CRITICAL CARE

COMMENTARY

Long-term mortality after critical care: what is the starting point?

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See related research by Cuthbertson et al., http://ccforum.com/content/17/2/R70

Abstract

Mortality is still the most assessed outcome in the critically ill patient and is routinely used as the primary end-point in intervention trials, cohort studies, and benchmarking analysis. Despite this, interest in patient-centered prognosis after ICU discharge is increasing, and several studies report quality of life and long-term outcomes after critical illness. In a recent issue of *Critical Care*, Cuthbertson and colleagues reported interesting results from a cohort of 439 patients with sepsis, who showed high ongoing long-term mortality rates after severe sepsis, reaching 61% at 5 years (from a starting point of ICU admission). Follow-up may start at ICU admission, after ICU discharge, or after hospital discharge. Using ICU admission as a starting point will include patients with a wide range of illness severities and reasons for ICU admission. As a result, important consequences of the ICU, such as rehabilitation and reduced quality of life, may be diluted in an unselected population. ICU discharge is another frequently used starting point. ICU discharge is a marker of better outcome and reduced risk for acute deterioration, making this an interesting starting point for studying long-term mortality, need for ICU readmission, and critical illness rehabilitation. Finally, using hospital discharge as the starting point will include patients with the minimal requirements to sustain an adequate condition in a non-monitored environment but will add a 'survivors bias'; that is, patients who survive critical illness are a special group among the critically ill. In this commentary, we discuss the heterogeneity in long-term mortality from recent studies in critical care medicine – heterogeneity that may be a consequence simply of changing the follow-up starting point – and propose a standardized follow-up starting point for future studies according to the outcome of interest.

Commentary

Critical illness may occur at any time of life, having permanent effects not only on one's health but on other aspects of life, including spiritual, social, and familiar issues [1]. Despite this, mortality is still the most frequently assessed outcome in critically ill patients and is routinely used as the primary end-point in intervention trials, cohort studies, and benchmarking analysis [2,3].

In recent years, the number of studies assessing survival and the overall medical condition of patients after ICU and hospital discharge has markedly increased [1]. However, there is still a need for additional sound data on reliable predictors of relevant, early and late, patient-centered outcomes [4]. In a recent issue of *Critical Care*, Cuthbertson and colleagues [1], using ICU admission as the starting point, reported an ongoing long-term mortality rate of 61% in patients with severe sepsis. Also using ICU admission as the starting point, Nesseler and colleagues [5] recently showed a long-term mortality of 45% among patients with septic shock. In contrast, Brinkman and colleagues [4] conducted a systematic review of long-term mortality of critically ill patients, whose data were drawn from 24 studies. The authors found that 24% of the patients died after hospital discharge. This number counterpoints the high mortality observed in the cited studies and highlights the importance of using the same starting point when comparing studies, as discussed by the authors [4].

To illustrate the importance of defining the follow-up starting point, we recovered data from recent trials and cohort studies of patients with sepsis and compared the reported mortality if starting point was changed. As depicted in Table 1, the difference of long-term mortality

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Table 1 Effect on long-term mortality rate of patients with sepsis if the starting point of follow-up is changed

Study	Longer follow-up reported	Shorter follow-up reported	Long-term mortality changing the starting point	Difference	Reduction
CATS [2] (n = 330)	51.2% (169/330) 90 days	45.5% (150/330) ICU	10.6% (19/180)	40.6%	79.3%
Nesseler *et al.* [5] (n = 93)	45.2% (42/93) 180 days	28% (26/93) ICU	23.9% (16/67)	21.3%	47.1%
Granja *et al.* [6] (n = 305)	39.7% (121/305) 180 days	24.6% (75/305) ICU	20.0% (46/230)	19.7%	49.6%
Baudouin *et al.* [7] (n = 150)	48.7% (73/150) 180 days	27.3% (41/150) ICU	29.4% (32/109)	19.3%	39.6%
Cuthbertson *et al.* [1] (n = 439)	60.8% (267/439) 5 years	39.2% (172/439) ICU	35.6% (95/267)	25.2%	41.4%
Angus *et al.* [8] (n = 1,690)	51.0%2.5 years	27.8% (469/1,690) 28 days	32.2%	18.8%	36.9%
VASST [3] (n = 778)	46.7% (360/771) 90 days	37.3% (290/778) 28 days	14.3% (70/488)	32.4%	69.4%
PROWESS-Shock [9] (n = 1,697)	33.4% (556/1,664) 90 days	25.3% (425/1,680) 28 days	10.4% (131/1,255)	23.0%	68.9%

CATS, Catecholamine study; *PROWESS*, Protein C worldwide evaluation in severe sepsis; *VASST*, Vasopressin versus norepinephrine infusion in patients with septic shock.

could reach 40.6% with data from the Catecholamine Study [2]. The 90-day mortality was 51.2% if we chose ICU admission as the starting point; however, if we chose ICU discharge (that is, excluding patients who died in the ICU), the long-term mortality was 10.6%. From the studies in Table 1, if the starting point follow-up is changed, the mean difference is 25.0% and the mean reduction in reported long-term mortality is 54.0%. This analysis has the important limitation that, when the follow-up starting point is changed to ICU discharge, the total observation period will be less than 90 days; that is, it will be equal to 90 days minus the ICU length of stay.

We believe that, despite important advances in describing the natural history of ICU patients, it is crucial to better define our research questions. Indeed, recommendations provided directions to improve the research in this topic [10,11], and standardization of some definitions and outcomes would result in studies that are more homogenous. First of all, what is the best starting point for the follow-up? Should follow-up start at ICU admission, after ICU discharge, or even after hospital discharge? Several studies have chosen ICU admission as the starting point. This definition, though practical, will include different strata of patients in regard to illness severity and reason for ICU admission, including a range of patients with scheduled ICU admission, which form a very distinct group. In fact, the first days of ICU admission are associated with higher risk of death and greatest vulnerability for the patient [10]. The first phase is followed by the recovery phase, which can be further complicated by secondary insults, especially hospital-acquired infections. Patients who had a secondary insult in the ICU are probably different than those who had a smooth course after admission and may not reflect the prognosis of all ICU survivors. ICU discharge can also be used as a starting point. At ICU discharge, residual organ failure and need for organ support are often reduced, as is the risk of deterioration. If this starting point is used, the risk of death is better balanced among critically ill patients, and this starting point is interesting for studying the role of important topics in long-term mortality, such as ICU readmission and critical illness rehabilitation [12]. Finally, using hospital discharge as the starting point will include patients who have the minimal requirements to sustain an adequate condition in a non-monitored environment and who therefore are more similar to patients who had no recent critical illness [13]. On the other hand, ICU survivors may represent patients with better previous health status (that is, patients who survived critical illness because of good previous health condition and status performance – in other words 'survivor bias').

In conclusion, the current literature defines 'long-term mortality' for outcomes that are not limited to post-discharge mortality, resulting in a myriad of possible interpretations. The heterogeneity of case mix and other factors usually make for an intricate analysis, but different starting points play a central role in the differences between studies. For intervention trials and for benchmarking, the starting point should be either the ICU admission or syndrome/disease diagnosis. For attributable mortality, ICU admission instead of time of diagnosis would be better, as recently reported for ventilator-associated pneumonia [13]. ICU discharge is a remarkable starting point to identify high-risk patients who could receive beneficial close attention in the hospital and in outpatient clinics [14]. Depending on the quoted problem, each starting point can bring useful information. Therefore, to achieve better answers, we must know where, in the natural course of critical illness, our question lies.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors equally contributed to the study.

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