Obesity and 1-Year Outcomes in Older Americans With Severe Sepsis*

Hallie C. Prescott, MD[1]; Virginia W. Chang, MD, PhD[2]; James M. O'Brien Jr, MD, MS[3]; Kenneth M. Langa, MD, PhD[1,4,5]; Theodore J. Iwashyna, MD, PhD[1,4,5]

Objectives: Although critical care physicians view obesity as an independent poor prognostic marker, growing evidence suggests that obesity is, instead, associated with improved mortality following ICU admission. However, this prior empirical work may be biased by preferential admission of obese patients to ICUs, and little is known about other patient-centered outcomes following critical illness. We sought to determine whether 1-year mortality, healthcare utilization, and functional outcomes following a severe sepsis hospitalization differ by body mass index.

Design: Observational cohort study.

Setting: U.S. hospitals.

Patients: We analyzed 1,404 severe sepsis hospitalizations (1999–2005) among Medicare beneficiaries enrolled in the nationally representative Health and Retirement Study, of which 597 (42.5%) were normal weight, 473 (33.7%) were overweight, and 334 (23.8%) were obese or severely obese, as assessed at their survey prior to acute illness. Underweight patients were excluded a priori.

Interventions: None.

Measurements and Main Results: Using Medicare claims, we identified severe sepsis hospitalizations and measured inpatient healthcare facility use and calculated total and itemized Medicare spending in the year following hospital discharge. Using the National Death Index, we determined mortality. We ascertained pre- and postmorbid functional status from survey data. Patients with greater body mass indexes experienced lower 1-year mortality compared with nonobese patients, and there was a dose-response relationship such that obese (odds ratio = 0.59; 95% CI, 0.39–0.88) and severely obese patients (odds ratio = 0.46; 95% CI, 0.26–0.80) had the lowest mortality. Total days in a healthcare facility and Medicare expenditures were greater for obese patients ($p < 0.01$ for both comparisons), but average daily utilization ($p = 0.44$) and Medicare spending were similar ($p = 0.65$) among normal, overweight, and obese survivors. Total function limitations following severe sepsis did not differ by body mass index category ($p = 0.64$).

Conclusions: Obesity is associated with improved mortality among severe sepsis patients. Due to longer survival, obese sepsis survivors use more healthcare and result in higher Medicare spending in the year following hospitalization. Median daily healthcare utilization was similar across body mass index categories. (*Crit Care Med* 2014; 42:1766–1774)

Key Words: body mass index; critical care; outcomes assessment; prognosis; sepsis; utilization

***See also p. 1935.**

[1]Department of Medicine, University of Michigan, Ann Arbor, MI.

[2]Steindhart School of Culture, Education, and Human Development, New York University, New York, NY.

[3]Riverside Methodist Hospital, Columbus, OH.

[4]VA Center for Clinical Management Research, HSR&D Center for Excellence, Ann Arbor, MI.

[5]Institute for Social Research, Ann Arbor, MI.

Dr. Prescott has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Prescott's institution received grant support (this work was supported by grants K08 HL091249, R01 AG030155, and U01 AG09740 from the National Institutes of Health [NIH] and IIR 11–109 from the Department of Veterans Affairs Health Services Research and Development Service). Dr. Chang received support for travel from other universities (for invited research presentations) and received support for article research from American Diabetes Association. Her institution received grant support from the American Diabetes Association and the NIH. Dr. O'Brien served as board member for Sepsis Alliance (Chairman of the Board), consulted for Ortho Clinical Diagnostics (Honorarium donated to Sepsis Alliance. Travel and accommodations provided to Dr. O'Brien), lectured for Siemens (Honorarium donated to Sepsis Alliance), lectured for GE (Honorarium donated to Sepsis Alliance. Travel and board provided), received support for travel from Wolters Kluwer, served on the Global Sepsis Alliance Executive Board, and organizes a charity tournament to benefit Sepsis Alliance (Spike Out Sepsis). Dr. Langa disclosed "Government" work and received support for article research from the NIH. His institution received grant support from the NIH. Dr. Iwashyna received support for article research from the NIH. His institution received grant support from the NIH and VA (competitively awarded grants).

For information regarding this article, E-mail: hprescot@med.umich.edu

DOI: 10.1097/CCM.0000000000000336

Given the high prevalence of obesity in the United States and growing costs of hospitalization for critical illness (1–4), it is important to understand the effects of obesity on critical illness. Despite population-based studies demonstrating higher general mortality (5–8) and pathophysiologic variations that would predict worse outcomes (9–13), studies examining the impact of obesity on critical illness have yielded mixed results (14–16)—that is, some studies suggest a possible "obesity paradox" wherein obesity is not harmful and may even be protective once one is ill.

Prior work has been criticized, however, for small sample sizes and use of underweight patients as nonobese comparisons (16). Furthermore, studies often use weight ascertained at ICU admission—potentially after fluid resuscitation or prior to diuresis for decompensated edema—rather than the patient's true outpatient weight. This practice may misclassify the body mass index (BMI) category in as many as 20% of patients (17).

Beyond these problems of nonrepresentative samples and misclassification of the key exposure variable, much of the existing research has assessed in-hospital mortality following ICU admission. This study design is susceptible to bias for two reasons. First, discharge practices vary across hospitals and have been shown to alter in-hospital mortality (18–20). Second, ICU admission thresholds vary markedly across institutions (21, 22) and may be systematically different in obese patients due to their greater nursing needs (16).

