Surviving Severe Sepsis: Is That Enough?*

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Sepsis and severe forms of sepsis is a frequent diagnosis in the ICU setting. "Sepsis is one of the oldest and most elusive syndromes in medicine" (1). The definition of severe sepsis includes a systemic inflammatory response to infection complicated by acute organ dysfunction (1). "Over 1,665,000 cases of sepsis occur in the United States each year, with a mortality rate up to 50%" (2). In the ICU setting survival of severe sepsis is a primary goal, however, quality-of-life (QoL) issues for these patients after discharge is of great concern to the patient and to their family and physicians who will be providing the follow-up care that may be complex and ongoing (3). Long after hospitalization, survivors of severe sepsis experience an impaired QoL and an ongoing feeling that they may be imposing a burden of care to their family and loved ones. This is especially true for survivors who where physically independent prior to severe sepsis, but after discharge are left with dependence on others in daily activities. Although the goal of care in the ICU setting is appropriately to cure sepsis and minimize morbidity, it may be that many survivors are not getting the ongoing care required for their complex physical, psychological, and emotional needs after discharge. A recent study reported that after 6 months, up to 80% of severe sepsis/septic shock survivors stopped coming to their follow-up consultations (4). It is important to study QoL for survivors of sepsis in order to provide patient-centered care and to assess goals of care frequently so survivors and their families are offered holistic care and are not lost to follow-up.

In this issue of *Critical Care Medicine*, Yende et al (5) provide a secondary data analysis of two previous international, randomized clinical trails: A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis (ACCESS) (6) and Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS)-SHOCK (7). Both the ACCESS (n = 1,984) and PROWESS–SHOCK (n = 1,697) clinical trials tested the efficacy of a specific pharmaceutical agent against placebo with no significant results in survival for the agent versus placebo in study patients diagnosed with severe sepsis. The study by Yende et al (5) used the data from both studies to explore and analyze any specific patient predictors related to QoL assessments in these patients. This analysis included only those patients who were functional and living independently at home prior to the diagnosis for severe sepsis. The authors hypothesized that the QoL after severe sepsis might impact clinical practice interventions for those patients who are at risk for long-term consequences such as impaired mobility and ability to independently perform activities of daily living.

The study design is a secondary analysis of the two international, randomized clinical trials as noted above, using the ACCESS data as a derivation cohort and PROWESS-SHOCK as a validation cohort. Yende et al (5) analyzed the patients from the previous studies who were "functional and living at home without help before sepsis hospitalization" (5) (n = 1,143 and n = 987, respectively). They used the Euro Quality of Life (EQ-5D) tool to measure QoL in this study. This tool is a common questionnaire used to measure health-related QoL (HRQOL) usually self-administered by the patient and assesses five QoL dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (8).

Their analysis showed the average age of patients living at home independently prior to hospitalization to be 61 and 63 years old, and greater than 30% died at 6 months (of these, 41.6% were not able to live independently). Their data also showed that QoL at 6 months post hospitalization was very poor, showing evidence of "problems in mobility, usual activities, and self-care domains" (5).

One major weakness in this study is that the patients did not directly fill out many of the EQ-5D questionnaires, but rather a proxy for the patients both at 6-month and 1-year follow-up. It would be expected in this patient population that many survivors of sepsis would not be able to fill out the questionnaire due to the disability caused from their severe sepsis. The authors also noted another limitation with the EQ-5D tool is that it has not been validated for this particular patient population and also that they did not have QoL measures from these patients prior to their severe sepsis as a comparison to the follow-up QoL measures. It would be of great interest to compare the presepsis QoL with the postsepsis QoL, at present we

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are left wondering what meaning a lower postsepsis score has for patients who are left with recent and serious health deficits.

One of the most striking strengths of this study is that they only looked at QoL data for those patients who lived independently previous to severe sepsis. QoL assessments of these patients at 6 months post discharge revealed poor overall QoL suggesting that perhaps surviving severe sepsis left many patients with an unacceptable QoL. This is not to say that in acute cases of severe sepsis that aggressive life-saving treatment ought not be done, but it does give us pause when severe illness effects multiple organ systems and which includes a prognosis of associated long-term physical and emotional deficits. Survival may mean a life of complicated and serious sequelae including "residual organ dysfunction, which may result in persistent symptoms such as dyspnea, fatigue, depression, impaired functional status and reduced HRQOL in comparison with the general population" (4). The most critical of ICU patients who survive to discharge are very similar to survivors of severe sepsis with respect to perceived poor QoL, cognitive, emotional, and physical complications, often with little improvement over time (9).. For such patients, conversations regarding what QoL might look like in 6 months, given the data we know from many studies on this topic, should be done by the ICU clinicians with patient and family while still in the ICU setting.

Potential changes in practice may be hinted at from the research by Yende et al (5) that include extending the 28-day all-cause mortality as a primary endpoint for sepsis trials to extend to 6 months and that "incorporates mortality and either quality of life or disability measures." In addition, the data here show that patients hospitalized for severe sepsis might benefit from early rehabilitation efforts while in the hospital and the use of specialized follow-up clinics that would target dimensions related to QoL. Such a clinic would be for survivors of a severe critical and complicated illness such as severe sepsis. In addition, I think this type of multidisciplinary clinic should also provide ongoing support for the family/support individuals involved in the life of a severe sepsis survivor as they often have a heavy burden of care and may experience some of the same QoL deficits felt by the survivor.

