Symptoms of Depression in Survivors of Severe Sepsis: A Prospective Cohort Study of Older Americans

Dimitry S. Davydow, M.D., M.P.H., Catherine L. Hough, M.D., M.Sc., Kenneth M. Langa, M.D., Ph.D., Theodore J. Iwashyna, M.D., Ph.D.

Objectives: *To examine if incident severe sepsis is associated with increased risk of subsequent depressive symptoms and to assess which patient characteristics are associated with increased risk of depressive symptoms.* **Design:** *Prospective longitudinal cohort study.* **Setting:** *Population-based cohort of older U.S. adults interviewed as part of the Health and Retirement Study (1998–2006).* **Participants:** *A total of 439 patients who survived 471 hospitalizations for severe sepsis and completed at least one follow-up interview.* **Measurements:** *Depressive symptoms were assessed with a modified version of the Center for Epidemiologic Studies Depression Scale. Severe sepsis was identified using a validated algorithm in Medicare claims.* **Results:** *The point prevalence of substantial depressive symptoms was 28% at a median of 1.2 years before sepsis, and remained 28% at a median of 0.9 years after sepsis. Neither incident severe sepsis (relative risk [RR]: 1.00; 95% confidence interval [CI]: 0.73, 1.34) nor severe sepsis–related clinical characteristics were significantly associated with subsequent depressive symptoms. These results were robust to potential threats from missing data or alternative outcome definitions. After adjustment, presepsis substantial depressive symptoms (RR: 2.20; 95% CI: 1.66, 2.90) and worse postsepsis functional impairment (RR: 1.08 per new limitation; 95% CI: 1.03, 1.13) were independently associated with substantial depressive symptoms after sepsis.* **Conclusions:** *The prevalence of substantial depressive symptoms in severe sepsis survivors is high but is not increased relative to their presepsis levels. Identifying this large subset of severe sepsis survivors at increased risk for major depression, and beginning interventions before hospital discharge, may improve outcomes.* (Am J Geriatr Psychiatry 2013; 21:887–897)

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Received September 26, 2011; revised January 30, 2012; accepted February 23, 2012. From the Departments of Psychiatry and Behavioral Sciences (DSD) and Medicine (CLH), University of Washington, Seattle, WA; Department of Internal Medicine (KML, TJI), and Institute for Social Research (KML, TJI), University of Michigan, Ann Arbor, MI; and the Ann Arbor Veterans Affairs Center for Clinical Management Research (KML, TJI), Ann Arbor, MI. Send correspondence and reprint requests to Dimitry S. Davydow, M.D., M.P.H., Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Box 359911, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. e-mail: ddavydo1@u.washington.edu

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Millions of Americans are surviving critical illnesses annually, and patient-centered outcomes such as emotional well-being are becoming increasingly important.[1,2] Serious acute illnesses such as acute lung injury and severe sepsis expose patients to enormous stressors such as respiratory insufficiency, pain, and delirium,[3] and survivors may face considerable physical limitations during recovery, which might plausibly cause depression.[3,4] Two systematic reviews of 24 cohort studies of general intensive care unit and acute lung injury survivors have found that 28% of patients surviving critical illnesses may have substantial depressive symptoms.[3,5] Major depression after critical illness is an important public health problem because depression is both a sizeable contributor to disability worldwide and independently associated with increased healthcare costs as well as adverse medical outcomes.[6–8] Depression may also hamper patients' ability to participate in their often-prolonged post-illness rehabilitation and thereby promote enduring disability.[2]

Yet, it is unclear if the illness experience, through either illness or treatment-related exposures, independently increases the risk of subsequent depression. Studies[9–13] have argued that critical illnesses and their associated treatment-related exposures may have a causal role in increasing the risk of subsequent depression; these studies have motivated a National Institutes of Health–funded randomized controlled trial of empiric escitalopram for patients undergoing mechanical ventilation (ClinicalTrials.gov identifier: NCT00872027). However, very few studies of post-critical illness depression are appropriately designed to test this hypothesis—only two[14,15] have examined the contribution of premorbid depression using a standardized measure, of which only one[15] examined pre–critical illness depressive symptoms prospectively in a small sample of critical illness survivors.

In particular, little is known about the mental health outcomes of survivors of severe sepsis, the most common noncardiac cause of critical illness.[16] Depression in this patient population is especially concerning in light of recent evidence that older patients who survive severe sepsis are at increased risk for incident cognitive impairment and functional disabilities.[17] Earlier studies[10,14,18] have suggested that post–critical illness physical and cognitive impairment may be associated with increased risk of depression. Because hundreds of thousands of patients develop severe sepsis annually,[16] ascertaining the prevalence of, and risk factors for, depressive symptoms in survivors is vital; depression could be a contributor to functional decline in these patients that is amenable to treatment.

The current study utilizes an ongoing longitudinal cohort of older Americans to examine whether incident severe sepsis is associated with an increased risk of subsequent substantial depressive symptoms. This approach offers the distinct advantages of national scope and prospective assessment of depressive symptoms with a consistent instrument, and avoids the challenges of using proxy or retrospective assessment of baseline symptoms.[19] We hypothesized that hospitalization for severe sepsis in-and-of-itself would not be significantly associated with an increased risk of subsequent substantial depressive symptoms after controlling for presepsis depressive symptoms. In addition, we tested for an increased risk of substantial depressive symptoms among patients with select baseline characteristics, severe sepsis-related exposures, and post–severe sepsis functional impairments, hypothesizing that patients with presepsis substantial depressive symptoms would be at increased risk for postsepsis substantial depressive symptoms.