Because of the limitations of the existing literature on mortality and lack of information on other patient-centered outcomes, we sought to investigate the association of obesity with 1-year mortality, healthcare utilization, and functional limitations in Medicare beneficiaries following a hospitalization for severe sepsis. We selected these additional outcome measures because of the high value patients place on living and functioning independently (23). We focused on severe sepsis because it is a very common diagnosis (24) that can be treated both within and outside the ICU.

METHODS

Study Population

The Health and Retirement Study (HRS) is an ongoing, nationally representative, cohort study of older Americans. Started in 1992, the HRS has enrolled nearly 30,000 participants, of whom 16,772 have agreed to link their data with Medicare (25). The cohort is reinterviewed every 2 years, with a follow-up rate consistently over 90% (25). Patients provided informed consent on enrollment in the HRS and again for linkage to Medicare. We studied all respondents with a baseline assessment in 1998–2004 for whom there were claims-based data on a subsequent severe sepsis hospitalization during 1998–2005. These patients were identified previously for inclusion in a study of cognitive and functional disability among sepsis survivors (26). This work was approved by the University of Michigan Institutional Review Board.

We used a commonly employed, validated claims-based definition of severe sepsis (27, 28). For patients with more than one severe sepsis hospitalization, each hospitalization was included. Patients were followed up for 1 year after their hospital discharge.

Data Abstraction

Characteristics of the hospitalizations were abstracted from Medicare claims, including acute dysfunction of the cardiovascular, neurologic, hematologic, hepatic, renal, and respiratory systems and the medical comorbidities included in the Charlson comorbidity index (29). Because diabetes may be associated with better outcomes in sepsis (30), we calculated an adjusted Charlson comorbidity score excluding diabetes, so that diabetes could be entered into multivariate analyses separately from other comorbidities. We determined critical care use from MedPAR files indicating admission to either an ICU or coronary care unit. We identified mechanical ventilation use by the presence of *International Classification of Diseases,* 9th Edition, Clinical Modification code 96.7 (including 96.7x) in any MedPAR procedure code field, a method that is validated (31) and has been used in epidemiologic studies of mechanical ventilation (32). Health-related limitations in the six activities of daily living (ADLs) and five instrumental ADLs were abstracted from the HRS survey immediately prior to and following the index hospitalization (33). Date of death was determined from the National Death Index and confirmed by HRS interviewers and the Medicare Denominator File.

We abstracted self-reported height and weight from the HRS surveys immediately preceding and following incident hospitalization. We calculated BMI using the equation: BMI (kg/m^2) = weight (kg)/height^2 (m^2). Because HRS surveys occur biennially and are random in relation to sepsis hospitalization, there was a variable time lag between baseline measurements and hospitalization (median, 1.1 yr).

We also determined self-reported race and wealth from the HRS survey prior to hospitalization. For our measure of wealth, we used the sum of all household assets and debts—including real estate (34). We standardized net assets to 2011 U.S. dollars using the Annual Gross Domestic Product Price Index (35) and made a six-category wealth variable where category one is net negative or zero assets, and categories 2 through 6 are quintiles of positive wealth (36).

Outcomes

The primary outcomes of interest were mortality, healthcare utilization, and functional status. We measured mortality in-hospital, at 90 days, and at 1 year. To assess healthcare utilization, we calculated inpatient facility use and Medicare spending in the year following hospital discharge. To measure inpatient facility use, we determined each patient's daily location in the year following hospital discharge with Center for Medicare & Medicaid Services MedPAR files. We then calculated the total days spent in an acute care hospital, long-term acute hospital (LTAC), skilled nursing facility, and home. We also determined the prevalence of transitions of care location, discharge to LTAC, and repeat hospital admissions. Finally, we calculated the Medicare spending associated with the acute sepsis hospitalization as well as total Medicare spending in the year following hospital discharge, including inpatient and outpatient care. To adjust for inflation, all Medicare spending was standardized to 2011 U.S. dollars using the Annual

Gross Domestic Product Price Index (35). To evaluate functional outcomes, we compared changes in total ADL and IADL limitation scores obtained from the HRS surveys immediately preceding and following incident sepsis hospitalization in survivors by BMI category.

Patients were assumed to be at home for any day they were known to be alive and not admitted to an acute care hospital, LTAC, or skilled nursing facility based on MedPAR records. Because Medicare does not pay for long-term custodial care provided by nursing facilities, patients residing in a nursing home on a permanent basis cannot be identified on a daily basis through MedPAR records (37, 38). Thus, while our results accurately count inpatient facility care funded by Medicare, they are conservative with respect to total service use.

Statistical Analysis

We present categorical data as numbers (%) and continuous data as means (SDs) or medians (interquartile range) depending on the distribution. We evaluated the relationship between BMI and outcome variables using BMI both as a continuous variable and as a categorical variable using World Health Organization classifications (kg/m2): normal, 18.5–24.9; overweight, 25–29.9; obese 30.0–34.9; and severely obese greater than or equal to 35.0 (39). Due to the small number of patients with a BMI greater than or equal to 35.0, we did not further subdivide these patients into those with BMI greater than or equal to 40.0. For all analyses, we excluded underweight (BMI < 18.5) patients due to previous research suggesting a "U" shaped relationship between BMI and mortality such that inclusion of underweight patients may bias results (16, 40, 41). For many of the analyses, we explored two separate samples (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A942): the 1,404 severe sepsis hospitalizations, which we refer to as "sepsis patients"; and the 1,087 hospitalizations who survived to hospital discharge, which we refer to as "sepsis survivors."