ICU clinicians see critically ill patients every day. The initial goal of care is aggressive and life-sustaining while trying to cure or treat underlying disease. To prognosticate specific morbidity- and mortality-related issues for each individual patient while in the ICU would be difficult to do. However, it is important for clinicians to acknowledge QoL issues based upon the literature and to discuss these issues with patients and their loved ones not only in the acute setting but also in the ongoing outpatient settings. Just as appropriate, clinical care is an expected standard in the ICU, so should QoL discussions and treatment options be an expected standard of care in the ICU. For some patients, surviving sepsis but being left with a life they perceive filled with physical, emotional, and cognitive deficits and poor QoL may not be enough.

REFERENCES

1. Angus DC, van der Poll T: Severe sepsis and septic shock. *N Engl J Med* 2013; 369:840–851
2. Schmidt G, Mandel J: Evaluation and Management of Severe Sepsis and Septic Shock in Adults. UpToDate, 2015. Available at: http://www.uptodate.com/contents/evaluation-and-management-of-severe-sepsis-and-septic-shock-in-adults. Accessed January 8, 2016
3. Hofhuis JG, Spronk PE, van Stel HF, et al: The impact of severe sepsis on health-related quality of life: A long-term follow-up study. *Anesth Analg* 2008; 107:1957–1964
4. Granja C, Dias C, Costa-Pereira A, et al: Quality of life of survivors from severe sepsis and septic shock may be similar to that of others who survive critical illness. *Crit Care* 2004; 8:R91–R98
5. Yende S, Austin S, Rhodes A, et al: Long-Term Quality of Life Among Survivors of Severe Sepsis: Analyses of Two International Trials. *Crit Care Med* 2016; 44:1461–1467
6. Opal SM, Laterre PF, Francois B, et al; ACCESS Study Group: Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: The ACCESS randomized trial. *JAMA* 2013; 309:1154–1162
7. Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group: Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366:2055–2064
8. Gusi N, Olivares P, Rajendram R: The EQ-5D health-related quality of life questionnaire. *In*: *Handbook of Disease Burdens and Quality of Life Measures*, 2010. Available at: http://link.springer.com/referenceworkentry/10.1007%2F978-0-387-78665-0_5#page-1. Accessed January 13, 2016, pp 87–99
9. Hopkins RO, Weaver LK, Collingridge D, et al: Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005; 171:340–347

Long-Term Quality of Life Among Survivors of Severe Sepsis: Analyses of Two International Trials*

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Objectives: To describe the quality of life among sepsis survivors.

Design: Secondary analyses of two international, randomized clinical trials (A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis [derivation cohort] and PROWESS-SHOCK [validation cohort]).

Setting: ICUs in North and South America, Europe, Africa, Asia, and Australia.

Patients: Adults with severe sepsis. We analyzed only patients who were functional and living at home without help before sepsis hospitalization (n = 1,143 and 987 from A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis and PROWESS-SHOCK, respectively).

Interventions: None.

Measurements and Main Results: In A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis and PROWESS-SHOCK, the average age of patients living at home independently was 63 and 61 years; 400 (34.9%) and 298 (30.2%) died by 6 months. In A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis, 580 patients had a quality of life measured using EQ-5D at 6 months. Of these, 41.6% could not live independently (22.7% were home but required help, 5.1% were in nursing home or rehabilitation facilities, and 5.3% were in acute care hospitals). Poor quality of life at 6 months, as evidenced by problems in mobility, usual activities, and self-care domains were reported in 37.4%, 43.7%, and 20.5%, respectively, and the high incidence of poor quality of life was also seen in patients in PROWESS-SHOCK. Over 45% of patients with mobility and self-care problems at 6 months in A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis died or reported persistent problems at 1 year.

Conclusions: Among individuals enrolled in a clinical trial who lived independently prior to severe sepsis, one third had died and of those who survived, a further one third had not returned to independent living by 6 months. Both mortality and quality of life should

be considered when designing new interventions and considering endpoints for sepsis trials. (*Crit Care Med* 2016; 44:1461–1467)
Key Words: quality of life; sepsis

Severe sepsis is defined as an infection associated with a systemic inflammatory response and acute organ dysfunction (1). It accounts for 10% of all ICU admissions, has a 90-day mortality of ≈ 30% (2), and is the leading cause of death in U.S. hospitals (3). Worldwide, best estimates suggest that severe sepsis develops in up to 19 million individuals each year (4).

Prior studies have shown that severe sepsis survivors incur long-term consequences, including developing new physical, psychiatric, and cognitive deficits (5–7). These deficits often limit their mobility and ability to perform day-to-day activities and may impair quality of life (8). As a greater proportion of patients survive hospitalization for severe sepsis, the population that is at risk for these long-term consequences will increase (9).

