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Timing of Limitations in Life Support in Acute Lung Injury Patients: A Multi-Site Study

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Abstract

Objective—Substantial variability exists in the timing of limitations in life support for critically ill patients. Our objective was to investigate how the timing of limitations in life support varies with changes in organ failure status and time since acute lung injury (ALI) onset.

Design, Setting, and Patients—This evaluation was performed as part of a prospective cohort study evaluating 490 consecutive ALI patients recruited from 11 intensive care units (ICUs) at three teaching hospitals in Baltimore, MD.

Interventions—None.

Measurements—The primary exposure was proportion of days without improvement in Sequential Organ Failure Assessment (SOFA) score, evaluated as a daily time-varying exposure. The outcome of interest was a documented limitation in life support defined as any of the following: (1) No CPR, (2) Do not re-intubate, (3) No vasopressors, (4) No hemodialysis, (5) Do not escalate care or (6) Other limitation (e.g., “comfort care only”).

Main Results—For medical ICU (MICU) patients without improvement in daily SOFA score, the rate of limitation in life support tripled in the first three days after ALI onset, increased again after Day 5, and peaked at Day 19. Compared to MICU patients, surgical ICU (SICU) patients had a rate of limitations that was significantly lower during the first five days after ALI onset. In all

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patients, more days without improvement in SOFA scores was associated with limitations in life support, independent of the absolute magnitude of the SOFA score.

Conclusions—Persistent organ failure is associated with an increase in the rate of limitations in life support independent of the absolute magnitude of SOFA score, and this association strengthens during the first weeks of treatment. During the first five days after ALI onset limitations were significantly more common in MICUs than SICUs.

Keywords

Intensive Care; Resuscitation Orders; Terminal Care; Withholding Treatment; Acute Lung Injury; Prospective Studies; Respiration; Artificial; Survival Rate; Time Factors; Intensive Care units; Life Support Care

Introduction

One in five Americans dies in an intensive care unit (ICU).[1] Between 50% and 90% of these deaths occur after limiting the use of life sustaining therapies.[2–5] Prior studies evaluating end-of-life decisions in the ICU have focused primarily on baseline characteristics of patients and physicians.[6, 7] While age, pre-existing comorbidities, and quality-of-life likely have a strong influence on ICU admission and the decision to initiate life support, over time, these factors may be over-shadowed by patients' trajectory of critical illness while receiving treatment in the ICU. Decisions about the appropriate use of life support are especially relevant in patients with acute lung injury (ALI) because they experience a high severity of illness, frequent multiple organ dysfunction, and survivors often experience new physical, cognitive, and psychological comorbidities with associated decreases in quality of life.[8–13] Although previous cohorts of critically ill patients likely included some patients with ALI, the incidence and timing of decisions to limit life support specifically for ALI patients has not been thoroughly explored. Our objectives were to evaluate the timing of new limitations in life support among patients with ALI, and to determine whether the persistence of organ dysfunction is associated with new limitations during the course of an ICU stay.

Materials and Methods

Study Cohort

As part of a prospective cohort study, mechanically ventilated patients who met the American-European Consensus criteria for ALI [14] were consecutively enrolled from 13 ICUs at four hospitals in Baltimore, Maryland between October 2004 and October 2007.[15] Patients in neurologic specialty ICUs were excluded to avoid enrolling patients with head trauma or primary neurologic disease. Key exclusion criteria were: 1) pre-existing illness with a life expectancy of <6 months; 2) pre-existing cognitive impairment or communication/language barriers; 3) no fixed address; 4) transfer to a study site ICU with pre-existing ALI of >24 hours duration; 5) >5 days of mechanical ventilation before ALI; and 6) a pre-existing limitation in life support at the time of study eligibility (except for a sole order for "no cardiopulmonary resuscitation" (CPR) in the event of a cardiac arrest). For this analysis we excluded research participants who had a sole "no CPR" limitation at ALI onset (n=24), so that all participants had no limitations in life support at ALI onset. In addition, participants recruited from two ICUs at the Veterans Affairs hospital study site (n=6) were excluded because medical records were inaccessible for independent verification of limitations of life support at the time of this analysis. Consequently, a total of 490 patients from 11 ICUs were available for this analysis. The institutional review boards of Johns Hopkins University and all participating study sites approved this research.

Primary Outcome

Patient records were evaluated on a daily basis while in the ICU for limitations in the use of life support. A limitation in life support was defined as any of the following: (1) No CPR, (2) Do not re-intubate, (3) No vasopressors, (4) No hemodialysis, (5) Do not escalate care or (6) Other limitation (e.g., “comfort care only”). These limitations were considered in this analysis when initiated either with or without a concomitant decision to withdraw life support.