To compare baseline demographics, hospital characteristics, healthcare resource use, and functional limitations across BMI categories, we used Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. To evaluate for trends across BMI categories, we also used a nonparametric trend test (42).

We used multivariable logistic regression to determine independent associations between BMI and mortality, rate of discharge to LTAC, 30-day readmission, and 90-day readmission. For each multivariate model, we included all available covariates that we deemed potentially important based on clinical judgment and past research (specific covariates are detailed in the footnotes of tables presenting results from multivariable models).

All analyses were conducted with Stata software version 12 (StataCorp, College Station, TX). We used hospitalization as the unit of analysis, adjusting for the nonindependence of observations within patients using Stata's vce(cluster) command. We used two-sided significance testing and considered a p value less than 0.05 to be significant.

RESULTS

Study Population

There were 1,524 severe sepsis hospitalizations in the HRS-Medicare cohort, of which 34 (2.2%) were excluded from the analysis for missing height and/or weight measurements and 86 (5.6%) were excluded for being underweight (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A942). Of the 1,404 severe sepsis hospitalizations included in the analysis, 597 (42.5%) were normal weight, 473 (33.7%) were overweight, and 334 (23.8%) were obese or severely obese.

Baseline demographic and hospitalization characteristics of the sepsis patients are provided in **Table 1**. The obese were, on average, younger ($p < 0.001$), more likely to be nonwhite ($p = 0.001$), more likely to be female ($p < 0.001$), and more likely to have diabetes ($p < 0.001$). They were also less wealthy ($p < 0.001$), experienced more acute renal dysfunction ($p = 0.001$), and had more baseline ADL limitations ($p = 0.02$).

Mortality

In unadjusted analyses, higher BMIs were associated with lower in-hospital, 90-day, and 1-year mortality. One-year mortality was 44.7% in severely obese, 46.0% in obese, 53.1% in overweight, and 62.0% in normal weight patients ($p < 0.001$ for trend). Kaplan-Meier survival curves are shown in **Figure 1**. Examining just the 1,087 patients who survived their acute hospitalization, higher BMIs were still associated with better 1-year mortality ($p < 0.001$ for trend).

The association between BMI and in-hospital, 90-day, and 1-year mortality remained significant in a multivariate logistic regression models accounting for potential confounders (**Table 2**). Compared with normal weight patients, obese (odds ratio [OR] = 0.59; 95% CI, 0.39–0.88) and severely obese patients (OR = 0.46; 95% CI, 0.26–0.80) had lower ORs for mortality. Limiting our analysis to the 1,087 sepsis survivors, the ORs

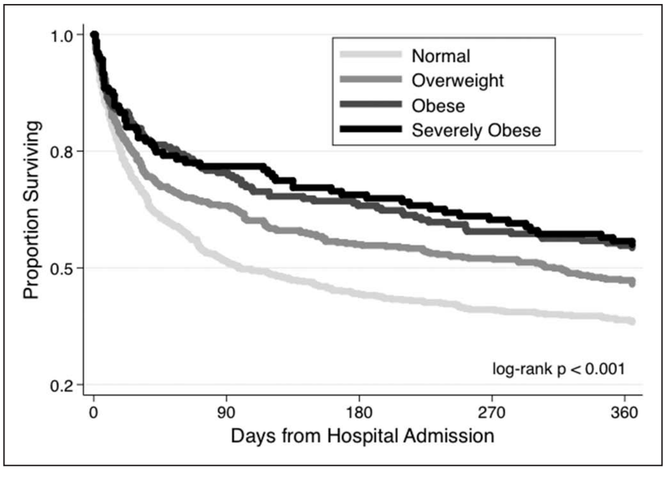

Figure 1. Survival of sepsis patients by body mass index (BMI) category.

TABLE 1. Demographic Information and Hospitalization Characteristics for Obese and Nonobese Sepsis Patients[a]

