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Late organ failures in patients with prolonged intensive care unit stays

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Abstract

Purpose—The purpose of this study was to characterize the organ failures that develop among patients with prolonged ICU stays, defined as those who spent a minimum of 14 days in an ICU.

Methods—We retrospectively studied a cohort of consecutive patients from a university hospital who were in an ICU for a minimum of 14 days during 2014–2016. We calculated daily Sequential Organ Failure Assessment (SOFA) scores from admission to ICU day 14. The primary outcome was the number of new late organ failures, defined as occurring on ICU day 4 through 14.

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Results—In a retrospective cohort of 3777 consecutive patients in six ICUs, 50 patients had prolonged ICU stays. Of those 50, new cardiovascular failure occurred in 24 (62%) on day 4 or later; persistent mechanical ventilation was present in only 28 (56%).

Conclusions—Strategies aiming to reduce the development of new late organ failures may be a novel target for preventing persistent critical illness.

Keywords

outcomes; prolonged ICU stay; chronic critical illness; prolonged mechanical ventilation; persistent critical illness

Some patients remain in the intensive care unit (ICU) long after initial resuscitation, but their ongoing critical care needs have not been characterized. This persistent critical illness—defined as when the patients “reason for being in the ICU is now more related to their ongoing critical illness rather than their original reason for admission to the ICU”—has been hypothesized to be caused by new cascading organ dysfunction, in contrast to simply slow resolution of presenting problems.⁽¹⁾ Population-based data in Australia and New Zealand suggest such cascades are the major driver of prolonged ICU use by the second week of ICU hospitalization.^(1, 2)

However, existing population-based data lack the clinical granularity necessary to understand organ dysfunction later in the ICU course. Therefore, we measured the frequency and types of new late organ failures occurring on and after ICU day 4 in a cohort of patients who spent 14 consecutive days in ICU. We also tested for differences on ICU admission between long-staying patients and those who died or were discharged alive earlier.

Methods

We conducted a retrospective study of all admitted patients across six ICUs in a single university hospital from 2014–2016, approved by the Institutional Review Board of the University of Michigan. Patients were excluded if under age 18, admitted to neurologic or trauma-burn ICU, transferred from another hospital, documented to have pre-existing neuromuscular disease or tracheostomy, or were in ICU in the previous 12 months. STROBE guidelines were followed.

We operationally defined persistent critical illness as 14 or more consecutive ICU days. This was intentionally chosen to be longer than the 10 day transition point identified in Australian and New Zealand ⁽²⁾ as population-based data are not yet available in the U.S., and we sought to minimize the risk of contamination by patients with “false positive” labels of persistent critical illness.

We identified daily organ failures using the Sequential Organ Failure Assessment (SOFA) organ component scores.⁽³⁾ We excluded the central nervous system given the variability of its assessment in sedated patients.⁽⁴⁾ Cardiovascular organ SOFA component score accounted for phenylephrine, dobutamine, and milrinone as in the NICE-SUGAR trial.⁽⁵⁾ Respiratory organ SOFA component preferentially scored the PaO₂/FiO₂ ratio. When the PaO₂ was not available, the SaO₂/FiO₂ ratio was used.^(6, 7) The etiology of new

cardiovascular failure by SOFA criteria was then determined by independent chart review by two critical care-trained investigators (EMV, AJA). Differences in opinion were discussed until consensus was obtained.

New late organ failure was defined as a worsening by 2 SOFA points in a single organ component from ICU day 4 to 14 compared the best organ function obtained during that time period; the cut-off of 2 was based on the definition of organ failure used by Sepsis 3.(8) Non-resolving organ failure was defined as a SOFA organ component score which was 2 in the coagulation, liver, cardiovascular and renal components and 3 in the pulmonary component (to capture ongoing mechanical ventilation) from ICU admission to day 14. The initial 3 calendar days of an ICU stay were excluded in order to avoid confusing failures that were part of the initial presentation to the ICU with those that developed truly in the ICU, by analogy to the cut-off operationally used to define hospital-acquired pneumonia.(9)

Multinomial logistic regression identified patient characteristics on ICU admission associated with prolonged stays. Covariates chosen *a priori* were limited to five.