We sought to determine long-term quality of life among severe sepsis survivors. We addressed two key limitations of prior studies. First, prior studies compared the quality of life among severe sepsis survivors with age-matched population-based controls (8). However, patients with sepsis often have a high burden of chronic diseases or functional limitations before developing sepsis, and thus, long-term impairments in quality of life may be due to sepsis itself or poor health before onset of sepsis. Second, these studies had a small sample size and included patients from a single geographic region. We assessed the quality of life in severe sepsis survivors enrolled in two large international clinical trials. We determined the quality of life at 6 months in patients who were functional and self-sufficient before the onset of sepsis. We conducted sensitivity analyses in young patients and those who did not have a chronic disease to assess the independent effect of sepsis on quality of life. Finally, we also examined the predictors of poor quality of life among survivors, particularly whether it is affected by the severity and type of organ dysfunction during the acute sepsis episode.

MATERIALS AND METHODS

We conducted a secondary analysis of patients enrolled in two clinical trials: A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis (ACCESS; n = 1,984) and PROWESS-SHOCK (n = 1,697). Details of these trials are published elsewhere (10, 11). The ACCESS and PROWESS-SHOCK trials tested the efficacy of Eritoran, a MD2:toll-like receptor 4 antagonist, and drotrecogin-α activated (recombinant human activated protein C), an anticoagulant and profibrinolytic enzyme, against placebo. In both trials, there was no difference in survival in patients who were assigned to receive the active agent or the placebo. We conducted primary and sensitivity analyses and analyzed predictors of reduced quality of life (see *Statistical Analysis* section) in ACCESS and validated the results of the primary analyses in the PROWESS-SHOCK trial.

To minimize the potential effect of preexisting functional impairment, we restricted analysis in both trials to subjects who were functional and living at home without help prior to hospitalization for severe sepsis (**online supplement**, Supplemental Digital Content 1, http://links.lww.com/CCM/B718). All subjects or their legal surrogate gave informed consent, and the Institutional Review Board at each site approved the study.

Patients

The ACCESS trial enrolled patients who were at least 18 years old with early severe sepsis or septic shock and at high risk of death. Severe sepsis was defined as documented evidence of infection, at least three criteria for systemic inflammatory response syndrome, and at least one major organ dysfunction. Septic shock was defined as hypotension requiring vasopressors. High risk of death was defined as having an Acute Physiology and Chronic Health Evaluation (APACHE) II score of at least 21 and not greater than 37. The PROWESS-SHOCK trial used similar entry criteria, except included only patients with persistent septic shock and had no enrollment restriction based on APACHE II score. Both trials included patients from North and South America, Europe, Africa, Asia, and Australia. In general, the exclusion criteria were similar and excluded patients who did not want to pursue aggressive care (online supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/B718).

Quality of Life

The primary outcome variable was quality of life, which was assessed over 1 year in the ACCESS trial and 6 months in the PROWESS-SHOCK trial. Quality of life was assessed using a previously validated instrument, EQ-5D (http://www.euroqol.org/home.html). It was chosen for both trials because it has been used in patients with sepsis previously (12, 13), it can be completed in a few minutes, and it is available in several languages. The EQ-5D measures the health state in five domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain can take one of the three responses: no problems, some or moderate problems, and extreme problems.

The EQ-5D was obtained by telephone interview either from the patient or proxy. The time window to obtain measures at 6 months was between months 5 and 7 and at 1 year was between months 11 and 13 after enrollment in the original trial.

Statistical Analysis

We report the clinical characteristics of the subjects prior to and at enrollment and their hospital course in both trials. In the ACCESS cohort, we conducted primary and sensitivity analyses and analyzed patterns of changes in select quality of life measures (mobility and self-care) between 6 months and 1 year and identified predictors of quality of life at 6 months. We validated the primary analyses in the PROWESS-SHOCK trial.

For the primary analyses, we determined where patients were located (home, acute care hospitals, nursing home, or

rehabilitation facilities), whether they needed assistance, and quality of life measures (frequency of patients who had problems with mobility, self-care, and usual activities and who reported pain or discomfort and anxiety or depression).

Patients hospitalized with severe sepsis are often older adults and have chronic diseases; thus, they may have reduced the quality of life prior to sepsis. Therefore, we conducted two sensitivity analyses in young patients (< 45 yr) and those who did not have a chronic disease to reduce likelihood of confounding because of these factors. We conducted these sensitivity analyses in the ACCESS cohort and defined a chronic disease as those individuals who reported cardiovascular, kidney, lung, connective tissue diseases, heart failure, diabetes, cancer, AIDS, dementia, and stroke.

We report patterns of changes in mobility and self-care between 6 months and 1 year in the ACCESS trial. We chose these outcomes because impairments in these domains were common, and these impairments are likely to affect the patient's functional status. We identified patients with problems in these domains at 6 months and the proportion that had persistent problems (reported some, moderate, or extreme problem), recovered completely (reported no problem), and died.

Finally, we used logistic regression to determine factors prior to and during the acute episode that were associated with poor quality of life in the ACCESS cohort. We constructed two models to predict problems with mobility and self-care at 6 months. For each model, covariates included demographic characteristics, chronic disease burden (defined as the presence or absence of a chronic disease), and duration of organ failure within the first 28 days, including mechanical ventilation, dialysis, and vasopressor support, as a proxy for the duration and severity of organ failure. We split each organ support variable into individuals who did and did not require the organ support, and among the later, we calculated the odds ratios for increase in organ support in increments of 7 or 14 days. We did not use daily sequential organ failure scores because these data were collected only on select days and require imputation. All analyses were done using SPSS 21 (IBM, New York, NY) or SAS 9.4 (SAS, Cary, NC).