Demographic or Hospitalization Characteristic	Normal ($n = 597$)	Overweight ($n = 473$)	Obese ($n = 202$)	Severely Obese ($n = 132$)
Age (yr), mean (SD)[b]	81.3 (8.6)	78.7 (8.6)	75.3 (8.1)	72.8 (8.0)
Male, *n* (%)[b]	277 (46.6)	274 (57.9)	93 (46.0)	37 (28.0)
Self-reported race/ethnicity, *n* (%)[b]				
White, non-Hispanic	457 (76.6)	324 (68.5)	138 (68.2)	90 (68.1)
Black	96 (16.1)	103 (21.8)	47 (23.3)	37 (28.0)
White, Hispanic	35 (5.9)	29 (6.1)	14 (6.9)	0 (0.0)
Other	9 (1.5)	17 (3.6)	3 (1.5)	5 (3.8)
Married or partnered, *n* (%)[b]	233 (39.0)	239 (50.6)	97 (48.0)	54 (40.9)
Wealth, *n* (%)[b]				
Net negative on zero assets	77 (12.9)	59 (12.5)	33 (16.3)	15 (11.4)
Quintile 1	87 (14.6)	81 (17.1)	34 (16.8)	50 (37.9)
Quintile 2	102 (17.1)	76 (16.1)	31 (15.4)	27 (20.5)
Quintile 3	100 (16.8)	90 (19.0)	39 (19.3)	10 (7.6)
Quintile 4	109 (18.3)	86 (18.2)	39 (19.3)	10 (7.6)
Quintile 5	122 (20.4)	81 (17.1)	26 (12.9)	15 (11.4)
Adjusted Charlson score[c], mean (SD)[b]	1.8 (1.7)	1.9 (1.6)	1.9 (1.8)	2.2 (1.7)
Diabetes, *n* (%)[b]	62 (10.4)	94 (19.9)	48 (23.8)	31 (23.5)
Total acute organ dysfunctions, mean (SD)	1.3 (0.6)	1.2 (0.6)	1.2 (0.5)	1.3 (0.7)
Individual acute organ dysfunctions, *n* (%)				
Cardiovascular	178 (29.8)	120 (25.4)	48 (23.8)	37 (28.0)
Hematologic	113 (18.9)	94 (19.9)	36 (17.8)	19 (14.4)
Hepatic	7 (1.2)	5 (1.1)	1 (0.5)	0 (0.0)
Neurologic	53 (8.9)	40 (8.5)	9 (4.5)	10 (7.6)
Renal[b]	233 (39.0)	205 (43.3)	106 (52.5)	70 (53.0)
Respiratory	168 (28.1)	127 (26.9)	52 (25.7)	41 (31.1)
Hospital length of stay (d), mean (SD)	10.4 (9.6)	11.5 (12.0)	11.5 (10.3)	12.5 (13.3)
Used an ICU, *n* (%)	283 (47.7)	232 (49.1)	101 (50.0)	73 (55.3)
Used mechanical ventilation, *n* (%)	168 (28.1)	127 (26.9)	52 (25.7)	41 (31.1)
Cognitive impairment, *n* (%)[b]				
Normal	491 (82.2)	418 (88.4)	170 (84.2)	122 (92.4)
Mild impairment	51 (8.5)	30 (6.3)	15 (7.4)	5 (3.8)
Moderate/severe impairment	55 (9.2)	25 (5.3)	17 (8.4)	5 (3.8)
Physical function deficiencies, mean (SD)				
Basic ADL, mean (SD)[b]	1.6 (2.0)	1.6 (1.9)	1.6 (1.9)	2.1 (1.9)
Instrumental ADL, mean (SD)	1.3 (1.7)	1.1 (1.6)	1.1 (1.5)	1.2 (1.4)

ADL = activities of daily living.

[a]Underweight patients were excluded a priori.

[b]Demographic or hospitalization characteristic is significantly different across body mass index categories.

[c]Adjusted Charlson comorbidity index score does not include diabetes.

TABLE 2. Multivariable Associations of Body Mass With Patient Outcomes for Sepsis Patients[a]

Variable	Adjusted OR (95% CI)[b]		
	Hospital Mortality	90-Day Mortality	1-Year Mortality
BMI, continuous, 1 unit increment	**0.96 (0.93–0.99)**	**0.95 (0.93–0.98)**	**0.96 (0.93–0.99)**
BMI category, referent is normal BMI			
Overweight	**0.69 (0.50–0.96)**	**0.62 (0.46–0.83)**	**0.65 (0.48–0.88)**
Obese	0.64 (0.40–1.01)	**0.53 (0.35–0.79)**	**0.59 (0.39–0.88)**
Severely obese	**0.54 (0.31–0.95)**	**0.43 (0.25–0.74)**	**0.46 (0.26–0.80)**
Obesity, dichotomous	0.71 (0.49–1.02)	**0.61 (0.44–0.85)**	**0.66 (0.48–0.92)**

OR = odds ratio, BMI = body mass index.

[a]Underweight patients were excluded a priori.

[b]Odds ratios are adjusted for age, race, gender, marital status, wealth, acute organ dysfunctions, ICU use, mechanical ventilation use, diabetes, other comorbidities, baseline cognitive status, and functional limitations.

Bold values are statistically significant.

for mortality were similar (**Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/A943).

To determine whether the lower mortality we observed in obese patients was driven predominantly by older patients in whom obesity is not associated with excess mortality (43–45), we divided our sample into patients younger than and greater than 70 years old. Obesity was associated with lower ORs for 1-year mortality in both age cohorts (**Supplemental Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/A944). We also found no evidence of an interaction between age and BMI in our multivariable regression models for predicting 1-year mortality ($p = 0.949$ for model using continuous BMI variable).

Healthcare Utilization

Among sepsis survivors, baseline healthcare utilization (prior to sepsis admission) did not differ by BMI category (**Table 3**). In the year following sepsis, however, patients with higher BMIs had more hospital readmissions ($p < 0.001$ for trend) and spent more days admitted to an inpatient facility ($p = 0.01$ for trend). However, the mean percentage of days alive spent admitted to a healthcare facility was not different by BMI category, suggesting that the increased healthcare utilization observed in obese survivors is due to longer survival rather than greater daily utilization.

