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Culture-Negative Severe Sepsis
Nationwide Trends and Outcomes

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BACKGROUND: Although 28% to 49% of severe sepsis hospitalizations have been described as being "culture negative," there are very limited data on the epidemiology and outcomes of those with culture-negative severe sepsis (CNSS). The objectives of this study were to investigate the proportion and trends of CNSS and its association with mortality.

METHODS: Using the Nationwide Inpatient Sample (NIS) database from 2000 to 2010, we identified adults hospitalized with severe sepsis. Those without any specific organism codes were identified as "with CNSS." We examined the proportion of CNSS hospitalizations and rates of mortality associated with it. We also assessed the independent effect of CNSS on mortality.

RESULTS: Of 6,843,279 admissions of patients with severe sepsis, 3,226,406 (47.1%) had culture-negative results. The age-adjusted proportion of CNSS increased from 33.9% in 2000 to 43.5% in 2010 ($P < .001$). Those with CNSS had more comorbidities, acute organ dysfunction (respiratory, cardiac, hepatic, and renal dysfunction), and in-hospital mortality (34.6% vs 22.7%; $P < .001$), although acute kidney injury requiring dialysis was less frequent (5.3% vs 6.1%; $P < .001$). CNSS was an independent predictor of mortality in those with severe sepsis (OR, 1.75; 95% CI, 1.72-1.77).

CONCLUSIONS: CNSS among hospitalized patients is common, and its proportion is on the rise. CNSS is associated with greater acute organ dysfunction and mortality. Having CNSS is an independent predictor of death.

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KEY WORDS: culture; mortality; sepsis

ABBREVIATIONS: CCI = Charlson comorbidity index; CNSS = culture-negative severe sepsis; CPSS = culture-positive severe sepsis; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NIS = Nationwide Inpatient Sample; SIRS = systemic inflammatory response syndrome

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Severe sepsis is one of the leading causes of death in the Unites States and results in a significant health-care burden.[1] Recent epidemiologic data have shown that the incidence of severe sepsis has increased over the past decade.[2] Although sepsis-associated mortality has been on the decline, it continues to affect more than one-fourth of those admitted to the hospital with severe sepsis.[2]

The clinical diagnosis of sepsis is based on the manifestations of the systemic inflammatory response syndrome (SIRS) in the presence of proven or suspected infection.[3] Although an infectious cause is fundamental to the definition of sepsis, in many cases isolation of specific organisms by culture remains challenging. Severe sepsis without a microbiologically documented infection is called "culture-negative severe sepsis" (CNSS). In a significant proportion of severe sepsis episodes, no specific organism can be identified.[4-9] Even in rigorous randomized controlled trials, approximately one-fourth of patients with severe sepsis remain culture negative.[10] In fact, a growing literature suggests a differential risk of mortality depending on the specific organism associated with a severe sepsis episode.[11-13]

Various multicenter studies have reported the proportion of CNSS admissions to be between 28% and 49% of all patients with severe sepsis.[4-9] Despite the abundance of CNSS, there is a remarkable paucity of investigations elucidating its epidemiology and outcomes. One previous study, limited by a small sample size and single-center design, found > 40% of cases of severe sepsis to be culture-negative.[14]

It is difficult to discern the reasons for culture negativity; however, some plausible explanations include administration of antibiotics before obtaining cultures, infections with fastidious organisms, and noninfectious causes of SIRS inappropriately deemed CNSS. In this regard, CNSS may represent a unique cohort of individuals. Therefore, understanding the epidemiology and outcomes of CNSS is of particular importance for the design of future clinical trials and for quality-improvement purposes. We conducted this study to understand the incidence, trends, and outcomes of patients hospitalized with CNSS. Our goals were to (1) investigate the proportion and trends of CNSS among severe sepsis hospitalizations and (2) investigate if being culture negative is an independent predictor of death in those with severe sepsis.

Methods

Study Design

We designed a retrospective study using data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) from 2000 to 2010. NIS is the largest all-payer inpatient care database publicly available in the United States. It includes data from a 20% stratified sample of US community hospitals.[15] Each hospitalization in this database is treated as an individual entry. The database contains information about age, race, and sex, along with primary insurance, hospital characteristics and teaching status, location (rural vs urban), size of the hospital, and hospital region. In addition, each hospitalization entry provides information about principal, secondary, and procedural diagnoses. As the current study was a retrospective analysis of a hospital-based discharge data set that is available publicly from the Agency for Healthcare Research and Quality, it did not require institutional review board approval.