RESULTS

Patient Characteristics

Of the 1,984 and 1,697 patients enrolled in ACCESS and PROWESS-SHOCK trials, 1,143 (57.6%) and 987 (58.1%) patients were fully functional and living at home without help prior to hospitalization with severe sepsis (**Fig. 1**).

For patients in the ACCESS cohort (derivation cohort) and included in this analysis, the mean age was 63.2 years and 454 (39.7%) were women (**Table 1**). Five hundred and eighty-six (51.3%), 340 (29.7%), and 80 (7.0%), 73 (6.4%), 64 (5.6%) were from Europe, North America, Asia, South America, and rest of the world, respectively. Three hundred and forty-seven (30.3%), 254 (14.0%), 235 (13.4%), 161 (8.9%), 142 (7.8%), and 58 (3.2%) had diabetes, pulmonary disease, cancer, kidney disease, ischemic heart disease, and heart failure, respectively. Eight hundred and twenty-seven patients (72.4%) had at least one or more chronic disease. At enrollment, the illness severity was high (1,269 [64%] had an APACHE II score of 25 or higher, and 397 [34.7%], 273 [23.9%], and 111 [9.7%] had dysfunction in two, three, and four or more organ systems, respectively).

In general, the demographic characteristics, chronic disease burden, and illness severity of patients analyzed from the

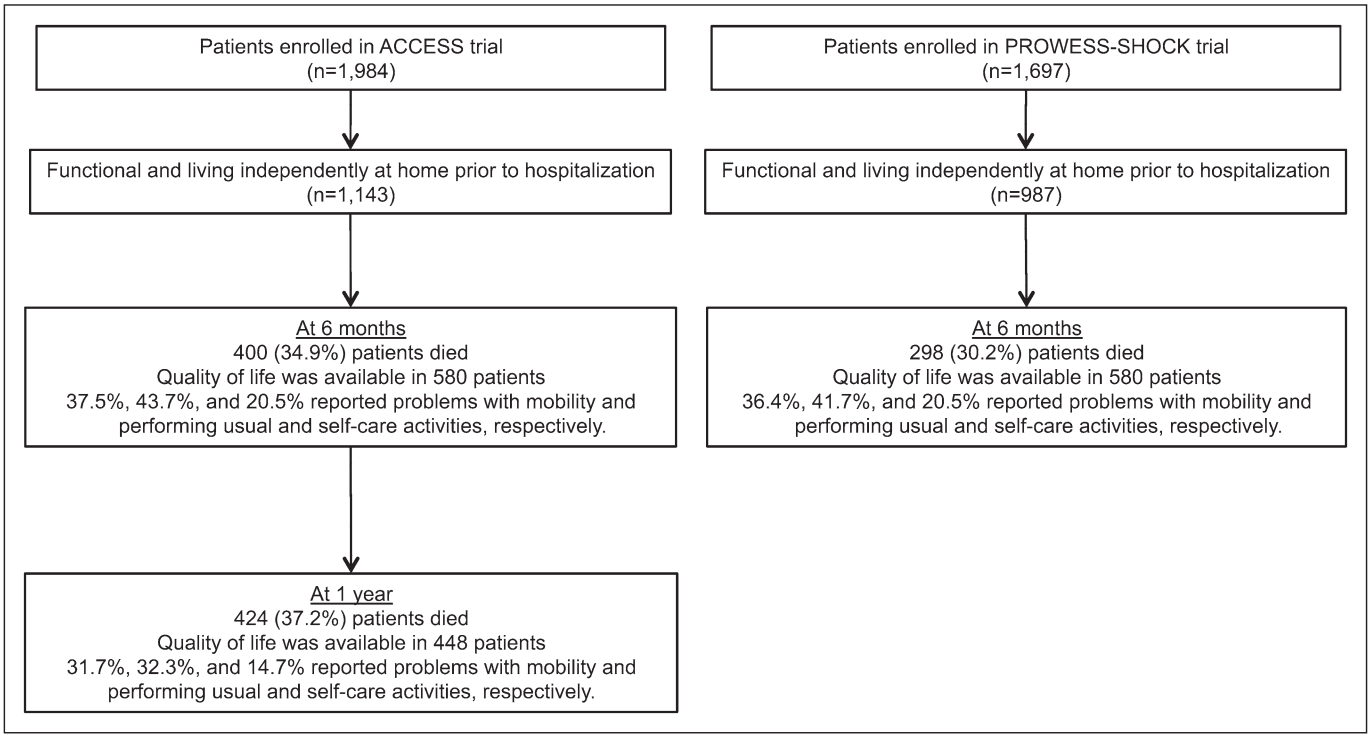

Figure 1. Flowchart describing the selection of analyses cohorts and number of patients with quality of life measures. ACCESS = A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis.