TABLE 3. Facility-Based HealthCare Utilization in the Year Preceding Sepsis and the Year Following Sepsis Among Patients Who Survived Their Sepsis Hospitalization

Outcome Measure	Pre-Sepsis (n = 1,087)				
	Normal (n = 436)	Overweight (n = 377)	Obese (n = 166)	Severely Obese (n = 108)	p[a]
Days alive, mean (SD)	365 (0)	365 (0)	365 (0)	365 (0)	1.00
Days at home, mean (SD)	343 (44)	336 (55)	339 (52)	341 (42)	0.19
Transitions of care, mean (SD)	2.9 (3.4)	3.8 (5.1)	3.4 (4.2)	3.4 (3.6)	0.47
Hospitalizations, mean (SD)	1.3 (1.5)	1.6 (2.2)	1.5 (1.8)	1.5 (1.6)	0.42
Days in a healthcare facility, mean (SD)	22 (41)	27 (47)	25 (38)	22 (28)	0.37
Days in a hospital, mean (SD)	10 (15)	14 (21)	15 (22)	14 (16)	0.13
Days in a long-term acute hospital, mean (SD)	1 (7)	1 (6)	1 (6)	1 (6)	0.71
Days in a skilled nursing facility, mean (SD)	11 (31)	13 (34)	9 (23)	7 (17)	1.00
Percentage of days alive in a healthcare facility, mean (SD)	6.1 (0.1)	7.5 (0.1)	6.7 (0.1)	6.1 (0.1)	0.37

[a]p values for differences across body mass index categories using Kruskal-Wallis test.

Bold values indicate significance within group differences from pre-sepsis baseline ($p < 0.5$ using Wilcoxon signed rank sum test).

Two comparisons are being made in this table. Interpretive example: days spent in a skilled nursing facility are greater post-sepsis than pre-sepsis (so post-sepsis values are bolded). However, differences in skilled nursing facility days are not different across body mass index categories pre-sepsis ($p = 1.00$) or post-sepsis ($p = 0.13$).

Similar to inpatient facility use, median Medicare spending in the year following hospital discharge—both overall and for each subcategory of Medicare spending (except hospice service)—was greater in patients with higher BMIs (**Table 4**). Unlike facility use, median daily Medicare spending was different by BMI category. However, the difference was driven entirely by the severely obese patients whose median daily expenditures were $125 higher than normal weight patients ($p = 0.01$). Median daily spending was not different between normal, overweight, and obese patients ($p = 0.65$). Exploring costs as means did not substantively change the results.

We did not identify differences in the ORs for discharge to an LTAC (OR = 1.03; 95% CI, 0.98–1.07), 30-day readmission (OR = 1.02; 95% CI, 0.99–1.05), or 90-day readmission (OR = 1.01; 95% CI, 0.99–1.04) by BMI among survivors (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/CCM/A943).

Functional Disability

There were 588 individuals who survived long enough to receive a follow-up functional assessment as part of the biennial HRS surveys, of which 215 (36.6%) were normal weight, 206 (35.0%) were overweight, 98 (16.7%) were obese, and 69 (11.7%) were severely obese. Mean baseline functional limitations were similar between normal weight (2.4), overweight (2.1), and obese patients (1.8) ($p = 0.24$) (**Fig. 2**). However, severely obese patients had more baseline limitations, at 2.9 ($p = 0.05$). Severely obese patients had fewer mean newly acquired limitations (1.1) than normal weight (1.9), overweight (1.6), or obese patients (2.1), although the differences across BMI category did not meet statistical significance in this relatively small population ($p = 0.15$). Total limitations following severe sepsis admission were not significantly different by BMI category ($p = 0.64$).

DISCUSSION

In this study, we have demonstrated that obesity is common among older Americans with severe sepsis, with nearly a quarter obese or severely obese in our sample. In this nationally representative population, obesity was independently associated with decreased mortality up to 1 year after hospitalization for sepsis. Obese patients who survive their sepsis hospitalization use more healthcare resources and require greater Medicare spending in the year following hospital discharge—but this apparent increase in resource use is the result of greater survival, not increased use per day alive. Obese patients were no more likely to experience declines in functional limitations following sepsis hospitalization than were nonobese patients.

Although our findings are in concert with several prior studies showing obesity is associated with decreased long-term mortality in ICU patients (17, 46–48), these results are in direct contradiction to what physicians predict for obese patients (49). With survey data from the HRS, we were able to show that the association between obesity and decreased mortality persists after adjustment for age and important potential confounders unavailable in administrative databases and past work, such as wealth, baseline cognitive status, and baseline functional limitations. Also, by studying a patient population defined by hospital admission for a specific diagnosis and not just a common admission location, we showed that the association is not due to a differential threshold for ICU admission in obese patients (although the possibility of differential threshold for hospital admission still exists). Our results were

Post-Sepsis ($n = 1,087$)				
Normal ($n = 436$)	**Overweight ($n = 377$)**	**Obese ($n = 166$)**	**Severely Obese ($n = 108$)**	p^a
230 (153)	**256 (147)**	**278 (134)**	**289 (126)**	< 0.01
199 (152)	**227 (148)**	**245 (138)**	**247 (143)**	< 0.01
3.0 (3.3)	3.3 (3.8)	3.6 (3.3)	4.5 (4.2)	< 0.01
1.2 (1.4)	1.4 (1.7)	1.5 (1.5)	1.9 (2.1)	< 0.01
33 (45)	**31 (44)**	**36 (43)**	**45 (47)**	< 0.01
11 (13)	14 (22)	15 (20)	20 (23)	< 0.01
2 (10)	**2 (8)**	2 (10)	**5 (12)**	0.31
21 (39)	**16 (33)**	**19 (33)**	**21 (33)**	0.13
29.0 (3.5)	**23.9 (3.3)**	**21.6 (29.8)**	**26.4 (3.2)**	0.07

robust to different classifications of obesity, and were present with prospectively measured BMI, assessed prior to the onset of current illness.