Study Population

We included all hospitalizations with severe sepsis during the study period. In accordance with the previous literature,[2,4,16] we defined severe sepsis as the use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for severe sepsis or septic shock, septicemia, bacteremia, or fungemia, with dysfunction of at least one organ. We used ICD-9-CM codes to identify specific organisms and infection sites associated with hospitalizations. We have provided the codes used in e-Tables 1-4. Severe sepsis hospitalizations that were not associated with codes for any specific organisms were identified as CNSS hospitalizations.

Study Variables

We used NIS variables to determine demographic characteristics (age, sex, and race), hospital characteristics (teaching status, location, bed size, and region), and primary payer. We divided hospitals into tertiles based on the annual volume of severe sepsis discharges (< 227, 227-474, and > 474 per year). The burden of comorbid diseases was identified using Deyo's modification of the Charlson comorbidity index (CCI).[17] We identified individuals receiving mechanical ventilation using ICD-9-CM procedure codes 96.70, 96.71, and 96.72. We defined septic shock as either the presence of the ICD-9-CM code for septic shock or a combination of severe sepsis and acute cardiovascular dysfunction.

Outcomes

Our primary outcomes of interest were the proportion of patients with severe sepsis who had negative culture results and the trend of CNSS hospitalizations. Our secondary outcomes of interest were the incidence and trends of mortality associated with CNSS in comparison to those associated with CPSS. In addition, we investigated if culture-negative results are an independent predictor of death in those with severe sepsis.

Statistical Analysis

We generated national estimates of the number of overall severe sepsis hospitalizations using weights provided in the NIS database. The χ^2 test was used to compare categorical variables, and linear regression was used to assess the significance of trends over time. Direct standardization of the age of the 2000 US standard population was performed to estimate the age-adjusted incidence of severe sepsis and mortality.[18] Stata, version 14.0 (StataCorp LP) was used for all statistical analyses.

We used a multivariable logistic regression model to estimate the odds of all-cause inpatient mortality. All clinically relevant variables were included in the final multivariable model, which was adjusted for age; sex; race; primary payer; CCI; hospital teaching status, location, region, volume (small, medium, and large), and bed size; individual organ dysfunctions; respiratory failure requiring mechanical ventilation; and, finally, the year of admission. Interactions of CNSS status were assessed with year of admission, age group, and hospital teaching status. We then used a linear combination of estimates to predict the independent effect of CNSS on mortality for specific age groups.

Missing data was < 1% for all variables except race, which was missing in approximately 20% of observations. Casewise deletion was used to handle missing data. To ensure that this methodology of handling missing data did not affect our results, we performed a sensitivity analysis by including missing values of race under the "missing" category for race in the logistic regression.

To further assess the robustness of our results we performed four additional sensitivity analyses, the details of which we have provided in e-Appendix 1.

Results

Proportion and Trends of CNSS

There were 6,843,279 (95% CI, 6,587,649-7,098,909) admissions in patients with severe sepsis in the period studied, 3,226,406 (95% CI, 3,102,039-3,350,773) of which were CNSS. The age-adjusted proportion of CNSS hospitalizations increased from 33.9% of all severe sepsis hospitalizations in 2000 to 43.5% of these hospitalizations in 2010 (P for trend < .001) (Fig 1).

Patient Characteristics Based on Culture Status

The proportion of CNSS hospitalizations was higher in those < 1 year or ≥ 70 years of age and in white patients. In comparison with patients with CPSS, those with CNSS were more often admitted to nonteaching hospitals (55% vs 50.6%; P < .001), had a higher comorbidity burden as evidenced by a higher CCI (28.2% vs 26.5% with CCI score > 3; P < .001), a higher number of acute organ system dysfunctions (27.0% vs 23.1% with more than three acute organ system dysfunctions; P < .001), and were more likely to have acute respiratory failure (52.1% vs 46.7%; P < .001), need mechanical ventilator support (37.7% vs 35.7%; P < .001), and have septic shock (41.1% vs 35.5%; P < .001), cardiovascular failure, hepatic failure, and metabolic dysfunction (Table 1). Infections identified at common sites, as shown in Table 2, were more commonly associated with CPSS.

