The heterogeneity of prolonged ICU hospitalisations

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Prolonged intensive care unit (ICU) hospitalisations are costly, increasing in prevalence and strain ICU resources.[1–4] One-year mortality is high and the recovery for survivors of prolonged ICU hospitalisations is typically long and marked by new morbidities.[3 4] Thus, with advances in critical care technology, patients with prolonged ICU hospitalisations, their families and physicians are challenged to make complex, high-stakes decisions without clear guidance about long-term prognosis.

Recent work has focused on *who* these patients are and *why* they remain in the ICU for prolonged periods of time.[5–8] Commonly measured patient characteristics on admission such as age and comorbidities have not consistently been associated with the need for prolonged ICU hospitalisations. (Of note, other premorbid patient characteristics, such as frailty, have not been studied as a risk factor for persistent critical illness.) These findings have challenged preconceived beliefs that prolonged ICU hospitalisations only occur for older patients or those with multiple comorbidities.[5 8] Instead, observational data suggest the development of new organ dysfunctions not present on admission contributes to the development of prolonged ICU hospitalisations.[6 7] This finding moves our understanding of prolonged ICU hospitalisations beyond the prototype of chronic critical illness—a patient with unresolving respiratory failure—and towards a more complete picture of how prolonged ICU hospitalisations emerge over time in the ICU.[3] (figure 1)

Hermans *et al* describe the long-term mortality and morbidity of patients with prolonged ICU hospitalisations who are matched to short-stayers (patients who remained in the ICU for <8 days).[9] The authors created three different matched cohorts to evaluate long-term mortality (total and post-28-day 5-year mortality) and morbidity. The authors performed a re-analysis of prospectively collected data of the EPaNIC-trial, which was a randomised control trial conducted in seven ICUs at the University of Hospitals of Leuven and Jessa and evaluated early versus late parenteral supplementation of enteral nutrition.[10]

Given the lack of consensus about the definition of a 'prolonged ICU hospitalisation', the authors operationally defined this construct as ≥8 days and utilised propensity matching with short-stayers. The cut-off of 8 days, while noted to be arbitrary by the authors, resonates with empirically derived population-level definitions of persistent critical illness.[11] In sensitivity analysis, Hermans *et al* noted that between ICU days 6 and 8, mortality was no longer associated to the severity of illness and diagnosis on admission. This affirms prior studies that demonstrate that, over time, ICU admission characteristics become increasingly less associated with a patient's inpatient mortality.[11 12] Hermans *et al* also found the patients with prolonged ICU stays developed more organ dysfunctions compared with patients with short-stays: mechanical ventilation >2 days, new dialysis, utilisation of vasopressors/inotropes>2 days, and elevated bilirubin. While it is not reported when in the ICU course these organ dysfunctions developed, it is plausible that at least some of these organ dysfunctions newly developed after admission.

The primary outcomes of their analyses were total and post-28-day 5-year mortality which were both higher for patients with prolonged ICU hospitalisations as compared with propensity matched short-stayers with an absolute total and post-28-day 5-year mortality difference of 12% and 11.1%, respectively. These findings are intriguing—the post-28-day 5-year mortality, to be clear, looks at only those who survive the initial 28 days after ICU admission, and therefore separates initial mortality from later mortality. The importance of this method allows for patient characteristics that are associated with short-term mortality (eg, severity of illness) to be disentangled from long-term mortality by using the survivors.[13] In Cox regression, patients with prolonged ICU hospitalisation compared with short-stayers were at increased risk of dying (total mortality HR: 1.447 (95% CI: 1.286 to 1.697) and post-28 day 5-year mortality HR: 1.556 (95% CI: 1.019 to 1.774)).

Secondary outcomes focused on morbidity as measured by the 6-min walking distance, handgrip strength and the physical function component of the SF-36. Activities of daily living were measured by the Barthel Index and quality of life was measured by the SF-36. Patients with prolonged ICU hospitalisations performed worse as compared with propensity matched short-stayers and notably rated their overall health as inferior compared with short-stayers.

Hermans *et al* then ask: what potentially modifiable in-ICU events are more common during prolonged ICU stays. Such an analysis must be interpreted with care, subject as it is to varying exposure times, inability to differentiate markers from causes and censoring of the extreme phenotype (eg, really bad care on ICU day four might lead to death and so may be more common in short ICU stays). With those caveats, an exploratory regression analysis of events occurring during the ICU stay found hypoglycaemia, use of any corticosteroids, use of any neuromuscular agents, use of any benzodiazepines for more than 1 day, the need for mechanical ventilation for >2 days, initiation of new dialysis and the occurrence of new infection were associated with increased total and post-28 day 5-year mortality.