Beyond mortality, obesity was associated with neither better nor worse outcomes in our study. Obese sepsis survivors acquired new functional limitations at a rate similar to normal weight patients. Obese survivors used inpatient healthcare facilities at a rate similar to normal weight patients although, as a result of their better mortality, obese patients used significantly more total healthcare resources in the year following hospital discharge. This last finding may have important public finance implications given the growing prevalence of obesity in new Medicare beneficiaries.

There are many potential reasons for the association between obesity and decreased mortality in sepsis and other critical illnesses. First, it may be due to a true protective effect of excess body weight. This may be the result of an altered inflammatory response to critical illness, as suggested by the attenuated proinflammatory cytokine levels in obese acute respiratory distress syndrome patients (50). Alternatively, obese patients could have a greater capacity to tolerate the extensive weight loss and deconditioning associated with critical illness (51).

The epidemiology and treatment of severe sepsis may also differ by BMI. A recent study by Arabi et al (48) demonstrated that obese patients with septic shock have a lower proportion of Gram-negative infections, lower proportion of pneumonia, and greater proportion of skin and soft-tissue infection. Several studies have also shown that obesity is associated with greater prevalence of renal failure in critical illness (52–54)—a finding present in our dataset as well. While this organ failure meets criteria for severe sepsis, it is associated with relatively better outcomes than respiratory, cardiovascular, or neurologic failures (55). Finally, several studies have shown that obese patients receive different—in some cases better and in other cases worse—treatment than normal weight patients (48, 17, 56).

We hypothesize that epidemiologic and treatment differences partially explain the survival advantage in obese patients and that biologic differences may explain the remaining portion of the survival advantage. Further examination of the epidemiologic, treatment, and biologic differences by BMI is certainly warranted with clinically nuanced datasets, but was not possible using our administrative dataset.

There are some potential limitations to our analysis. We used self-reported height and weight which may be underreported and overreported, respectively, contributing to an underestimation of BMI (57). Prior analysis of HRS data suggests that reporting errors are small and less problematic when BMI is evaluated as a continuous variable (57). Because HRS surveys occur biennially, there was as much as a 2-year lag between baseline survey and incident sepsis admission (median, 1.1 yr). Thus, measures of height, weight, wealth, cognitive status, and

TABLE 4. Medicare Spending on the Incident Hospitalization and Healthcare in the Year After Hospital Discharge

Outcome Measure	Normal (*n* = 436)	Overweight (*n* = 377)	Obese (*n* = 166)	Severely Obese (*n* = 108)	*p*[a]
Cost of incident hospitalization, median (IQR)	7,885 (5,384–15,124)	8,895 (5,721–16,451)	8,680 (5,343–18,711)	8,051 (5,457–17,122)	0.48
Total Medicare spending in 1 yr after hospital discharge, median (IQR)[b]	28,896 (10,415–67,041)	31,210 (9,823–77,362)	41,047 (14,207–86,354)	74,717 (28,231–190,702)	< 0.001
Inpatient facility, median (IQR)	16,462 (4,006–47,083)	17,124 (3,126–48,577)	26,645 (3,823–53,451)	46,053 (14,026–30,144)	< 0.001
Physical services, median (IQR)	4,143 (1,373–9,226)	4,743 (1,539–11,551)	6,146 (2,719–13,200)	10,674 (4,405–30,144)	< 0.001
Outpatient facility, median (IQR)	473 (0–1,683)	860 (33–2,582)	826 (165–3,123)	1,858 (146–5,828)	< 0.001
Home health services, median (IQR)	0 (0–4,075)	0 (0–4,815)	52 (0–6,335)	3,176 (0–15,703)	< 0.001
Durable medical equipment, median (IQR)	0 (0–1,074)	98 (0–2,015)	566 (0–2633)	778 (0–5,745)	< 0.001
Hospice services, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.48
Healthcare spending per day alive in the 1 yr after hospital discharge, median (IQR)	201 (70–600)	172 (69–549)	188 (77–559)	326 (109–853)	0.02[c]

IQR = interquartile range.

[a]*p* value for difference across body mass index categories using Kruskal-Wallis test.

[b]Index hospital spending is not included in this measure.

[c]Comparing just normal weight, overweight, and obese patients, there was no difference in costs per day alive ($p = 0.65$).

All costs are standardized to 2011 U.S. dollar. Total costs are the costs in the year following hospitalization, excluding the cost of the incident hospitalization.

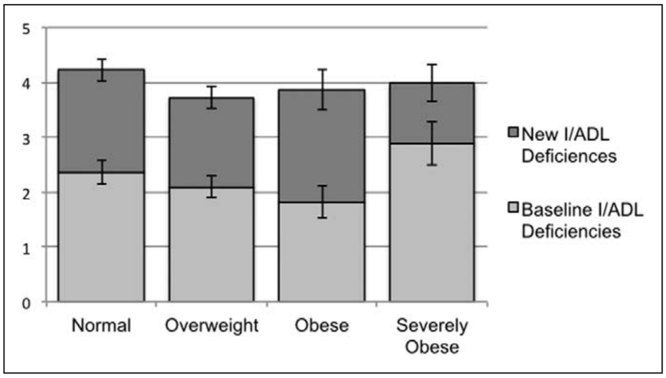

Figure 2. Functional limitations before and after sepsis hospitalization. Mean number of functional limitations (±SE) as measured by deficiencies in activities and instrumental activities of daily living (I/ADLs) are depicted. There were differences in baseline limitations ($p = 0.05$), but no differences in newly acquired or total limitations across body mass index categories ($p = 0.15$ and 0.64, respectively).