Primary Exposure

The primary exposure for this analysis was the proportion of days since ALI onset during which a patient’s SOFA score remained the same or increased, corresponding to no improvement or worsening of organ function. The SOFA score was developed as an objective quantitative description of the degree of organ dysfunction in critically ill patients over time.[16]. Total score (range 0 to 24) is calculated as the sum of a 4-point scale used to measure organ dysfunction for each of the following six body systems: respiratory, circulatory, renal, hematologic, hepatic, and central nervous system, with greater dysfunction given a higher score. SOFA scores were missing for only 9 of 8,673 (0.10%) days of observation. These missing scores were imputed by multiple imputation and included in analysis. The proportion of ICU days since ALI onset without improvement in SOFA score was calculated as the number of days that a patient failed to improve divided by the number of days since ALI onset. The proportion of improved days was first measured on Day 1 by comparing a patient’s Day 1 SOFA score with that on the day of ALI onset (Day 0). We also considered additional measures of SOFA score for inclusion in the analysis, including whether the SOFA score had improved in the previous 24-hours, change in SOFA score from the day of ALI onset, and change in SOFA score over the past 3 or 7 days. However, the addition of these measures to the existing model did not substantially improve fit, as evaluated using likelihood ratio tests, and thus were excluded from the final model.

Covariates

The following baseline covariates hypothesized to be potentially associated with the use of life support were included in the analysis: patient age, sex, race (white vs non-white), days of hospitalization prior to ALI onset, indicator of hospital study site (1, 2, or 3), ICU type (medical vs surgical), Charlson comorbidity index[17], cancer history, Acute Physiology and Chronic Health Evaluation II (APACHE II) severity of illness score at ICU admission [18], and the Functional Comorbidity Index [19] measure of baseline physical functional status. In addition, the individual daily scores for each of the 6 body systems which comprise the SOFA score were entered into the model as time-varying covariates; thus, allowing the estimation of limitation rates for prototypical patients with the combination of organ system failures typical in this ALI cohort.

Statistical Analyses

All patients were analyzed from ALI onset until the day that a limitation in life support first occurred. For illustrative purposes, results are displayed to day 21 at which point the majority of outcomes had occurred. Cardiac arrest and discharge from the ICU were treated as censoring events. For this analysis, flexible parametric survival regression models were used, with restricted cubic splines of the Weibull distribution (with knots at 3, 7, and 21 days) used for the baseline hazard function.[20–22] The shape of the baseline hazard was determined by maximizing Akaike’s Information Criterion (AIC) and favoring simple models in the case of near ties of AIC values. All models were adjusted for covariates as previously described.

Each covariate was evaluated for a time-dependent effect by fitting interaction terms with time and comparing models with and without time-dependent effects using likelihood ratio tests. Only the estimated effect of the primary exposure (proportion of days without improvement in SOFA score) and a single covariate (ICU type) on the rate of limitations varied significantly with time. Thus, relative hazards obtained from the regression models for these variables were modeled as functions of time. Analysis was conducted using STATA 11.0 (StataCorp, College Station, TX).

Results

Among the 490 patients in our analysis, median age was 52 years (interquartile range 42 – 62), 43% were female, 80% were treated in medical ICUs, and 56% survived to ICU discharge (Table 1). Half of all patients were hospitalized for <2 days prior to ALI onset. Patients in SICUs were more likely to be male and white than MICU patients, and their median APACHE II score was lower at ICU admission (Table 1). During the first five days after ALI onset, 18% of MICU patients and 3% of SICU patients had new limitations in life support. A total of 192 patients (39%) had limitations prior to ICU discharge or cardiac arrest in the ICU. The median time from ALI onset to any limitation in life support was 7 days (interquartile range 3 – 16).

To illustrate how the timing of limitations in life support changed, the survival model was used to estimate the number of limitations in life support each day among 100 prototypical patients with median values for all continuous covariates and mode values for all binary covariates in a MICU and in a SICU (Figure 1). Notably, over the first three days in a MICU, the point estimate for the rate of first limitation was more than three-fold greater for patients with no improvement in daily SOFA score versus patients with daily improvement, and then decreased thereafter, reaching a nadir at Day 5. However, in SICU patients, this pattern was not observed, with the rate of limitations continuously increasing over time. Among both MICU and SICU patients with no improvement in daily SOFA scores, the rate of limitations peaked at Day 19.