TABLE 1. Clinical Characteristics of Sepsis Survivors Who Were Fully Functional Prior to Hospitalization

Variable	A Controlled Comparison of Eritoran and Placebo in Patients With Severe Sepsis Cohort (*n* = 1,143)	PROWESS-SHOCK Cohort (*n* = 987)
Demographics		
Age, mean (SD), yr	63.2 (14.6)	61.6 (15.7)
Women, *n* (%)	454 (39.7)	414 (41.9)
Race, *n* (%)		
White	958 (83.8)	852 (86.3)
Black	55 (4.8)	32 (3.2)
Asian/non-Japanese	29 (2.5)	59 (6.0)
Japanese	71 (6.2)	0 (0)
Others	30 (2.6)	44 (4.5)
Region, *n* (%)		
Europe	586 (51.3)	742 (75.2)
North America	340 (29.7)	121 (12.3)
South America	73 (6.4)	34 (3.4)
Asia	80 (7.0)	90 (9.1)
Rest of the world	64 (5.6)	0 (0)
Chronic diseases, *n* (%)[a]		
Diabetes	347 (30.3)	225 (22.8)
Chronic pulmonary disease	254 (14.0)	143 (14.7)
Cancer	235 (13.4)	173 (17.5)
Moderate or severe renal disease	161 (8.9)	72 (7.3)
Ischemic heart disease	142 (7.8)	97(9.8)
Heart failure	129 (7.1)	36 (3.6)
Stroke or transient ischemic attack	85 (4.7)	39 (4.0)
Moderate or severe liver disease	58 (3.2)	37 (3.7)
Infection site,[a] *n* (%)		
Lung	571 (44.1)	468 (47.4)
Genitourinary	189 (25.2)	98 (9.9)
Abdomen	268 (20.7)	319 (32.3)
Skin/soft tissue	95 (7.3)	69 (7.0)
Primary blood stream	37 (2.9)	163 (16.5)
Catheter-related bacteremia	24 (1.9)	–
Central nervous system	40 (3.1)	15 (1.5)
Other	70 (5.4)	34 (3.4)
Illness severity		
Acute Physiology and Chronic Health Evaluation score II, mean (SD)	26.8 (4.3)	24.8 (8.0)
With organ dysfunctions, *n* (%)		
1	362 (31.7)	15 (1.5)
2	397 (34.7)	122 (12.4)
3	273 (23.9)	326 (33.0)
4	98 (8.6)	385 (39.0)
5	13 (1.1)	139 (14.1)
Type of organ dysfunctions,[a] *n* (%)		
Acute lung injury/acute respiratory distress syndrome	116 (10.1)	773 (78.3)
Thrombocytopenia	95 (8.3)	248 (25.1)
Lactic acidosis	291 (25.5)	460 (47.1)
Shock	551 (48.2)	987 (100)
Acute kidney injury	90 (7.9)	746 (75.6)
Duration of organ support		
Mechanical ventilation, median (IQR)	7 (2–15)	6 (2–15)
Dialysis, median (IQR)	0 (0–2)	0 (0–3)
Vasopressor use, median (IQR)	3 (2–7)	4 (2–7)
Length of stay		
ICU, median (IQR)	11 (6–22)	11 (6–21)
Hospital, median (IQR)	21(10–28)	22 (12–29)
Mortality, *n* (%)		
6-mo mortality		
Alive	626 (54.7)	580 (58.8)
Dead	400 (34.9)	298 (30.2)
Missing	117 (10.2)	109 (11)
1-yr mortality[b]		
Alive	467 (40.8)	–
Dead	424 (37.2)	–
Missing	252 (22)	–

IQR = interquartile range.

[a]Numbers do not add up to 100% because patients may be part of more than one category.

[b]1-yr mortality not available for the PROWESS-SHOCK cohort.

Dashes indicate no data available.

PROWESS-SHOCK cohort (validation cohort) were similar to those analyzed from the ACCESS trial (Table 1). Additional details are provided in the online supplement (Section IV) (Supplemental Digital Content 1, http://links.lww.com/CCM/B718).

Mortality

In the ACCESS trial, 289 (25.3%), 363 (31.8%), and 400 (34.9%) patients died at 28 and 90 days and at 6 months, respectively. In the PROWESS-SHOCK trial, 202 (20.5%), 273 (27.7%), and 298 (30.2%) patients died at the same time points, respectively.

Quality of Life

At 6 months, of the 1,143 patients in the ACCESS trial, 626 (54.7%), 400 (34.9%), and 117 (10.2%) were alive, dead, and lost to follow-up, respectively (Table 1). A quality of life measure was obtained in 580 patients (78%; 580/743 patients who had not died by 6 mo; Fig. 1). Of these, 58.4% were home and fully functional, 22.7% were home but required help, 5.1% were in nursing home or rehabilitation facilities, and 5.3% were in acute care hospitals (living status was not known for 8.5% patients).

At 1 year, 467 (40.8%), 424 (37.2%), and 252 (22%) were alive, dead, and lost to follow-up, respectively (Table 1). A quality of life measure was obtained for 448 patients (62.3%; 448/719 patients who had not died by 1 yr). Of these, 69% of the survivors were at home and fully functional, 17% were at home but required help, 3.1% were in nursing home or rehabilitation facilities, and 3.1% were in acute care hospitals (living status was not known or 7.8% patients).