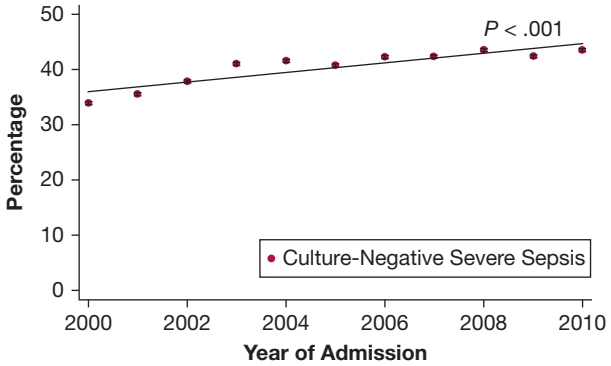

Figure 1 – *Trends of culture-negative severe sepsis (CNSS) hospitalizations.*

Mortality Based on Culture Status

Unadjusted mortality was higher in those with CNSS compared with those with CPSS (34.6% vs 22.7%; P < .001). Although age-adjusted mortality declined in both patients with CPSS and those with CNNS, it was still significantly higher in CNSS than in CPSS (Fig 2). After multivariable adjustment, culture-negative status was an independent predictor of mortality in those with severe sepsis (OR, 1.75; 95% CI, 1.72-1.77) (Table 3). There was an 11% improvement in the odds of death with each passing year (OR, 0.89; 95% CI, 0.89-0.90). On exploratory analysis, the interaction term between culture-negative status and year of admission was not significant (interaction P = .3), suggesting similar odds for improvement in mortality over the years, regardless of culture status. However, CNSS had a differential effect on mortality for different age groups, as evidenced by a significant interaction term between the variable for age groups and culture-negative status (interaction P < .001) (e-Fig 2). The interaction term between CNSS and hospital teaching status was also significant (interaction P = .02), with CNSS being associated with a 72% increase in the odds of death in teaching hospitals (OR, 1.72; 95% CI, 1.68-1.76) vs 78% in nonteaching hospitals (OR, 1.78; 95% CI, 1.75-1.81).

Sensitivity Analyses

Culture-negative status was associated with a 74% increased odds of mortality in those with severe sepsis (OR, 1.74; 95% CI, 1.72-1.76) in the analysis that used missing values of race as a "missing" category for the variable of race in the regression model (e-Table 5). Culture-negative status continued to be an independent predictor of mortality in the propensity-matched sample (OR, 1.75; 95% CI, 1.73-1.76) (e-Table 6). Culture-negative status was also an independent predictor of death when those with acute cardiac dysfunction were excluded from the cohort (OR, 1.68; 95% CI, 1.65-1.71) (e-Table 7).

TABLE 1] Baseline Characteristics of Patients Hospitalized With Severe Sepsis

Characteristic	CNSS, % (n = 3,226,406)	CPSS, % (n = 3,616,873)	*P* Value
Age group, y			< .001
< 1	2.5	2.0	
1-4	0.3	0.6	
5-9	0.2	0.3	
10-14	0.2	0.4	
15-19	0.5	0.7	
20-29	1.8	2.3	
30-39	3.4	3.9	
40-49	7.3	8.4	
50-59	13.4	14.5	
60-69	17.5	18.1	
70-79	23.0	22.7	
≥ 80	29.9	26.0	
Sex			< .001
Male	50.1	50.9	
Race			< .001
White	55.7	55.8	
Black	11.6	12.4	
Hispanic	7.4	7.7	
Asian	2.1	2.3	
Native American	0.5	0.5	
Other	2.1	2.3	
Missing	20.6	19.0	
Primary payer			< .001
Medicare	64.5	61.7	
Medicaid	11.1	12.6	
Private	18.7	19.9	
Self-pay	3.1	3.1	
No charge	0.3	0.3	
Other	2.3	2.3	
Charlson comorbidity index score			< .001
< 3	71.8	73.5	
3-4	16.2	15.8	
≥ 5	12.0	10.7	
Respiratory dysfunction	52.1	46.7	< .001
Cardiac dysfunction	41.1	35.5	< .001
Hepatic dysfunction	5.9	5.0	< .001
Acute kidney injury	49.0	48.5	< .001
Acute kidney injury requiring dialysis	5.3	6.1	< .001
Hematologic dysfunction	16.1	19.8	< .001
Metabolic dysfunction	18.5	15.1	< .001
Neurologic dysfunction	13.0	13.0	.9
Septic shock	41.1	35.5	< .001
Mechanical ventilation use	37.7	35.7	< .001