The time-varying, adjusted relative hazards for limitations in life support are reported in Table 2 and Figure 2. The relative hazard of a limitation was always numerically greater for patients with fewer days of improvement in SOFA score and for patients in MICUs. However, as depicted in Figure 2, only some of these differences reached statistical significance. More specifically, the relative hazard of a limitation for MICU patients without improvement in SOFA score compared to patients with daily improvement ranged from 1.85 to 9.20, and achieved statistical significance between days 5 and 20. Consequently, two ALI patients with the same baseline characteristics who have both survived in the ICU for one week and have the same SOFA scores in every organ system may not have the same immediate risk of a limitation in life support. Limiting the use of life support is more likely for the patient who has had fewer days of improvement in overall organ dysfunction during the past week. The relative hazard of a limitation for MICU patients without improvement in SOFA score relative to SICU patients without improvement ranged from 1.22 to 3.46 and was statistically significant on the first five days following ALI onset, after which time the rates of first limitations for MICU and SICU patients were similar.

Discussion

Our analyses of this multi-site, prospective, cohort study of ALI patients had three major findings. First, the timing of limitations in life support for ALI patients treated in MICUs demonstrated an early peak around Day 3 and a second peak 2 – 3 weeks later for patients without consistent improvement in organ function. Second, patients in SICUs are initially

much less likely to have limitations in life support than MICU patients, but this difference dissipated by Day 14. Finally, patients who failed to show consistent improvement in organ function had higher limitation rates than patients who displayed improvement, even when the absolute magnitude of organ dysfunction on the day of evaluation was the same.

The small number of MICU patients with a first limitation more than two weeks after ALI onset makes our estimates at those times imprecise. However, there are several clinical observations that may support the observed pattern of an early peak around Day 3 and a second peak later on. For instance, there may be early meetings with patient surrogates that include discussions about limiting the use of life support or about time-limited trials of life support therapies.[23] The pattern also may represent two distinct groups of patients: those for whom meetings about prognosis and goals of care occur during the first three days following ALI onset, and those for whom such meetings do not occur until the patient fails to show consistent improvement in organ function. Family meetings may not occur for some subgroups of patients because identifying appropriate patient surrogates and scheduling meetings can be time-consuming and difficult [24, 25]. It is also possible that some intensivists simply choose not to present the option of limiting life support unless patients show several days of steady deterioration.[26]

The observed difference in the timing of limitations between medical and surgical ICUs may be a result of differences in the patient populations which were not captured by the covariates in our models. The observed preference for life support interventions in the SICU is also consistent with previous research describing an informal “covenant of care” between surgeons and their patients.[27] In a survey of 2,100 surgeons practicing in the U.S., the majority reported refusing to operate on patients with preferences for limiting life support and only half considered it acceptable to honor a patient or surrogate request to withdraw life support on postoperative Day 7.[28, 29] In our study cohort, limiting life support postoperatively in the SICU also may have been viewed as undesirable if physicians viewed ALI as an avoidable complication.[30] However, for patients who remained critically ill for at least a week, the rate of limitations in life support in a SICU vs MICU was not significantly different. Further study is required to determine whether this indicates that informal agreements about the postoperative use of life support are of limited duration.

This study has a number of potential limitations. Not all potentially relevant factors associated with limitations in life support were evaluated in this study (e.g. proxy perception of patient’s pre-ICU quality of life, differences in physician specialty and training, and physician attitudes to limiting life support) which may have resulted in residual confounding in evaluating the association between persistent organ dysfunction and limitations in life support and in the comparison of medical versus surgical patients. Our cohort was limited to acute lung injury patients at three teaching hospitals in a single city, limiting generalizability of findings especially given known regional variability ICU care at the end-of-life [31, 32]. Our outcome of interest included both documented decisions not to initiate additional forms of life support as well as decisions to withdraw existing life support. We expect that isolated decisions not to initiate a treatment were less likely to be documented compared to decisions to withdrawal life support yielding some potential measurement error. However, we believe that the broader definition used in this study better reflects the range of decisions made in an ICU setting about the use of life-sustaining interventions. Finally, this study cannot describe how the shared decision-making process influenced the timing of limitations in life support. Without data on when meetings about the use of life support occurred, or on the goals of care expressed by patient surrogates, we cannot attribute the observed outcomes to differences in the behaviors of physicians or families.

In conclusion, the timing of limitations in life support for patients with ALI is complex and dynamic over the first weeks of treatment. Patients in MICUs versus SICUs had significantly more limitations during the first five days after ALI onset. In both MICUs and SICUs, a lack of consistent improvement in organ function is associated with new limitations in life support independent of the absolute magnitude of organ failure.