A large proportion of patients reported a problem with mobility, usual activities, and self-care over 1 year. Of the 580 survivors with an EQ-5D measure at 6 months, more than a third reported problems with mobility (218 patients; 37.5%) and usual activities (254 patients; 43.7%), and 119 patients (20.5%) reported problems performing self-care. Of the 580 responses, 496 (85.5%) were obtained from the patients and proxies reported 84 (14.5%) responses. The proxies included spouse or significant other (36.9%), child (26.2%), parent (7.1%), sibling (3.6%), friends (1.2%), other family members (9.5%), paid caregiver (13.1%), and others (2.4%).

Among the 448 survivors with a quality of life at 1 year, 142 (31.7%), 145 (32.3%), and 66 (14.7%) reported problems with mobility, usual activities, and self-care activities, respectively. A large proportion of patients also reported pain or discomfort and anxiety or depression at 1 year (41.4% and 35.2% reported pain or discomfort; 29.4% and 25% reported anxiety or depression by 6 and 12 mo, respectively). Of the 448 responses, 388 (86.6%) were obtained from the patients, proxies reported 52 (11.6%) responses, and data were missing in an additional 8 patients (1.8%). The proxies included spouse or significant others (42.3%), child (30.8%), parent (5.8%), sibling (7.7%), friends (1.9%), other family members (3.8%), and paid caregiver (5.8%).

Long-term follow-up was limited to 6 months in the PROWESS-SHOCK trial. At 6 months, of the 987 patients, 580 (58.8%), 298 (30.2%), and 109 (11%) were alive, dead, and lost to follow-up, respectively (Table 1). At 6 months, the findings were similar to the ACCESS trial; 61% were home and fully functional, 26.6% were home but required help, 4.1% were in a nursing home or rehabilitation facilities, and 3.6% were in acute care hospitals. The EQ-5D data were available for 580 survivors at 6 months. Of these, 211 patients (36.4%) reported problems with mobility, 242 (41.7%) with performing usual activities, and 119 (20.5%) reported problems performing self-care. Two hundred and seventy-six patients (47.7%) reported pain or discomfort, and 205 (35.5%) reported anxiety or depression.

Sensitivity Analyses

In the ACCESS cohort, the proportion of patients who reported a problem with mobility, usual activities, and self-care was similar among those with and without a chronic disease (**Fig. 2**). The proportion of patients who reported some problem with mobility and self-care was lower among those younger than 45 years (17.9% and 7.7%), but a third (30.8%) were unable to return to usual activities by 6 months.

Patterns of Quality of Life Between 6 Months and 1 Year

Of the 218 patients in the ACCESS cohort who reported problem with mobility at 6 months, 105 (48.1%) reported persistent problem with mobility, 15 survivors (6.8%) had died, and 45 patients (20.6%) reported no problems with mobility by 1 year (status of an additional 53 patients was unknown). Similarly, of the 119 patients who reported some problem with self-care at 6 months, 42 survivors (35.3%) reported a persistent problem with self-care, 12 (10.1%) had died, and 36 patients reported no problems with self-care by 1 year (status of an additional 29 patients was unknown). Thus, most patients who reported problems with mobility or self-care at 6 months had poor subsequent outcomes.

Predictors of Impaired Quality of Life

Table 2 shows predictors of problems with mobility and self-care at 6 months in the ACCESS cohort; age was an important predictor, but the presence of chronic disease before sepsis was not. Treatment with mechanical ventilation or dialysis for 14 or more days was associated with problems with mobility and self-care, but the duration of vasopressor support was not an important predictor.

DISCUSSION

Two large international trials independently studying separate treatments for severe sepsis revealed strikingly similar findings. Approximately one third of patients who were functionally independent and residing at home before the onset of sepsis had died by 6 months, and a third of the survivors reported problems with mobility and performing self-care or usual activities. Most patients were unable to live at home independently and either required assistance at home or resided in nursing home or rehabilitation facilities or they were in acute care hospitals. Furthermore, in the ACCESS cohort, half of