Results

During 2014–2016, study ICUs admitted 3777 patients who did not meet exclusion criteria. Of these, 50 patients had ICU lengths of stay greater than 14 days, defining persistent critical illness here. (Table 1)

Among patients admitted to the ICU, lower total SOFA scores on ICU admission were associated with discharge alive without developing persistent critical illness (RRR 0.75, 95% CI: 0.69, 0.81), but did not distinguish those who developed persistent critical illness from those who died (RRR 0.97, 95% CI: 0.89, 1.05). In contrast, patients with higher Charlson comorbidity scores were more likely to die (RRR 1.51, 95% CI: 1.29, 1.76) or be discharged alive (RRR 1.28, 95% CI: 1.10, 1.49) than develop persistent critical illness. Younger age was associated with being more likely to be discharged alive without the development of persistent critical illness (RRR 0.79 per decade of age, 95% CI: 0.65 – 0.95), but did not distinguish those who die from those who develop persistent critical illness. (Table 2)

Of the 50 patients with ICU stays greater than 14 days, 22% (n=11) had no new organ failures, 30% (n= 15) had only 1 organ fail; 48% (n= 24) of the patients had more than 1 organ fail between days four and 14. The most common new late organ failure was cardiovascular failure (n= 24 patients, 61.5%). New respiratory, renal, liver, and coagulation organ failures occurred in 13 (33% of the 39), 14 (36%), 14 (36%), and five (13%) patients respectively (with 27, 14, 15, 17 and five new events among those patients during ICU days 4–14). Chart review demonstrated the most common etiology of cardiovascular failure was presumed to be sepsis (n= 19/27 events, 70.4%) compared to hypovolemia (n= 5, 18.5%), cardiogenic (n= 2, 7.4%) and tension pneumothorax (n= 1, 3.7%).

All 50 patients underwent invasive mechanical ventilation at some point during their first 14 days. Of them, 32% (n= 16) were persistently intubated and never extubated during the first 14 days, with 88% (n= 14/16) having P/F ratios 200 on ICU day 14. Of the 34 patients

extubated at some point in the first 14 days, 53% (n=18) remained successfully extubated through ICU day 14, but 47% (n= 16) were re-intubated before day 14. Of those 16 re-intubated, four were extubated again and 12 remained intubated, 67% (n= 8) of whom had P/F ratios > 200 on ICU day 14. The 22 patients extubated yet still in ICU on day 14 had been extubated for a median of 5 days (IQR 3, 8).

Discussion

In this retrospective cohort, lower admission illness severity was associated with earlier discharge rather than development of persistent critical illness, and lower comorbidity was associated with persistent critical illness rather than early discharge from the ICU or death in the first two weeks in ICU; younger age was less associated with the development of persistent critical illness. Among those with persistent critical illness, four in five developed at least one new late organ failure, most commonly cardiovascular. Respiratory failure was persistent in only half (n= 28) long-staying patients; when present, it was marked by ongoing hypoxemia. Finally, re-intubation after extubation was common and typically occurred several days later.

Our study has limitations. First, it is a six ICU, single center, retrospective cohort. However, these patients have characteristics typical of patients at teaching institutions. Second, we did not measure organ failures or indications for ICU care not represented by SOFA scores. Third, study ICUs used stepdown units and long term acute care centers (LTAC), which were not considered ICUs, diverting some patients who at other hospitals might stay in ICU.(10) If LTACs preferentially took patients with simple single organ respiratory failure, that would bias downwards the incidence of such patients in our cohort. However, two-thirds of patients admitted to LTACs are never mechanically ventilated, showing little preference for respiratory failure.(10) Fourth, it is unknown if the patients with a higher Charlson comorbidity index were more likely to die as a result of the withdrawal of care or limitations of care. The literature on intracranial hemorrhages has shown that early care limitations are independently associated with both short and long-term mortality despite adjustment for expected predictors; this raises questions as to how often deaths are due to unsupportable physiologic instability, or rather to the prognostication of the eventual development of such physiologic instability, or of the perception that ongoing support was discordant with the patient's values.(11)