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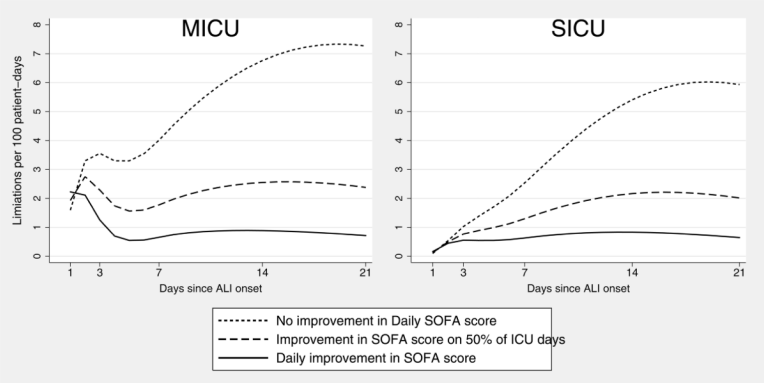

Figure 1. Rate of Limitations in Life Support Over 21 Days After Acute Lung Injury Onset

Estimates for the rate of limitations in life support over 21 days among prototypical patients in this acute lung injury cohort, assuming median values for continuous covariates and mode values for binary covariates.

Abbreviations: MICU, Medical Intensive Care Unit; SICU, Surgical Intensive Care Unit; SOFA, Sequential Organ Failure Assessment score; ALI, acute lung injury

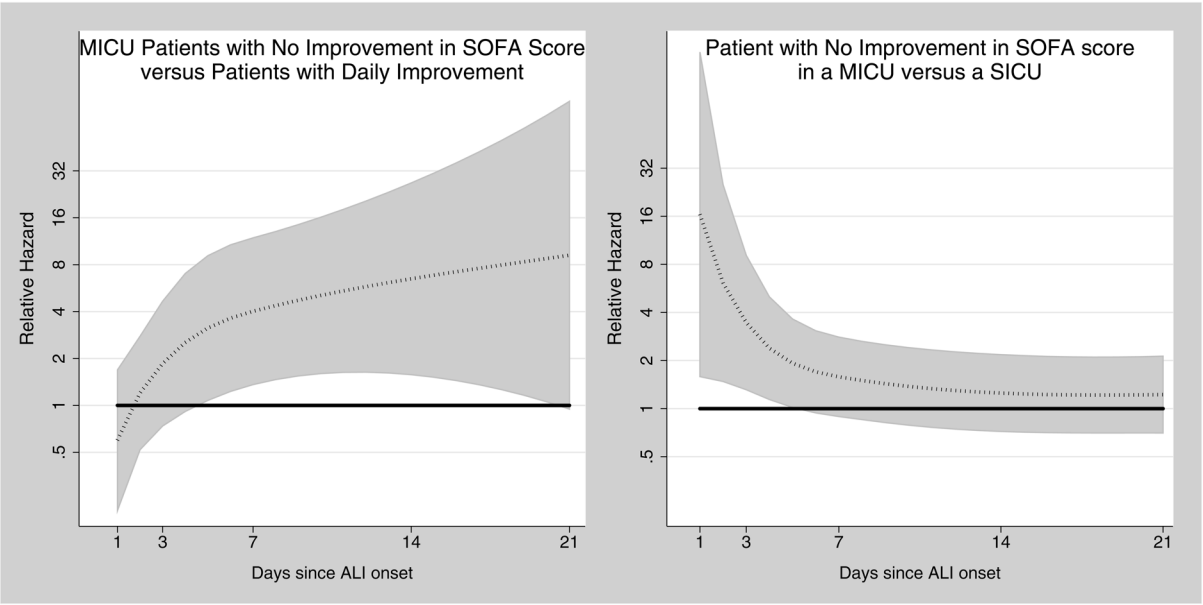

Figure 2. Time-Dependent Relative Hazards of Limitations in Life Support Over 21 Days After Acute Lung Injury Onset

Time dependent relative hazards (dotted line) and 95% confidence intervals (shaded areas) for limitations in life support over 21 days of follow-up for prototypical patients in this acute lung injury cohort. Horizontal solid line at a relative hazard of 1.0 indicates no difference in the rate of limitations in life support for compared groups.

