other, unknown, none	1.00	(0.79-1.26)
Primary diagnostic category		
Respiratory	1.00	Referent
Neurological	1.21	(0.97-1.52)
Cardiovascular	0.92	(0.76-1.10)
Infectious	0.89	(0.73-1.08)

Trauma/burn	1.05	(0.83-1.34)
Gastrointestinal and hepatic	1.03	(0.80-1.32)
Cancer	1.05	(0.81-1.35)
Miscellaneous	1.01	(0.83-1.24)
Admission source to ICU		
Emergency department	1.00	Referent
OR / recovery room / procedure	0.97	(0.80-1.18)
Hospital floor / observation	1.07	(0.93-1.23)
Direct admission	0.90	(0.69-1.18)
ICU length of stay prior to w/d		
< 2 days	1.00	Referent
2-4 days	0.99	(0.85-1.15)
5-8 days	0.86	(0.74-1.01)
> 8 days	0.96	(0.81-1.13)
Number of non-pulmonary organ failures (per organ)	1.11	(1.04-1.19)
Service at time of death		
Medical	1.00	Referent
Surgical	1.26	(1.04-1.53)
Neurology / neurosurgical	0.92	(0.71-1.19)
Use of life sustaining interventions during 4 days prior to withdrawal		
Vasopressors	1.66	(1.48-1.87)
Dialysis	1.02	(0.85-1.22)
IV fluids	1.18	(1.03-1.35)

* Cox proportional hazards model adjusted for parent study intervention and stratified by hospital and Charlson/Deyo comorbidity score

e-Table 4. Multivariable logistic regression model of the predictors of death ≥ 24 hours after terminal ventilator withdrawal.

	All patients (n=1505)	
Predictor*	**Odds Ratio**	**95% CI**
Age (per 10 years)	1.13	(0.88-1.00)
Female	1.83	(1.00-3.34)
Race		
White, non-Hispanic	1.00	Referent
Other race/ethnicity	0.75	(0.35-1.79)
Number of non-pulmonary organ failures (per organ)	0.81	(0.64-1.04)
Service at time of death		
Medical	1.00	Referent
Surgical	0.58	(0.24-1.39)
Neurology / neurosurgical	1.12	(0.39-3.23)
Use of life sustaining interventions during 4 days prior to withdrawal		
Vasopressors	0.38	(0.26-0.57)
Dialysis	0.31	(0.12-0.82)
IV fluids	0.72	(0.45-1.16)

* Logistic regression model adjusted for education, primary insurance, diagnostic category, admission source to ICU, ICU length of stay prior to withdrawal, use of dialysis during four days prior to withdrawal, and Charlson score. Confidence intervals adjusted for clustering in study center.

e-Figure 1. Distribution of the time to death (hours) after terminal withdrawal for the 140 patients who died after discharge from the intensive care unit (ICU). The time of ICU discharge was used as time zero.