(Continued)

TABLE 1] *(Continued)*

Characteristic	CNSS, % (n = 3,226,406)	CPSS, % (n = 3,616,873)	*P* Value
Hospital teaching status			< .001
Teaching	45	49.4	
Hospital bed size			.1
Small	11.0	11.5	
Medium	24.6	24.1	
Large	64.4	64.5	
Hospital volume			.6
Small	32.8	33.1	
Medium	34.0	33.8	
Large	33.2	33.1	
Hospital location			< .001
Urban	89.3	91.1	
Hospital region			< .001
Northeast	18.7	20.8	
Midwest	20.8	21.2	
South	41.8	37.3	
West	18.8	20.7	
Year of admission			< .001
2000	4.0	5	
2001	4.7	5.5	
2002	5.5	6.2	
2003	6.8	6.7	
2004	7.6	7.8	
2005	8.8	8.7	
2006	9.7	9.4	
2007	10.9	10.6	
2008	13.2	12.3	
2009	13.5	13.6	
2010	15.3	14.2	

CNSS = culture-negative severe sepsis; CPSS = culture-positive severe sepsis.

TABLE 2] Infection Sites Based on Culture Status

Infection Site	CNSS, % (n = 3,226,406)	CPSS, % (n = 3,616,873)	*P* Value
Lung infection	33.5	37.3	< .001
Renal infection	26.4	37.7	< .001
Gastrointestinal infection	14.3	21.6	< .001
Skin and subcutaneous tissue infection	6.2	7.5	< .001
Joint/bone infection	1.4	3.0	< .001
Infective endocarditis	0.5	2.5	< .001
Meningitis, intracranial and intraspinal abscess	0.3	1.5	< .001
Others	33.7	20.4	< .001

See Table 1 legend for expansion of abbreviations.

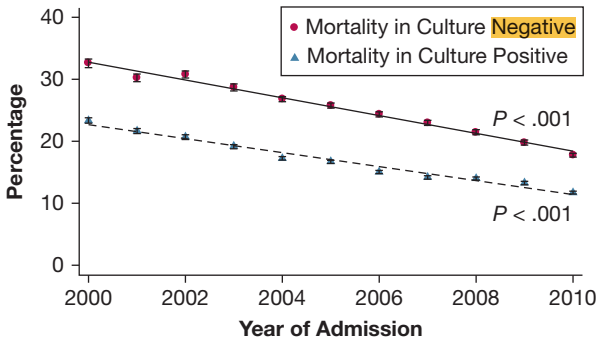

Figure 2 – *Trends of mortality in patients with severe sepsis by culture status.*

Similarly, in the cohort that included only patients who survived the first 3 days of hospitalization, having culture-negative status was still a significant predictor of mortality (OR, 1.26; 95% CI, 1.24-1.28) (e-Table 8). Finally, when only unique observations were used, there was still an increase in the age-adjusted proportion of CNSS over the years and a culture-negative status was associated with increased odds of mortality (OR, 1.77; 95% CI, 1.74-1.80) (e-Fig 3, e-Table 9).

Discussion

To the best of our knowledge, this is the first study looking at the epidemiology and outcomes of CNSS in the US population. Using nationally representative data, we show that the proportion of CNSS among patients with sepsis has grown steadily over the past decade such that by the year 2010, 49% of severe sepsis hospitalizations were culture negative. During the period of our study, the number of CNSS hospitalizations rose at a rate of 28.1% per year; in contrast, the total number of severe sepsis hospitalizations rose by 22.3% per year. This is particularly remarkable, because if the current rate continues, CNSS will constitute the predominant form of severe sepsis in the near future. CNSS is less common when a specific source of infection can be identified. Further, we found that in-hospital all-cause mortality rates associated with CNSS were significantly higher than those associated with CPSS. This difference persisted after multivariable adjustment; the diagnosis of CNSS conferred a 75% excess risk of death compared with CPSS.