METHODS

Study Sample

Our study cohort comes from the Health and Retirement Study (HRS), a longitudinal investigation of community-dwelling U.S. adults older than 50 years. The study began in 1992, and to date over 27,000 individuals have participated. Subjects (and their spouses, if married) are reinterviewed every 2 years. The HRS follow-up rate has exceeded 90%–95%, including proxies,[20] and 16,772 participants have consented for linkage of their Medicare claims records with study data. The HRS protocol was approved by the University of Michigan institutional review board. Study participants provided informed consent upon enrollment and again for linkage to Medicare claims.

The present study examines all HRS respondents with at least one interview from 1998 to 2004 and for whom there were Medicare claims–based data for a subsequent hospitalization for severe sepsis from 1998 to 2005. All patients were observed through death or the 2006 survey. Our analyses focus on severe sepsis hospitalizations that patients survived long enough to complete at least one interview.

Demographic and Clinical Characteristics

We obtained data on demographics (i.e., age, race and ethnicity, sex, education, and marital/partnered status), alcohol use, and smoking from the HRS interviews.

Severe sepsis-related clinical characteristics were abstracted from the Medicare claims, including chronic medical conditions to compute a Charlson Comorbidity Index score,[21] an organ dysfunction score (the sum of the number of organ failures of cardiovascular, neurologic, hematologic, hepatic, renal, or respiratory origin),[16,22] hospital length of stay, admission to an intensive care unit, and requirements for mechanical ventilation, major surgery, and dialysis.

Definition of Severe Sepsis

We utilized a clinically validated and widely used claims-based definition of severe sepsis.[16,23–26] The definition requires evidence of a concomitant infection and new-onset organ dysfunction during a single hospitalization, consistent with the international consensus conference definitions of severe sepsis.[24] We focus on severe sepsis as a single syndrome, rather than the underlying inciting infections, in line with current thinking that emphasizes the importance of the common host response in the pathogenesis and treatment of severe sepsis.[27–32] For patients who had more than one distinct septic hospitalization, each hospitalization was included, with appropriate adjustment of the standard errors as described later.

Depressive Symptoms

The HRS assessed depression at each wave with an 8-item version of the Center for Epidemiologic Studies Depression Scale (CES-D).[33] Previous studies[34,35] have reported that this modified version loses little of the structure and precision of the original scale. Using a cutoff score of 3 or more has been found to have a sensitivity of 71% and specificity of 79% for the diagnosis of major depression compared with structured diagnostic interview.[36] We used a cutoff score of 4 or higher on the 8-item CES-D to define substantial depressive symptoms because this threshold was estimated to be comparable with the cutoff score of 16 or higher on the full CES-D by HRS investigators,[37] and has been used in several previous studies.[38–40] We defined presepsis substantial depressive symptoms as a CES-D score reaching threshold at any interview before severe sepsis, whereas postsepsis substantial depressive symptoms was defined similarly for any interview after severe sepsis.

Cognitive and Functional Impairment

The HRS assessed cognitive impairment in two ways as described in detail elsewhere.[17] Briefly, participants were administered versions of the Telephone Interview for Cognitive Status. For those patients who were unable to be interviewed themselves, a proxy respondent completed assessments of cognitive impairment. We defined thresholds on the cognitive assessments for mild and moderate to severe cognitive impairment based on previous HRS studies.[17,41]

To examine functional status, respondents (or their proxies) were asked if they required assistance with any of six activities of daily living (ADLs): walking, dressing, bathing, eating, getting into or out of bed, and toileting, or five instrumental ADLs (IADLs): preparing a hot meal, shopping for groceries, making telephone calls, taking medicines, and managing money. We summed the number of impairments in ADLs and IADLs to create a total functional impairment score.[17]

Statistical Analysis

Our unit of analysis for all analyses was the hospitalization. Our outcome variable for all analyses was the presence of substantial depressive symptoms, operationalized as a dichotomous variable defined as a score of 4 or more depressive symptoms on the 8-item CES-D. We conducted two classes of analyses as described further:

Severe Sepsis and Substantial Depressive Symptoms. To test the hypothesis that severe sepsis is associated with an increased risk of substantial symptoms of depression, we used so-called "fixed effects" models, which

use the longitudinal nature of the data to control for all stable characteristics of the patients.[17] We grouped patients who survived a severe sepsis hospitalization by the number of interviews they had completed since the severe sepsis episode. In these models, time from admission for severe sepsis to interview was measured to the day as a continuous variable. We used a hospitalization-level fixed effect, sometimes called conditional models.[42] These results controlled for the patient's depressive symptoms status before his or her severe sepsis episode. Because our outcome was not rare, we used fixed-effects Poisson regression analyses to estimate the relative risk (RR) and 95% confidence intervals (95% CIs) for post−severe sepsis substantial depressive symptoms.[43] We implemented this analysis using *xtpoisson, fe* in STATA 11 (Stata Corporation, College Station, TX). However, *xtpoisson* as currently implemented in STATA does not allow for correction of the standard errors to take into account the HRS' complex sampling design.[44,45] Because there was a relatively small number of sepsis survivor cases per sampling strata in the HRS, we did not anticipate the HRS sampling design to undermine our application. Nonetheless, we replicated our analyses using within-person conditional logistic regression, implemented using STATA's *clogit* command. We found that our interpretation was invariant to whether or not sampling design was accounted for using a Taylor series linearized approximation (results available from authors upon request), and present the results of our fixed-effects Poisson regression models here. Additional information about our statistical approach is included in the appendix on statistical methods for the analyses (see Appendix; available online).