Abbreviations: ICU, intensive care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; SOFA, sequential organ failure assessment; ALI, acute lung injury

Table 1

Patient characteristics and outcomes for acute lung injury cohort

Patient Characteristics	All patients (N = 490)	MICU (N = 394)	SICU (N = 96)
Age; median (IQR)	52 (42 – 62)	51 (41 – 61)	54 (44 – 65)
Female	43%	45%	38%
Non-white	41%	45%	24%
Charlson Comorbidity Index; median (IQR)	2 (1 – 4)	2 (1 – 4)	2 (0 – 3)
Cancer History	18%	18%	22%
Functional Comorbidity Index; median (IQR)	1 (1 – 3)	1 (1 – 3)	2 (1 – 3)
Study site hospital indicator			
1	38%	44%	14%
2	31%	35%	14%
3	31%	21%	73%
ICU Admission Source[a]			
Emergency department	42%	45%	29%
Hospital floor	39%	42%	28%
Another ICU	13%	12%	16%
Operating room	4%	0%	23%
Other	1%	1%	4%
APACHE II at ICU admission; median (IQR)	26 (20 – 33)	27 (21 – 34)	21 (17 – 27)
Total SOFA score at ALI onset; median (IQR)	9 (7 – 12)	10 (7 – 13)	8 (6 – 11)
Days in Hospital Prior to ALI Onset; median (IQR)	2 (1 – 6)	2 (1 – 6)	3 (1 – 8)
Days in ICU Prior to ALI Onset; median (IQR)	1 (0 – 2)	0 (0 – 2)	1 (0 – 3)
Patient Outcomes			
First event[a]			
Discharged alive from ICU	48%	45%	61%
Limitation in use of life support[b]	39%	42%	28%
Cardiopulmonary resuscitation[c]	13%	13%	10%
Survived to ICU discharge	56%	52%	73%

Abbreviations: IQR, Interquartile Range; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment; ALI, acute lung injury; CNS, central nervous system

[a] Proportions do not add to 100% due to rounding

[b] Of these patients, 14%, 11%, and 26% survived to ICU discharge for All patients, MICU patients and SICU patients, respectively.

[c] Of these patients 24%, 21%, and 40% survived to ICU discharge for All patients, MICU patients and SICU patients, respectively.

Table 2

Time-Dependent Adjusted Relative Hazards* for Limitation in Life Support after Acute Lung Injury Onset

Proportion of ICU days with SOFA score improvement from prior day		Day 3 RH (95% CI)	Day 7 RH (95% CI)	Day 14 RH (95% CI)	Day 21 RH (95% CI)
MICU	100%	Reference	Reference	Reference	Reference
	75%	1.18 (0.93 – 1.52)	1.44 (1.08 – 1.94)	1.62 (1.10 – 2.42)	1.78 (0.90 – 3.56)
	50%	1.39 (0.86 – 2.24)	2.06 (1.16 – 3.64)	2.60 (1.22 – 5.56)	3.13 (0.87 – 11.21)
	25%	1.61 (0.80 – 3.26)	2.89 (1.26 – 6.64)	4.13 (1.38 – 12.36)	5.39 (0.89 – 32.59)
	0%	1.85 (0.74 – 4.66)	4.02 (1.36 – 11.89)	6.49 (1.57 – 26.77)	9.20 (0.95 – 89.39)
SICU	100%	Reference	Reference	Reference	Reference
	75%	1.39 (0.93 – 2.09)	1.70 (1.04 – 2.80)	1.72 (1.03 – 2.87)	1.85 (0.81 – 4.25)
	50%	1.83 (0.90 – 3.68)	2.71 (1.16 – 6.35)	2.87 (1.12 – 7.37)	3.33 (0.75 – 14.87)
	25%	2.31 (0.89 – 5.96)	4.14 (1.32 – 13.00)	4.72 (1.27 – 17.56)	5.87 (0.75 – 46.08)
	0%	2.84 (0.88 – 9.15)	6.13 (1.50 – 25.00)	7.62 (1.46 – 39.85)	10.18 (0.79 – 131.72)
ICU Type†	Surgical	Reference	Reference	Reference	Reference
	Medical	3.46 (1.31 – 9.11)	1.59 (0.89 – 2.80)	1.25 (0.72 – 2.18)	1.22 (0.70 – 2.13)

Abbreviations: ICU, intensive care unit; SOFA, sequential organ failure assessment; MICU, medical intensive care unit; SICU, surgical intensive care unit; 95% CI, 95% confidence interval; ALI, acute lung injury

*The relative hazard describes the relative risk of having a first limitation in life support on a specific day in the ICU. For example, a patient with a relative hazard of 1.66 on day 7 has a 66% increased risk of having a limitation on day 7 compared to the reference patient. Model is adjusted for age, race, sex, hospital study site indicator, days of hospitalization prior to ALI onset, Acute Physiology and Chronic Health Evaluation II score at ICU admission, Charlson Comorbidity Index, Cancer history, Functional Comorbidity Index, and time-varying SOFA score organ system components.

†Calculated for patients with no improvement in SOFA score (i.e. proportion of ICU days with SOFA score improvement from prior day = 0%)