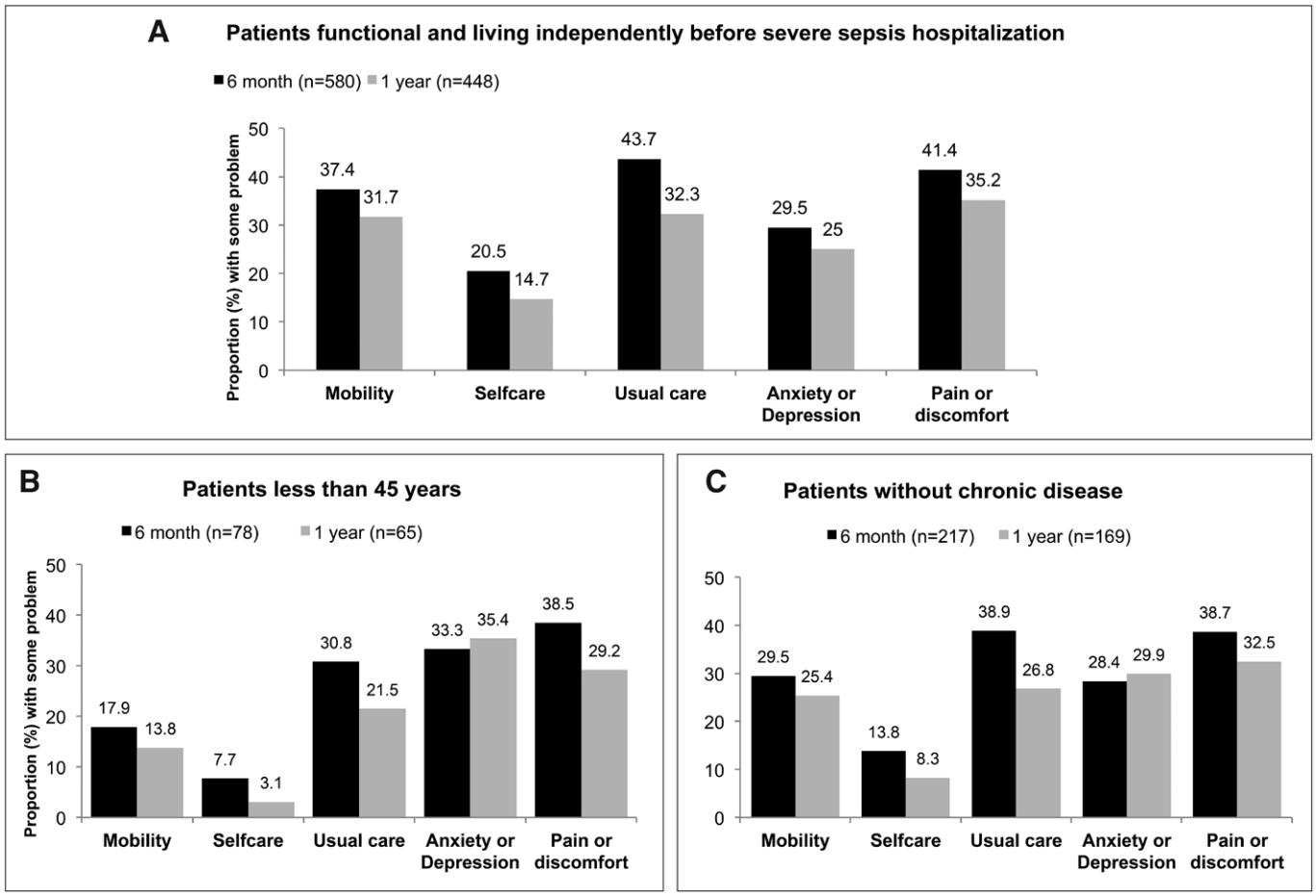

Figure 2. Proportion of patients who reported problems with mobility, self-care, and usual activities for all patients (**A**) who were functional prior to onset of severe sepsis and in the subsets that were young (< 45 yr old) (**B**) and without chronic diseases (**C**).

these patients either died or did not improve by 1 year. The poor quality of life in survivors is less likely to be attributed to advanced age or high burden of chronic diseases and likely due to persistent critical illness and prolonged treatment with mechanical ventilation or dialysis.

Our findings are consistent with prior studies and have important implications (5, 6, 8). First, there is a need to identify strategies during the hospital course, such as early rehabilitation, or after hospital discharge, such as follow-up clinics (7), to improve quality of life for severe sepsis survivors. Second, currently, U.S. Food and Drug Administration recommends using 28-day all-cause mortality as a primary endpoint for sepsis trials. However, using mortality alone would ignore functional impairments that occur among sepsis survivors and affect quality of life. Future sepsis trials should consider a composite endpoint that incorporates mortality and either quality of life or disability measures. These measures are patient-centered outcomes, and they are likely to increase caregiver burden. Our findings suggest that quality of life or disability measures obtained at 6 months may be adequate rather than waiting longer because half of patients who reported problems with mobility or self-care either died or did not improve subsequently. Third, consistent with prior studies, our findings showing that a third of sepsis survivors need assistance demonstrate the high societal costs of caring for sepsis survivors. As the incidence of sepsis increases and the short-term mortality decreases, cost of caring for sepsis survivors will likely increase over time.

Our study has several strengths. First, our findings of similar long-term outcomes in two large, contemporary cohorts strength the inferences that can be drawn from our data. Second, patients were enrolled from various countries; thus, our results may be considered widely generalizable. Third, our primary analysis was restricted to those who were functional and living independently prior to hospitalization with severe sepsis, and we also conducted sensitivity analysis in young adults and those without chronic diseases; thus, we sought to minimize confounding because of advanced age or preexisting chronic disease. That our findings were similar in the primary and sensitivity analyses suggests that we succeeded in minimizing such confounding.