These findings begin to shed light on the long-term outcomes of patients with prolonged ICU hospitalisations with a focus not just on mortality but also, importantly, on morbidity and its drivers. In this study, propensity matching after randomisation to the EPaNIC-trial facilitated comparison between similar patients, and demonstrated that: (1) patients with prolonged ICUs can be matched to similar patients with short-stays on admission, and (2) implies that patient characteristics on admission (eg, age, gender, comorbidities, type, and severity of illness) do not fully explain

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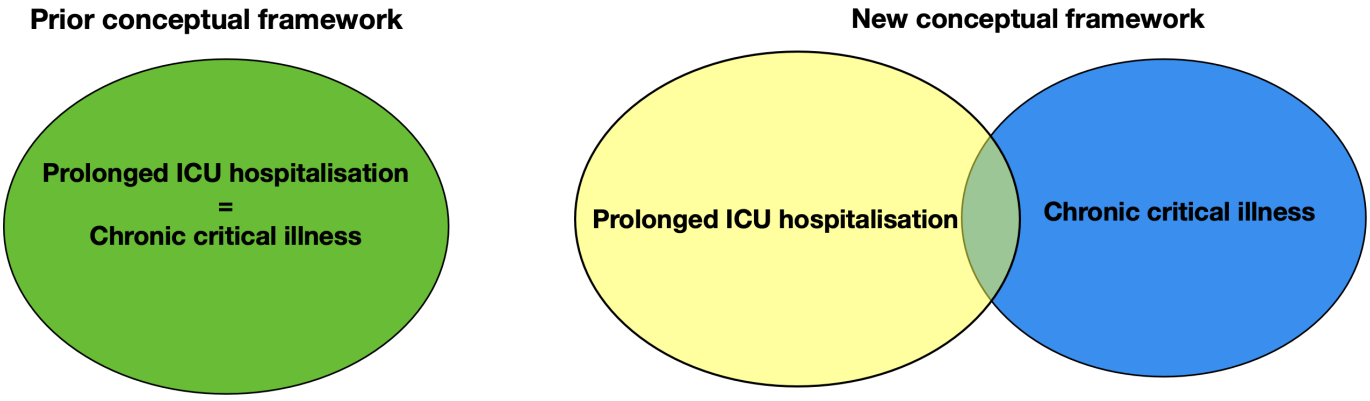

Figure 1 New framework of prolonged ICU hospitalisations.

the increased long-term mortality. Consequently, providers should take caution on utilising patient characteristics on admission for prognostication in patients with prolonged ICU stays.

It is worth noting that the patients with prolonged ICU hospitalisations differ in important ways from patients previously labelled as having 'chronic critical illness'—defined by unresolving respiratory failure. In this cohort, the patients with prolonged ICU hospitalisations had a 5-year survival of 51.8% which is significantly higher than the previously reported 1-year mortality for the chronically critically ill of 40%–60%.[3] The functional limitations were also not as bleak for the patients with prolonged ICU stays as compared with the patients with chronic critical illness with one oft-quoted study reporting only 12% of chronic critically ill patients being functional in the first year after the hospitalisation.[3]

Hermans *et al* also highlight potentially modifiable events (eg, hypoglycaemia, utilisation of benzodiazepines and steroids) in the ICU that are associated with long-term mortality and morbidity. If validated in other cohorts, these findings provide a starting point for a deeper dive into *why* prolonged ICU hospitalisations are happening and whether poor patient outcomes in this population are modifiable or preventable. This line of investigation may lead to the development of interventions that ultimately change the trajectory for patients with prolonged ICU hospitalisations.

Prior to intervention development, though, one needs to consider the limitations of the work of Hermans *et al*.[9] This study was based on a cohort of patients from two centres in Europe, and the findings may not be generalisable to other ICUs. The adjustment for confounders was limited due to available data and may cause residual confounding, thereby overestimating the risk of mortality and morbidity. Furthermore, the baseline, pre-hospitalisation functional status of the patients was unknown. Therefore, it is possible that the differences in functional outcomes seen in this study were not a result of the prolonged ICU exposure, but, instead, related to poorer baseline function. Finally, the authors operationally defined eight or more days as a prolonged ICU stay, which is not directly comparable to other studies of prolonged ICU hospitalisations that do not use this timeframe. Using terms consistently in research is paramount to moving our collective understanding of how to best care and prognosticate for these patients and their families and points to a need for consensus in research definitions.

For too long have we assumed that all prolonged ICU hospitalisations are synonymous with prolonged mechanical ventilation, overlooking the events that are occurring in the ICU driving these stays. The findings of Hermans *et al* help to illuminate the events that are occurring in the ICU, driving prolonged ICU hospitalisations and reinforcing the limited role patient characteristics at the time of ICU admission have on prognostication for long-term outcomes. Moving forward, this study raises difficult questions and challenges about how to improve care for patients with prolonged ICU stays: how do we prognosticate for these patients and families when commonly used admission characteristics such as age, comorbidities and severity of illness are not useful; how do we guide patients and their families through complex, high-stakes decisions; and can we truly intervene sooner to prevent prolonged ICU hospitalisations or improve long-term outcomes?

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