An important methodologic challenge in the analyses for the present study was that a substantial proportion of subjects (24%) were missing postsepsis depression measurements, typically because the primary respondent was alive but unable to participate, so a proxy respondent was used. The HRS protocol did not ask proxies to report on depression measures.[36] We took two approaches to quantifying the extent to which our results might be systematically biased by the possibility that survivors who had proxies were more likely to be depressed. First, we used propensity score adjustment to account for the likelihood of missing postsepsis depression data.[46] Second, we conducted simulation analyses in which we examined how much our results would change if we randomly assigned different prevalences of substantial depressive symptoms to patients who had converted from self-respondents presepsis to requiring a proxy postsepsis; we tested prevalences of 17%, 45%, and 95%, based on previous studies that used proxy reports of patient depression.[47−49] (For further details, see Appendix, Supplemental Digital Content 1; available online).

Patient Characteristics and Risk of Postsepsis Substantial Depressive Symptoms. To examine patient characteristics and clinical factors associated with an increased risk of postsepsis substantial depressive symptoms, we used Poisson regression models with robust error variances.[43] Since a history of previous major depression is known to be a potent predictor of depression in the context of stress,[50] we initially tested the association of presepsis substantial depressive symptoms with postsepsis substantial depressive symptoms without adjustment. We then added three groups of potential confounding variables chosen a priori that have been found to be important in depression and general medical/critical illness-related research[3,9,10,12,51]: (1) demographics (age, sex, race, education, marital status), health-risk behaviors (alcohol use and smoking), and medical comorbidity (Charlson score); (2) severe sepsis episode characteristics (organ dysfunction score, hospital length of stay, intensive care unit admission, mechanical ventilation, major surgery, and dialysis); and (3) post−severe sepsis function (level of cognitive impairment and total ADL and IADL impairments) as well as nonresponse propensity scores.

As a sensitivity analysis, we also examined whether our results were affected by using a cutoff score of 5 or higher to define substantial depressive symptoms on the 8-item CES-D.[52]

We used two-sided significance tests for all analyses with statistical significance set at a p value of 0.05. Analyses were performed with appropriate components of the IBM SPSS Statistics 18 (SPSS Inc., Chicago, IL) and STATA 11 (Stata Corporation) statistical software programs.

RESULTS

From 1998 to 2005, 516 HRS respondents survived 623 hospitalizations for severe sepsis (Figure 1). Of the surviving hospitalizations, 439 individuals (85%)

completed at least one follow-up depression assessment. Patients were observed for up to four surveys before severe sepsis (mean: 6.9 years) and up to four surveys (mean: 7.1 years) afterward. Table 1 describes the 471 hospitalizations for severe sepsis that completed at least one depression assessment. Their mean age at hospitalization was 75.3 years. As in other cohorts of patients who survive severe sepsis (16), nearly half were admitted to an intensive care unit, one quarter underwent major surgery, and mean length of stay was 10.8 days (SD: 10.3 days).

Pre- and Postsepsis Depressive Symptom Prevalences

Figure 2 presents the point prevalence of substantial depressive symptoms before and after severe sepsis. The point prevalence of presepsis substantial depressive symptoms was 28% (95% CI: 24%, 31%) at the most recent interview before sepsis, a median of 1.2 years presepsis. The point prevalence of postsepsis substantial depressive symptoms was unchanged, at 28% (95% CI: 23%, 32%) at the first interview after severe sepsis, a median of 0.9 years later.

Effects of Severe Sepsis on Subsequent Substantial Depressive Symptoms

In fixed-effects regression, which controls for all patient characteristics that do not change over time, the incidence of severe sepsis was not associated with subsequent substantial depressive symptoms (Table 2). In a first sensitivity analysis, in which we adjusted for nonresponse propensity scores, we found the same result.

FIGURE 1. Health and Retirement Study Cohort for Post–Severe Sepsis Depression Analyses. CES-D: Center for Epidemiologic Studies Depression Scale.

