Commentary

Looking beyond 28-day all-cause mortality

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Abstract

A growing body of evidence indicates that survivors of intensive care have an impaired quality of life. It is not entirely clear from the available literature whether this impairment is a complication of critical illness or a complication of therapy. There is little evidence to guide physicians to treatments in the intensive care unit that will minimize the effects of critical illness on these sequelae. Although the study by Rublee and colleagues in this issue of *Critical Care* provides little clinically useful information about the effects of antithrombin III on quality of life, it provides some insight into the challenges that investigators will encounter as we try to incorporate these outcomes into studies of critical illness.

Keywords outcomes research, quality of life, sepsis

In this issue of *Critical Care*, Dale Rublee and colleagues look beyond 28-day all-cause mortality, assessing the effects of antithrombin III on quality of life in sepsis survivors [1]. Although many of us would like to think that the battle has been won when a patient leaves the intensive care unit (ICU) after severe sepsis or acute respiratory distress syndrome (ARDS), a growing body of literature indicates that survivors of intensive care have an increased risk of death and have a significantly impaired quality of life after they leave the ICU. There are several possible mechanisms for these long-term effects, and many patients may be affected by several of them. Survival may be impaired simply because people with severe co-morbid diseases are most likely to get critically ill. Alternatively, critical illness may leave patients immunosuppressed and at risk for further complications that lead to early death. Hypoxemia, septic encephalopathy, and sedative medication may cause cognitive dysfunction [2]. Critical illness neuromyopathy, steroids, and bedrest may cause profound weakness [3]. The trauma of critical illness and false memories may cause post-traumatic stress disorder and depression [4]. Financial burdens continue well after hospital discharge [5]. Tracheostomy scars, striae from anasarca, decubitus ulcers, and digits lost to ischemia may affect patients' self image.

The study by Rublee and colleagues [1] is an analysis of secondary endpoints in the Kybersept (antithrombin III) trial that failed to show a statistically significant effect on 28-day mortality [6]. They compared the Karnofsky performance scale and six domains of a visual analogue scale of quality of life: mobility, physical activity, communications–speech, alertness, energy, and overall quality of life. The authors performed at least 63 statistical comparisons across variables, time points, and populations to identify several situations in which antithrombin III seemed to have a statistically significant effect on quality of life. It is difficult to assess the importance of this effect because the clinically significant difference in percentage change in their visual analogue scale is unknown. Because the results are all expressed as change from a baseline assessment when the patients were critically ill, we cannot tell their actual status at each time point. Despite these limitations, this study raises several important questions that critical care investigators must answer as we design studies of quality of life after critical illness.

What do differences in quality of life after critical illness mean?

Physicians treat angina and asthma to improve patients' quality of life. We do not expect therapy for severe sepsis to improve patients' quality of life; at best we hope to return patients to their pre-morbid health status [7]. Ideally, we can find management techniques that minimize the effects of a critical illness on long-term quality of life. Conflicts may arise between treatments that are life-saving and those that affect

ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

quality of life after critical illness. For example, it is possible that lung-protective ventilation for ARDS using increased sedation, lower oxygenation, and permissive hypercapnea saves lives but leads to worse cognitive function than a strategy using large tidal volume oriented toward normoxia and eucapnea [2,8]. There are as yet insufficient data to assess this trade-off [8]. Functional status and quality of life are extremely important to patients' decisions about life-sustaining treatment, and much better data are needed to allow us to predict future health status [9].

How should informative censoring be analyzed?

Dead people do not contribute data to studies of quality of life. When death competes with a non-mortality endpoint such as quality of life, a phenomenon called 'informative censoring' can occur. A treatment that increases mortality may preferentially lead to the death of debilitated patients who would have had very poor quality of life if they had survived. Similarly, a treatment that saves the lives of very ill debilitated patients may rescue these patients so that they are healthy enough to contribute very poor quality-of-life data to the study. Life-saving therapy in the ICU can seem to worsen quality of life, and harmful treatments can seem to improve quality of life. It is therefore problematic to adopt a therapy in the ICU solely on the basis of its apparent effect on quality of life unless we know that this effect is not purchased by increasing mortality in the most debilitated. There are statistical techniques for studying a non-mortality endpoint in the face of competing mortality and these should be used by intensivists to evaluate the effects of interventions on quality of life after critical illness [10,11].

Which outcome measures should be used?

Intensivists are used to attempts in the complex body of literature in critical care to identify the 'best' severity of illness measure [12]. A similar, even more extensive, body of literature exists that explores the 'best' quality-of-life instruments [13]. Entire journals are devoted to these questions. There is no single perfect instrument to measure all aspects of health status. Experts debate the responsiveness, validity, clinical significance, and practicability of these instruments in various patient populations. Selecting a general measure-of-health status that has been used extensively, such as the SF (Short Form)-36 or EuroQOL, allows investigators to compare their results with a mature database of patients with many different diseases. Studying measures of function, for example muscle strength, cognitive ability, and psychiatric status, can provide invaluable information for understanding the mechanisms of a reduced health-related quality of life. Investigators interested in establishing the cost-utility of a therapy should use a health status measure that can be converted to patient utilities.

Where do we go from here?

Reducing the long-term impairment associated with critical illness presents a set of new challenges to clinicians in the ICU. We need more information on the natural history of functional impairment after critical illness. We need association studies that link factors before, during, and after treatment in the ICU with health status. Continuing clinical trials in critical care can provide this information on risk factors by including long-term follow-up for survival and quality of life in their data collection. In the very near future we should expect clinical trials exploring the effects of ICU and post-ICU interventions targeted at improving quality of life after intensive care.

Competing interests

None declared.

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