Our study has limitations. Although EQ-5D has been widely used, it has not been validated for patients recovering from sepsis. In particular, EQ-5D may not be accurate in individuals with cognitive impairments (14). We also did not calculate quality-adjusted life years because each health state is assigned a value set based on the country of origin, and this value set is not available for participants from several countries included

TABLE 2. Predictors of Mobility and Self-Care at 6 Months for Sepsis Survivors Who Were at Home and Functional Prior to Hospitalization ($n = 580$) in the Cohort of A Controlled Comparison of Eritoran and placebo in patients with Severe Sepsis Trial

Variables (Reference Category)	Measures	Mobility		Self-Care	
		Unadjusted Model OR (95% CI)	Adjusted Model OR (95% CI)	Unadjusted Model OR (95% CI)	Adjusted Model OR (95% CI)
Age		1.03 (1.01–1.04)[a]	1.03 (1.02–1.05)[a]	1.04 (1.02–1.05)[a]	1.05 (1.03–1.07)[a]
Sex (female)	Men	0.91 (0.64–1.27)	0.75 (0.52–1.09)	1.03 (0.68–1.55)	0.80 (0.51–1.26)
Race (white)	Blacks	0.97 (0.46–2.04)	1.39 (0.62–3.14)	1.33 (0.58–3.05)	2.92 (1.16–7.34)[a]
	Others	0.74 (0.41–1.36)	0.71 (0.36–1.39)	1.14 (0.57–2.24)	1.28 (0.59–2.76)
Chronic disease (none)	Yes	1.74 (1.21–2.49)[a]	1.48 (0.99–2.21)	2.02 (1.28–3.18)[a]	1.64 (0.99–2.71)
Duration of organ support					
Ventilator (no support)	1–14 support days	1.10 (0.68–1.80)	1.36 (0.81–2.30)	0.92 (0.50–1.68)	0.94 (0.49–1.78)
	> 14 support days	2.07 (1.19–3.58)[a]	2.27 (1.19–4.34)[a]	2.60 (1.36–4.94)[a]	2.56 (1.21–5.41)[a]
Dialysis (no support)	1–14 support days	0.94 (0.56–1.57)	0.96 (0.55–1.68)	1.49 (0.83–2.67)	1.44 (0.76–2.74)
	> 14 support days	4.97 (2.35–10.53)[a]	5.12 (2.23–11.75)[a]	4.40 (2.21–8.75)[a]	4.33 (1.91–9.83)[a]
Vasopressor (no support)	1–7 support days	0.45 (0.25–0.80)[a]	0.38 (0.21–0.72)[a]	1.31 (0.59–2.89)	1.28 (0.55–3.00)
	> 7 support days	0.79 (0.40–1.57)	0.44 (0.20–0.98)	2.58 (1.07–6.19)[a]	1.33 (0.49–3.62)

OR = odds ratio.
[a]Significant at p value of less than 0.05.

in our study. Although we limited our analysis to patients who were living at home without help, quality of life was not available before onset of severe sepsis hospitalization. Thus, we may have overestimated the impairment in quality of life because of severe sepsis. We also did not collect quality of life measures using EQ visual analog scale. Finally, data were missing for some patients. Often, these data are missing for those with worse values, and we may have underestimated the frequency of some limitations.

CONCLUSIONS

Approximately one third of patients who survived hospitalization for severe sepsis had died at 6 months. Another third experienced problems with mobility and self-care and were not able to live independently at this time point. Half of the survivors who had these problems at 6 months had either died by 1 year or had persistent problems. In addition to mortality, future studies should consider persistent functional impairment as an outcome measure and examine strategies to improve both longevity and quality of life in patients who survive severe sepsis.

REFERENCES

1. Angus DC, van der Poll T: Severe sepsis and septic shock. *N Engl J Med* 2013; 369:840–851
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
3. National Center for Health Statistics. Available at: http://www.cdc.gov/nchs/data/databriefs/db118.htm#hospitaldeaths. Accessed October 1, 2015
4. Adhikari NK, Fowler RA, Bhagwanjee S, et al: Critical care and the global burden of critical illness in adults. *Lancet* 2010; 376:1339–1346
5. Iwashyna TJ, Ely EW, Smith DM, et al: Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; 304:1787–1794
6. Shah FA, Pike F, Alvarez K, et al: Bidirectional relationship between cognitive function and pneumonia. *Am J Respir Crit Care Med* 2013; 188:586–592
7. Hofhuis JG, Spronk PE, van Stel HF, et al: The impact of severe sepsis on health-related quality of life: A long-term follow-up study. *Anesth Analg* 2008; 107:1957–1964
8. Winters BD, Eberlein M, Leung J, et al: Long-term mortality and quality of life in sepsis: A systematic review. *Crit Care Med* 2010; 38:1276–1283
9. Iwashyna TJ, Cooke CR, Wunsch H, et al: Population burden of long-term survivorship after severe sepsis in older Americans. *J Am Geriatr Soc* 2012; 60:1070–1077
10. Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group: Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366:2055–2064
11. Opal SM, Laterre PF, Francois B, et al; ACCESS Study Group: Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: The ACCESS randomized trial. *JAMA* 2013; 309:1154–1162
12. Granja C, Dias C, Costa-Pereira A, et al: Quality of life of survivors from severe sepsis and septic shock may be similar to that of others who survive critical illness. *Crit Care* 2004; 8:R91–R98
13. Karlsson S, Ruokonen E, Varpula T, et al; Finnsepsis Study Group: Long-term outcome and quality-adjusted life years after severe sepsis. *Crit Care Med* 2009; 37:1268–1274
14. Holland R, Smith RD, Harvey I, et al: Assessing quality of life in the elderly: A direct comparison of the EQ-5D and AQoL. *Health Econ* 2004; 13:793–805