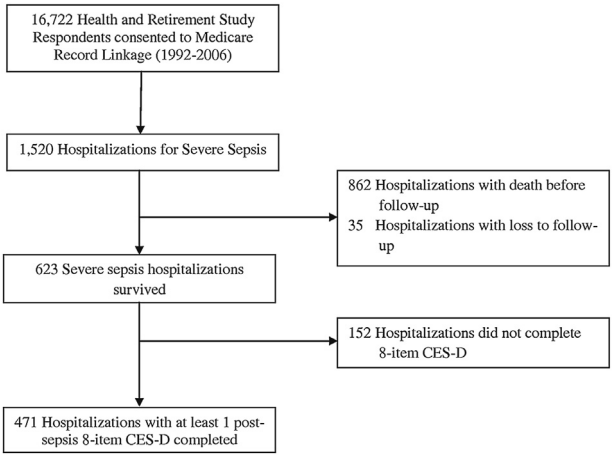
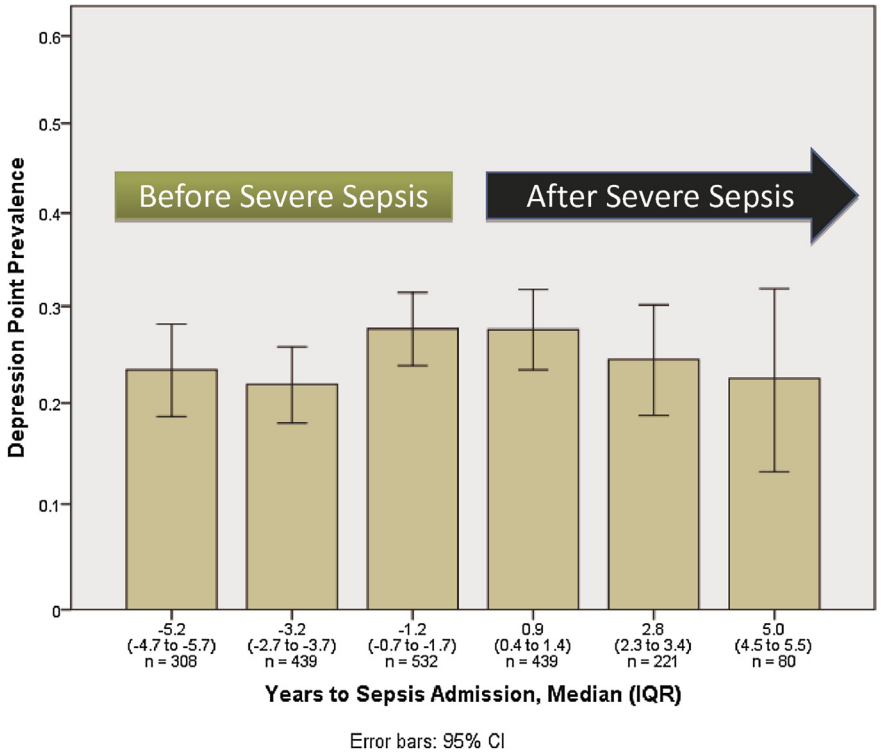


TABLE 1. Patient and Clinical Characteristics of Severe Sepsis Survivors With Postsepsis Depression Data

Variables	Postsepsis Depression Data Present (N = 471)
Panel A: Demographic and Social Characteristics	
Age (years)	75.3 (8.4)
Female	248 (52.6%)
Race	
White	378 (80.2%)
Black	87 (14.0%)
Other	6 (1.3%)
Education	
High school or less	177 (37.6%)
Some college	166 (35.2%)
College graduate	128 (27.2%)
Living arrangement	
Married/partnered	256 (54.3%)
Unmarried but living with others	78 (16.6%)
Unmarried and living alone	135 (28.7%)
Alcohol use (days/week)	1.6 (1.1)
Smoking status	
Never smoked	146 (31.0%)
Former smoker	256 (54.4%)
Current smoker	69 (14.6%)
Charlson Comorbidity Index score	1.9 (1.5)
Presepsis cognitive function	
Normal	441 (93.6%)
Mild to moderate impairment	22 (4.7%)
Moderate to severe impairment	8 (1.7%)
Presepsis ADL/Instrumental ADL impairments	1.7 (2.5)
Missing presepsis depression data	9 (1.9%)
Panel B: Characteristics of the severe sepsis hospitalization	
Organ Dysfunction Score	1.2 (0.4)
Acute conditions	
Cardiovascular dysfunction	125 (26.5%)
Neurologic dysfunction	36 (7.6%)
Hematologic dysfunction	100 (21.2%)
Hepatic dysfunction	2 (0.4%)
Renal dysfunction	184 (39.1%)
Respiratory dysfunction	94 (20.0%)
Admitted to an intensive care unit	220 (46.7%)
Required mechanical ventilation	94 (20.0%)
Required major surgery	106 (22.5%)
Required dialysis	22 (4.7%)
Hospital length of stay (days)	10.8 (10.3)
Postsepsis cognitive function	
Normal	456 (96.8%)
Mild to moderate impairment	6 (1.3%)
Moderate to severe impairment	9 (1.9%)
Postsepsis ADL/Instrumental ADL impairments	1.2 (2.1)

Notes: All values are mean (SD) or no. (%) unless otherwise indicated. ADL: activities of daily living.