Conclusion

Our findings imply that using mechanical ventilation to define persistent critical illness (and target interventions) will miss patients who have ongoing needs for critical care. Furthermore, these data imply that long-staying patients in ICU often cannot be understood as merely failing to resolve their problems. Instead, new organ failure(s) characterize the inability to progress to ICU discharge. If replicated in additional populations, it implies that cascades of organ failures typify persistent ICU care. Exploring such cascades may yield insights into multi-organ interactions and suggest interventions to interrupt those cascades.

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Abbreviations

ICU	Intensive Care Unit
IQR	Interquartile Range
LTAC	Long-term Acute Care Hospital
SOFA	Sequential Organ Failure Assessment
SD	Standard deviation
RRR	Relative risk ratio

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Highlights

- Lower admission illness severity was associated with earlier discharge rather than development of persistent critical illness, and lower comorbidity was associated with persistent critical illness rather than death or earlier discharge in the first two weeks in ICU
- Four in five of long-staying ICU patients developed at least one new late organ failure, which was cardiovascular in nature in most cases.
- Respiratory failure and the need for mechanical ventilation was present in only half (of all long-staying ICU patients and, in most such cases, it was marked by ongoing hypoxemia.
- Only one in five patients in this cohort did not develop new late organ failures, but instead had persistent respiratory or cardiovascular failure from admission

Table 1

Demographics of the patients admitted to ICU from 2014–2016

Demographics	Patients with a prolonged ICU stay N = 50	Patients without a prolonged ICU stay N= 3727
Gender (Male), % (N)	60% (30)	59% (2211)
Age, median, (IQR)	64 (58,74)	62 (51,71)
Race, % (N)		
White	76% (38)	84% (3129)
Other	24% (12)	16% (598)
Type of ICU, % (N)		
Medical	18% (9)	29% (1081)
Surgical	22% (11)	27% (1012)
Cardiac	58% (29)	43% (1592)
Other	0% (0)	2% (72)
Charlson Co-morbidity Index, median (IQR)	2 (1,4)	3 (1,5)
ICU LOS, median (IQR)	21 (17, 28)	2 (1, 4)
Hospital LOS, median (IQR)	39 (28, 50)	7 (5, 12)
In-Hospital Death, % (N)	30% (15)	8.2% (305)
Median Total Hospital Charge ^a (IQR)	\$736,726 (522,424, 974,616)	\$112,782 (78,419, 174,965)

ICU: Intensive Care Unit; IQR: Interquartile range; LOS: Length of stay

^aCharges were not available for 2 patients with prolonged ICU stays.

Table 2

Association of Patient-Level Characteristics comparing patients with prolonged ICU stays to patients without prolonged ICU stays who are discharged either alive or dead. A Multivariable Logistic Regression on ICU admission.

Compared to those with prolonged ICU stays				
	Patients without prolonged ICU stays and alive		Patients without prolonged ICU stays and deceased	
	RRR	95% CI	RRR	95% CI
Age (per decade)	0.79	0.65 – 0.95	0.92	0.75 – 1.14
Sex (vs Female)	1.03	0.58 – 1.83	0.81	0.44 – 1.51
Race				
Other (vs White)	0.51	0.26 – 1.00	0.44	0.21 – 0.99
Charlson Comorbidity Index (per point)	1.28	1.10 – 1.49	1.51	1.29 – 1.76
Total SOFA score (per point)	0.75	0.69 – 0.81	0.97	0.89 – 1.05

ICU: Intensive care unit; RRR: Relative risk ratio; CI: confidence interval; SOFA: Sequential Organ Failure Assessment, using the NICE-SUGAR Study modification