functional status may not precisely reflect patient status at the time of sepsis admission. Similarly, there was up to a 2-year lag between hospital discharge and follow-up functional assessment, relevant to the analyses in Figure 2. Many patients did not survive long enough to complete a follow-up assessment. We used a claims-based definition of severe sepsis that, while not as accurate as prospective clinical assessment, has a high positive predictive value and better sensitivity than other claims-based definitions (28). As a result of studying a Medicare population, our patients were mostly over 65 years (mean, 79.0 yr). This age group captures only about 60% of adult sepsis admissions nationally (24). Furthermore, because the detrimental effects of obesity may wane with age (43–45), our findings may not apply for younger sepsis patients, although our sensitivity analysis did not suggest that the relationship between BMI and mortality varied by age. We did not include severity of illness measures, such as Acute Physiology and Chronic Health Evaluation scores, as they were not available through our administrative databases—although we instead included presence of acute organ dysfunctions (55). Because our data are from 1999 to 2005, it may not accurately represent the distribution of BMI in current Medicare beneficiaries hospitalized with sepsis.

CONCLUSIONS

In summary, we have shown that obesity is associated with improved short- and long-term mortality in older patients with severe sepsis. Daily healthcare utilization and newly acquired functional limitations are no worse in obese survivors than those with normal weight. However, as a result of their decreased mortality, obese sepsis survivors use more healthcare and produce higher Medicare spending in the year following hospitalization.

ACKNOWLEDGMENTS

The Health and Retirement Study is performed at the Institute for Social Research, University of Michigan. We appreciate the expert programming of Mohammed Kabeto, MS, and Laetitia Shapiro, MS, at the University of Michigan.

REFERENCES

1. Mokdad AH, Serdula MK, Dietz WH, et al: The spread of the obesity epidemic in the United States, 1991–1998. *JAMA* 1999; 282:1519–1522
2. Wang Y, Beydoun MA: The obesity epidemic in the United States–Gender, age, socioeconomic, racial/ethnic, and geographic characteristics: A systematic review and meta-regression analysis. *Epidemiol Rev* 2007; 29:6–28
3. Wang YC, Colditz GA, Kuntz KM: Forecasting the obesity epidemic in the aging U.S. population. *Obesity (Silver Spring)* 2007; 15:2855–2865
4. 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
5. Thompson D, Edelsberg J, Colditz GA, et al: Lifetime health and economic consequences of obesity. *Arch Intern Med* 1999; 159:2177–2183
6. Flegal KM, Graubard BI, Williamson DF, et al: Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005; 293:1861–1867
7. Flegal KM, Kit BK, Orpana H, et al: Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. *JAMA* 2013; 309:71–82
8. Mehta NK, Chang VW: Mortality attributable to obesity among middle-aged adults in the United States. *Demography* 2009; 46:851–872
9. Kahn BB, Flier JS: Obesity and insulin resistance. *J Clin Invest* 2000; 106:473–481
10. Yang R, Barouch LA: Leptin signaling and obesity: Cardiovascular consequences. *Circ Res* 2007; 101:545–559
11. Caballero AE: Endothelial dysfunction in obesity and insulin resistance: A road to diabetes and heart disease. *Obes Res* 2003; 11:1278–1289
12. Yudkin JS, Stehouwer CD, Emeis JJ, et al: C-reactive protein in healthy subjects: Associations with obesity, insulin resistance, and endothelial dysfunction: A potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; 19:972–978
13. Singer G, Granger DN: Inflammatory responses underlying the microvascular dysfunction associated with obesity and insulin resistance. *Microcirculation* 2007; 14:375–387
14. Akinnusi ME, Pineda LA, El Solh AA: Effect of obesity on intensive care morbidity and mortality: A meta-analysis. *Crit Care Med* 2008; 36:151–158
15. Oliveros H, Villamor E: Obesity and mortality in critically ill adults: A systematic review and meta-analysis. *Obesity (Silver Spring)* 2008; 16:515–521
16. Hogue CW Jr, Stearns JD, Colantuoni E, et al: The impact of obesity on outcomes after critical illness: A meta-analysis. *Intensive Care Med* 2009; 35:1152–1170
17. O'Brien JM Jr, Philips GS, Ali NA, et al: The association between body mass index, processes of care, and outcomes from mechanical ventilation: A prospective cohort study. *Crit Care Med* 2012; 40:1456–1463
18. Hall WB, Willis LE, Medvedev S, et al: The implications of long-term acute care hospital transfer practices for measures of in-hospital mortality and length of stay. *Am J Respir Crit Care Med* 2012; 185:53–57
19. Vasilevskis EE, Kuzniewicz MW, Dean ML, et al: Relationship between discharge practices and intensive care unit in-hospital mortality performance: Evidence of a discharge bias. *Med Care* 2009; 47:803–812
20. Kahn JM, Werner RM, Carson SS, et al: Variation in long-term acute care hospital use after intensive care. *Med Care Res Rev* 2012; 69:339–350
21. Gershengorn HB, Iwashyna TJ, Cooke CR, et al: Variation in use of intensive care for adults with diabetic ketoacidosis. *Crit Care Med* 2012; 40:2009–2015
22. Seymour CW, Iwashyna TJ, Ehlenbach WJ, et al: Hospital-level variation in the use of intensive care. *Health Serv Res* 2012; 47:2060–2080