FIGURE 2. **Point Prevalence of Substantial Depressive Symptoms Among Severe Sepsis Survivors. There was no loss to follow up (by definition), but patients who required a proxy respondent after their severe sepsis episode were missing depression data because proxies were not asked to report on patient depressive symptoms. We conducted several sensitivity analyses to ensure our results were robust to this issue of missing postsepsis depression data (Tables 2–4). CI: confidence interval; IQR: interquartile range.**



In our second sensitivity analysis, in which we varied the prevalence of substantial depressive symptoms among survivors who had converted from self-respondents before sepsis to requiring a proxy after sepsis, we found no significant independent associations between incident severe sepsis and subsequent depressive symptoms in any of our simulations—including the extreme case where the randomly imputed prevalence of substantial depressive symptoms among patients who had converted from self-respondents before sepsis to requiring a proxy after sepsis was 95% (Table 3).

In a third sensitivity analysis, we used the total 8-item CES-D score as a continuous variable in a fixed effects regression, assessing the total load of depressive symptoms rather than a dichotomous variable; again, there was no association between severe sepsis and depressive symptoms. There was also no association between severe sepsis and subsequent substantial depressive symptoms when we used a more stringent cutoff on the 8-item CES-D.

Factors Associated With Postsepsis Substantial Depressive Symptoms

In unadjusted Poisson regression analyses, substantial symptoms of depression at any interview before severe sepsis was associated with 2.62-times the risk (95% CI: 2.00, 3.43; $z = 7.01$; $p < 0.001$) of substantial depressive symptoms at any interview after severe sepsis compared with patients without presepsis substantial depressive symptoms. After sequential adjustment for baseline characteristics and severe sepsis–related clinical characteristics, only presepsis clinically significant depressive symptoms and female sex were consistently associated with postsepsis substantial depressive symptoms (see Tables 1 and 2, Supplemental Digital Content;

available online, which present the results of sequential adjusted analyses in tabular form). Notably, neither any single clinical characteristic of the severe sepsis–related hospitalization nor the entire set of covariates in a joint test (χ^2: 8.20, *df*: 6; p = 0.22) was significantly associated with risk of postsepsis substantial depressive symptoms after controlling for presepsis substantial symptoms of depression.

When we controlled for postsepsis cognitive and functional impairment, only presepsis substantial depressive symptoms (RR: 2.20; 95% CI: 1.67, 2.90; z = 5.56; p <0.001) and an increasing number of ADL and IADL impairments after sepsis (RR: 1.08; 95% CI: 1.04, 1.13; z = 3.49; p <0.001) were significantly associated with postsepsis substantial depressive symptoms. Adjustment for nonresponse propensity scores (Table 4) did not significantly change the results. In addition, our results were not substantively affected by using a cutoff of 5 or more depressive symptoms to define substantial depressive symptoms on the 8-item CES-D.

TABLE 2. Severe Sepsis and Subsequent Clinically Significant Depressive Symptoms in Survivors

	Relative Risk (95% Confidence Interval)	z	p
Analysis unadjusted for nonresponse propensity			
Before sepsis (per additional year)	1.05 (0.99–1.11)	1.59	0.11
Effect of sepsis	1.00 (0.73–1.34)	−0.01	0.99
After sepsis (per additional year)	1.03 (0.93–1.13)	0.52	0.60
Adjusted for nonresponse propensity			
Before sepsis (per additional year)	1.03 (0.97–1.10)	1.08	0.28
Effect of sepsis	0.95 (0.69–1.31)	−0.30	0.76
After sepsis (per additional year)	1.01 (0.91–1.12)	0.19	0.85

Notes: Results of fixed-effects Poisson regression with hospitalization-level fixed effects, controlling for all time-invariant characteristics of the patient.

DISCUSSION

This examination of the largest, prospectively assessed cohort of older severe sepsis survivors demonstrates several previously unrecognized features of the association between severe sepsis and depression. First, the prevalence of substantial depressive symptoms is quite high among severe sepsis survivors—both before and after their hospitalization. Both the prevalence of substantial depressive symptoms at the last HRS interview before severe sepsis (28%) and the first interview after sepsis (28%) are considerably higher than the 1-year prevalence of substantial depressive symptoms in a study of U.S. community-dwelling older adults assessed with the same standardized instrument.[53] Second, severe sepsis was not independently associated with an increased risk of subsequent substantial depressive symptoms, suggesting that surviving a severe illness by itself may not be sufficient as a cause of depression. Third, a history of depression was the most potent risk factor associated with substantial depressive symptoms after severe sepsis,

TABLE 3. Sensitivity Analyses of Severe Sepsis and Subsequent Depression With Imputation of Depression Prevalence of New Postsepsis Proxy-Requiring Respondents

	17% Depression Prevalence Among New Postsepsis Proxy-Requiring Respondents[45]	45% Depression Prevalence Among New Postsepsis Proxy-Requiring Respondents[46]	95% Depression Prevalence Among New Postsepsis Proxy-Requiring Respondents[47]
Median RR for Effect of Sepsis	0.90	1.03	1.16
95% range for point estimates of effect of severe sepsis (2.5th percentile–97.5th percentile for point estimate of RRs for effect of sepsis)	0.82–0.99	0.93–1.13	1.13–1.20
Percentage of all simulations with statistically significant positive association between severe sepsis and depression	0	0	0

Notes: RR: relative risk.

The results presented are from three sets of simulations of the fixed-effects regression analyses in which we imputed the presence of substantial depressive symptoms based on random assignment to patients who had converted from self-respondents presepsis to requiring a proxy postsepsis. These simulations were replicated 100 times.

TABLE 4. Fully Adjusted Associations of Patient and Clinical Characteristics Associated With Substantial Depressive Symptoms Among Survivors of Severe Sepsis

	Relative Risk (95% Confidence Interval)	z	p
Presepsis patient characteristics			
Substantial symptoms of depression at any HRS survey presepsis	2.20 (1.66–2.90)	5.56	<0.001
Age	0.99 (0.96–1.02)	−0.81	0.42
Female	1.32 (1.00–1.75)	1.93	0.05
Black	0.80 (0.58–1.09)	−0.65	0.52
Education beyond high school	0.99 (0.75–1.32)	−0.07	0.95
Single and living alone	1.22 (0.88–1.68)	1.19	0.24
Alcohol use (days/week)	1.00 (0.87–1.16)	0.04	0.97
Current smoker	0.73 (0.45–1.19)	−1.26	0.21
Charlson Comorbidity Index score	1.05 (0.96–1.14)	1.13	0.26
Severe sepsis–related hospitalization characteristics			
Organ dysfunction score	0.95 (0.70–1.30)	−0.30	0.77
Admitted to an intensive care unit	0.81 (0.60–1.09)	−1.40	0.16
Required mechanical ventilation	1.18 (0.82–1.71)	0.91	0.37
Required major surgery	1.11 (0.78–1.59)	0.58	0.56
Required dialysis	0.64 (0.32–1.28)	−1.27	0.21
Hospital length of stay	0.99 (0.97–1.00)	−1.48	0.14
Postsepsis characteristics			
Mild to moderate cognitive impairment	1.03 (0.60–1.76)	0.10	0.92
Total ADL/instrumental ADL impairments	1.08 (1.03–1.13)	3.49	<0.001

Notes: ADL: activities of daily living; HRS: Health and Retirement Study.

Adjusted for nonresponse propensity.

Since only nine patients with moderate to severe cognitive impairment had a post–severe sepsis depression measure, the model omitted this covariate.

even after adjusting for baseline patient characteristics, sepsis-related clinical factors, and postsepsis functional impairment. To our knowledge, this study is the first investigation of depressive symptoms in survivors of severe sepsis, and is only the second study of post–critical illness depression to include a standardized measure of depressive symptoms administered to patients prospectively and before their critical illness.[15]

In contrast to the interpretation of past work, we found no significant associations between severe sepsis and subsequent depressive symptoms. Previous studies identified similar high rates of depression after intensive care unit admissions and acute lung injury.[3,5] Our results confirm these findings of a high post-illness prevalence of depressive symptoms, but substantially alter the interpretation by demonstrating that high prevalence is to be unchanged from levels of depressive symptoms before the illness, at least among older Americans. Previous studies[9,10,12] have also identified exposure to specific aspects of care as potential risk factors for subsequent depression, which we did not replicate. This discrepancy may be rooted in previous studies' inability to adequately control for premorbid depression, as depression is independently associated with acute care and intensive care unit admissions for medical illnesses.[54,55] Furthermore, some of these studies examined very early postdischarge depression, which is not well measured in the HRS. However, the median time from hospitalization for severe sepsis and first follow-up assessment in our study was 0.9 years (interquartile range: 0.4–1.4 years), suggesting that the HRS allows the assessment of medium- and long-term associations with acute hospitalizations.

Depression in older patients surviving severe sepsis may be especially debilitating. Studies of older primary care patients have found that depression is an independent predictor of cognitive and functional decline.[56,57] In light of earlier HRS findings that an incident severe sepsis episode is associated with subsequent cognitive and functional impairments,[17] substantial depressive symptoms in severe sepsis survivors could exacerbate their cognitive and functional decline or limit their ability to actively participate in rehabilitation.[58] Furthermore, the high prevalence of substantial symptoms of depression before severe sepsis suggests that additional study is needed to examine if major depression is a potentially modifiable risk factor for sepsis, particularly in light of emerging evidence suggesting a bidirectional relationship between depression and medical conditions such as cardiovascular disorders and diabetes.[51]

A large body of previous research has established that critical illnesses are associated with subsequent neuromuscular dysfunction.[59,60] If functional impairment is a cause of depression after severe sepsis, then efforts targeting early physical and cognitive rehabilitation in the intensive care unit, which have been shown to improve functional outcomes at hospital discharge,[61] could prevent the development of subsequent depression. Furthermore, because

premorbid depression appears to convey considerable risk for substantial symptoms of depression in the aftermath of severe sepsis, hospital programs that target older patients surviving severe sepsis with a history of depression—whether or not formally diagnosed—for careful monitoring of their subsequent mental health may improve outcomes. Studies of interventions that combine screening and treatment for comorbid depression and medical conditions in older adults have demonstrated reductions in depressive symptoms,[62] as well as improved physical functioning and medical outcomes.[62,63]