23. Fried TR, Bradley EH, Towle VR, et al: Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 2002; 346:1061–1066
24. Elixhauser A, Friedman B, Stranges E: Septicemia in U.S. Hospitals, 2009. HCUP Statistical Brief #122. October, 2011. Rockville, MD, Agency for Healthcare Research and Quality. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb122.pdf. Accessed January 23, 2013
25. Health and Retirement Study. Available at: http://hrsonline.isr.umich.edu/. Accessed October 18, 2012
26. 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
27. 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
28. Iwashyna TJ, Odden A, Rohde J, et al: Identifying patients with severe sepsis using administrative claims: Patient-level validation of the Angus implementation of the international consensus conference definition of severe sepsis. *Med Care* 2012 Sep 18. [Epub ahead of print]
29. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45:613–619
30. Esper AM, Moss M, Martin GS: The effect of diabetes mellitus on organ dysfunction with sepsis: An epidemiological study. *Crit Care* 2009; 13:R18
31. Quan H, Parsons GA, Ghali WA: Validity of procedure codes in International Classification of Diseases, 9th revision, clinical modification administrative data. *Med Care* 2004; 42:801–809
32. Wunsch H, Linde-Zwirble WT, Angus DC, et al: The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010; 38:1947–1953
33. Fonda S, Herzog AR: Documentation of Physical Functioning Measured in the Health and Retirement Study and the Asset and Health Dynamics among the Oldest Old Study. Survey Research Center, University of Michigan, Ann Arbor, MI, 2004
34. RAND Income and Wealth Imputation Files: RAND Center for the Study of Aging. Available at: http://hrsonline.isr.umich.edu/modules/meta/rand/README_incwlth.pdf. Accessed March 12, 2013
35. U.S. Department of Commerce Bureau of Economic Analysis Website. 2012. Available at: http://www.bea.gov/iTable/iTable.cfm?ReqID=9&step=1. Accessed November 27, 2012
36. Hajat A, Kaufman JS, Rose KM, et al: Do the wealthy have a health advantage? Cardiovascular disease risk factors and wealth. *Soc Sci Med* 2010; 71:1935–1942
37. Iwashyna TJ: On the detection of nursing home use in Medicare claims. *Health Serv Outcomes Res Methodol* 2003; 4:187–196
38. Yun H, Kilgore ML, Curtis JR, et al: Identifying types of nursing facilities using Medicare claims data: An algorithm and validation. *Health Serv Outcomes Res Methodol* 2010; 10:100–110
39. BMI Classification: World Health Organization. 2013. Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed March 5, 2013
40. Finkielman JD, Gajic O, Afessa B: Underweight is independently associated with mortality in post-operative and non-operative patients admitted to the intensive care unit: A retrospective study. *BMC Emerg Med* 2004; 4:3
41. O'Brien JM Jr, Phillips GS, Ali NA, et al: Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. *Crit Care Med* 2006; 34:738–744
42. Cuzick J. A Wilcoxon-type test for trend. *Stat Med* 1985; 4:87–90
43. Diehr P, Bild DE, Harris TB, et al: Body mass index and mortality in nonsmoking older adults: The Cardiovascular Health Study. *Am J Public Health* 1998; 88:623–629
44. Bender R, Jöckel KH, Trautner C, et al: Effect of age on excess mortality in obesity. *JAMA* 1999; 281:1498–1504
45. Stevens J, Cai J, Pamuk ER, et al: The effect of age on the association between body-mass index and mortality. *N Engl J Med* 1998; 338:1–7
46. Peake SL, Moran JL, Ghelani DR, et al: The effect of obesity on 12-month survival following admission to intensive care: A prospective study. *Crit Care Med* 2006; 34:2929–2939
47. Abhyankar S, Leishear K, Callaghan FM, et al: Lower short- and long-term mortality associated with overweight and obesity in a large cohort study of adult intensive care unit patients. *Crit Care* 2012; 16:R235
48. Arabi YM, Dara SI, Tamim HM, et al; The Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group: Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: An international multicenter cohort study. *Crit Care* 2013; 17:R72
49. O'Brien JM Jr, Aberegg SK, Ali NA, et al: Results from the national sepsis practice survey: Predictions about mortality and morbidity and recommendations for limitation of care orders. *Crit Care* 2009; 13:R96
50. Stapleton RD, Dixon AE, Parsons PE, et al: The association between body mass index and plasma cytokine levels in patients with acute lung injury. *Chest* 2010; 138:568–577
51. Herridge MS, Cheung AM, Tansey CM, et al; Canadian Critical Care Trials Group: One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; 348:683–693
52. Druml W, Metnitz B, Schaden E, et al: Impact of body mass on incidence and prognosis of acute kidney injury requiring renal replacement therapy. *Intensive Care Med* 2010; 36:1221–1228
53. Shashaty MG, Meyer NJ, Localio AR, et al: African American race, obesity, and blood product transfusion are risk factors for acute kidney injury in critically ill trauma patients. *J Crit Care* 2012; 27:496–504
54. Soto GJ, Frank AJ, Christiani DC, et al: Body mass index and acute kidney injury in the acute respiratory distress syndrome. *Crit Care Med* 2012; 40:2601–2608
55. Lone NI, Walsh TS: Impact of intensive care unit organ failures on mortality during the five years after a critical illness. *Am J Respir Crit Care Med* 2012; 186:640–647
56. Chang VW, Asch DA, Werner RM: Quality of care among obese patients. *JAMA* 2010; 303:1274–1281
57. Meng H, He XZ, Dixon D: Self-reported versus measured height and weight in the health and retirement study. *J Am Geriatr Soc* 2010; 58:412–413