This study does have several important limitations. First, we studied older Americans. The associations with severe sepsis and depressive symptoms may be different in younger patients. However, sepsis has been called the "quintessential disease of aging,"[64] and over half of patients with severe sepsis are of age 65 years and older.[16] Second, since we assessed depressive symptoms with a questionnaire and not a diagnostic interview, a diagnosis of major depression could not be made. Third, the 8-item CES-D has been used in many relevant populations,[38–40] but has not been specifically validated for use before and after severe sepsis. Fourth, we used a claims-based definition of severe sepsis, which although not the same as prospective clinical assessment, has been validated and widely used.[16,23–26] Fifth, our study focused on patients who survived severe sepsis with treatments utilized in a range of U.S. hospitals at a specific point in time. New treatments for sepsis, as well as changes in life support or other hospital practices, may modify the sequelae of severe sepsis, even if these outcomes are not an explicit target of care. Furthermore, as longitudinal sampling weights are not available at this time for the HRS/Medicare data, these data was analyzed as a cohort of individual patients from a wide range of hospitals rather than to provide strict generalizability to the national depression prevalence. Finally, the possibility of residual confounding remains as in any observational study.

In conclusion, using a nationwide sample of older adults, we found that patients surviving severe sepsis have a prevalence of substantial depressive symptoms considerably higher than general population estimates. We did not find evidence that severe sepsis or its treatment-related exposures are associated with increased risk of subsequent depressive symptoms. However, we did identify that the risk of substantial depressive symptoms after a hospitalization for severe sepsis was 2.2-times higher for patients with premorbid substantial depressive symptoms. In addition, greater postsepsis functional impairment was also associated with substantial depressive symptoms. Future research to find interventions that prevent or ameliorate depressive symptoms in the aftermath of severe sepsis is particularly important given the enormous toll that sepsis and depression take on older patients, their families, and the healthcare system.

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References

1. Iwashyna TJ: Survivorship will be the defining challenge of critical care in the 21st century. Ann Intern Med 2010; 153: 204–205
2. Needham DM, Feldman DR, Kho ME: The functional costs of ICU survivorship: collaborating to improve post-ICU disability. Am J Respir Crit Care Med 2011; 183:962–964
3. Davydow DS, Gifford JM, Desai SV, et al: Depression in general intensive care unit survivors: a systematic review. Intensive Care Med 2009; 35:796–809
4. Boyd CM, Ricks M, Fried LP, et al: Functional decline and recovery of activities of daily living in hospitalized, disabled older women: The Women's Health and Aging Study I. J Am Geriatr Soc 2009; 57:1757–1766
5. Davydow DS, Desai SV, Needham DM, et al: Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosom Med 2008; 70:512–519
6. Lopez AD, Mathers CD, Ezzati M, et al: Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006; 367:1747–1757
7. Katon W, Lin E, Russo J, et al: Increased medical costs of a population-based sample of depressed elderly patients. Arch Gen Psychiatry 2003; 60:897–903

8. Pan A, Lucas M, Sun Q, et al: Increased mortality risk in women with depression and diabetes mellitus. Arch Gen Psychiatry 2011; 68:42–50
9. Nelson BJ, Weinert CR, Bury CL, et al: Intensive care unit drug use and subsequent quality of life in acute lung injury patients. Crit Care Med 2000; 28:3626–3630
10. Hopkins RO, Key CW, Suchyta MR, et al: Risk factors for depression and anxiety in survivors of acute respiratory distress syndrome. Gen Hosp Psychiatry 2010; 32:147–155
11. Dowdy DW, Dinglas V, Mendez-Tellez PA, et al: Intensive care unit hypoglycemia predicts depression during early recovery from acute lung injury. Crit Care Med 2008; 36:2726–2733
12. Dowdy DW, Bienvenu OJ, Dinglas VD, et al: Are intensive care factors associated with depressive symptoms 6 months after acute lung injury? Crit Care Med 2009; 37:1702–1707
13. Herridge MS, Tansey CM, Matté A, et al: Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011; 364:1293–1304
14. Weinert C, Meller W: Epidemiology of depression and antidepressant therapy after acute respiratory failure. Psychosomatics 2006; 47:399–407
15. Davydow DS, Hough CL, Russo JE, et al: The association between intensive care unit admission and subsequent depression in patients with diabetes. Int J Geriatr Psychiatry 2012; 27(1): 22–30. http://dx.doi.org/10.1002/gps.2684
16. 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
17. 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
18. Jackson JC, Hart RP, Gordon SM, et al: Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med 2003; 31:1226–1234
19. Gifford JM, Husain N, Dinglas VD, et al: Baseline quality of life before intensive care: a comparison of patient versus proxy responses. Crit Care Med 2010; 38:855–860
20. Health and Retirement Study: Sample sizes and response rates. http://hrsonline.isr.umich.edu/sitedocs/sampleresponse.pdf. Accessed March 6, 2011
21. Charlson ME, Pompei P, Ales KL: A new method for classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; 40:373–383
22. Quan H, Sundararajan V, Halfon P, et al: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43:1130–1139
23. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979–2000. N Engl J Med 2003; 34:1546–1554
24. Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250–1256
25. Weycker D, Akrhas KS, Edelsberg J, et al: Long-term mortality and medical care charges in patients with severe sepsis. Crit Care Med 2003; 31:2316–2323
26. Lee H, Doig CJ, Ghali WA, et al: Detailed cost analysis of care for survivors of severe sepsis. Crit Care Med 2004; 32:981–985
27. Angus DC: Management of sepsis: a 47-year-old woman with an indwelling intravenous catheter and sepsis. JAMA 2011; 305: 1469–1477
28. Annane D, Bellissant E, Cacvaillon J-M: Septic shock. Lancet 2005; 365:63–78
29. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296–327
30. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368–1377
31. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699–709
32. Zahar J-R, Timsit J-F, Garrouste-Orgeas M, et al: Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality. Crit Care Med 2011; 39:1886–1895
33. Radloff LS: The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1: 385–401
34. Soldo BJ, Hurd MD, Rodgers WL, et al: Asset and health dynamics of the oldest old: an overview of the AHEAD study. J Gerontol B Psychol Soc Sci 1997; 52:1–20
35. Kohout FJ, Berkman LF, Evans DA, et al: Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. J Aging Health 1993; 5:179–183
36. Turvey CL, Wallace RB, Herzog R: A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. Int Psychogeriatr 1999; 11: 139–148
37. Steffick D: Documentation of Affective Functioning Measures in the Health and Retirement Study. Ann Arbor, MI, Survey Research Center, 2000
38. Langa KM, Valenstein MA, Fendrick AM, et al: Extent and cost of informal care giving for older Americans with symptoms of depression. Am J Psychiatry 2004; 161:857–863
39. Zivin K, Llewellyn DJ, Lang IA, et al: Depression among older adults in the United States and England. Am J Geriatr Psychiatry 2010; 18:1036–1044
40. Mezuk B, Bohnert ASB, Ratliff S, et al: Job strain, depressive symptoms, and drinking behavior among older adults: results from the Health and Retirement Study. J Gerontol B Psychol Sci Sco Sci 2011; 66:426–434
41. Langa KM, Larson EB, Karlawish JH, et al: Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? Alzheimers Dement 2008; 4:134–144
42. Allison PD: Fixed Effects Regression Models. Thousand Oaks, CA, Sage Publications, 2009
43. Zou G: A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004; 159:702–706
44. Health and Retirement Study: Sample evolution: 1992–1998. http://hrsonline.isr.umich.edu/sitedocs/surveydesign.pdf. Accessed January 30, 2012
45. Levy PS, Lemeshow S: Sampling of populations. New York, NY, John Wiley & Sons, 1999
46. Rao RS, Sigurdson AJ, Doody MM, et al: An application of a weighting method to adjust for non-response in standardized incidence-ratio analysis of cohort studies. Ann Epidemiol 2005; 15:129–136
47. Steffens DC, Fisher GG, Langa KM, et al: Prevalence of depression among older Americans: the Aging, Demographics, and Memory Study. Int Psychogeriatr 2009; 21:879–888
48. Peters KR, Rockwood K, Black SE, et al: Characterizing neuropsychiatric symptoms in subjects referred to dementia clinics. Neurology 2006; 66:523–528

49. Peters KR, Rockwood K, Black SE, et al: Neuropsychiatric symptom clusters and functional disability in cognitively-impaired not-demented individuals. Am J Geriatr Psychiatry 2008; 16:136–144
50. Kendler KS, Gardner CO, Prescott CA: Toward a comprehensive developmental model for major depression in men. Am J Psychiatry 2006; 163:115–124
51. Katon WJ: Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003; 54:216–226
52. Polsky HR, Doshi JA, Marcus S, et al: Long-term risk for depressive symptoms after a medical diagnosis. Arch Intern Med 2005; 165: 1260–1266
53. Han B: The impact of age, gender, and race on the relationship between depression and self-rated health in community-dwelling older adults: a longitudinal study. Home Health Care Serv Q 2001; 20:27–43
54. Himelhoch S, Weller WE, Wu AW, et al: Chronic medical illness, depression, and use of acute medical services among Medicare beneficiaries. Med Care 2004; 42:512–521
55. Davydow DS, Russo JE, Ludman E, et al: The association of comorbid depression and intensive care unit admission in patients with diabetes: a prospective cohort study. Psychosomatics 2011; 52:117–126
56. Spitzer RL, Kroenke K, Linzer M, et al: Health-related quality of life in primary care patients with mental disorders. Results from the PRIME-MD 1000 Study. JAMA 1995; 274: 1511–1517
57. Steffens DC, Snowden M, Fan MY, et al: Cognitive impairment and depression outcomes in the IMPACT Study. Am J Geriatr Psychiatry 2006; 14:401–409
58. DiPietro L: Physical activity in aging: changes in patterns and their relationships to health and function. J Gerontol A Biol Sci Med Sci 2001; 56:S13–S22
59. Hough CL, Steinberg KP, Thompson BT, et al: Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. Intensive Care Med 2009; 35:63–68
60. Callahan LA, Supinski GS: Sepsis-induced myopathy. Crit Care Med 2009; 37:S354–S367
61. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients. Lancet 2009; 373:1874–1882
62. Katon WJ, Lin EHB, Von Korff M, et al: Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010; 363:2611–2620
63. Callahan CM, Kroenke K, Counsell SR, et al: Treatment of depression improves physical functioning in older adults. J Am Geriatr Soc 2005; 53:367–373
64. Milbrandt EB, Eldadah B, Nayfield S, et al: Toward an integrated research agenda for critical illness in aging. Am J Respir Crit Care Med 2010; 182:995–1003