Phua et al[14] characterized the frequency and associated mortality of CNSS and found that 41.5% of admissions with severe sepsis were culture negative. Further, in their study, patients who were culture negative had a lower severity of illness scores, fewer comorbid conditions, and lower mortality than culture-positive patients. Although the proportion of patients with CNSS in our study is remarkably similar to that of Phua et al's study, we found a higher burden of comorbid disease and higher mortality rates in our culture-negative cohort. These differences are likely secondary to differences in sample size, patient population, geographic location, lack of information regarding the means of diagnosis (eg, procalcitonin, polymerase chain reaction techniques) and the multicentricity of our data. The study by Phua et al[14] was conducted at a single-center university hospital, whereas our study included multiple hospitals with varying levels and standards of care. In addition, the patients included in our study were older (mean age of patients with CNSS and those with CPSS was 66.6 and 64.8 years, respectively, compared with 62 and 64 years, respectively, in their study). Although we did not have access to granular data to generate acute illness scores, the total number of acute organ dysfunctions was higher in the CNSS group (27.0% vs 23.1%; $P < .001$), suggesting a higher acuity of illness in the CNSS cohort. Another interesting finding of our study was that when compared with CPSS, acute kidney injury requiring dialysis was less frequent in individuals with CNSS, although overall acute kidney injury was higher. This could reflect the perceptions of patients, family, and providers that may lead to the lesser use of dialysis in this cohort because of their higher complexity and poorer outcomes.

With the implementation of Surviving Sepsis Campaign guidelines, studies have shown improvement in the proportion of blood being drawn for cultures before administration of antibiotics.[19,20] This should have been expected to improve culture positivity rates for these admissions; however, our results suggest a decrease in culture positivity rates over time. The potential reasons for this discrepancy include aggressive empirical outpatient therapy of infections, early administration of antibiotic therapy before cultures are drawn in patients in whom severe sepsis is recognized, and readmissions of those with severe sepsis. Other potential explanations include increasing infections with viruses, especially in immunocompromised hosts, that may cause a severe sepsis-like picture and undercoding of specific organisms by coders unless it is specified in the physician note.

We also found that mortality associated with severe sepsis was significantly higher in those with CNSS. This difference in mortality persisted after multivariable adjustment and several sensitivity analyses. The odds of increased mortality was seen in both teaching and

TABLE 3] Predictors of Mortality in Patients With Severe Sepsis

Characteristic	OR	95% CI
Culture status		
Positive	Reference	
Negative	1.75	1.72-1.77
Age group, y		
20-29	Reference	
< 1	0.58	0.52-0.64
1-4	0.71	0.62-0.81
5-9	0.73	0.63-0.85
10-14	0.85	0.75-0.97
15-19	0.79	0.71-0.87
30-39	1.18	1.12-1.24
40-49	1.40	1.34-1.47
50-59	1.66	1.58-1.75
60-69	2.10	1.99-2.22
70-79	2.95	2.79-3.12
≥ 80	4.80	4.53-5.09
Sex		
Male	Reference	
Female	1.02	1.01-1.03
Race		
White	Reference	
Black	1.00	0.97-1.02
Hispanic	0.96	0.93-0.99
Asian	0.93	0.88-0.98
Native American	0.97	0.89-1.05
Other	1.00	0.95-1.04
Primary payer		
Medicare	Reference	
Medicaid	1.09	1.06-1.12
Private	1.00	0.98-1.02
Self-pay	1.32	1.25-1.39
No charge	1.18	1.02-1.36
Other	1.20	1.12-1.29
Charlson comorbidity index score		
Each additional score (base 0)	1.12	1.12-1.13
Respiratory dysfunction		
Absent	Reference	
Present	3.26	3.18-3.33
Cardiac dysfunction		
Absent	Reference	
Present	1.99	1.95-2.02
Renal dysfunction (acute kidney injury) requiring dialysis		
Absent	Reference	
Present	1.56	1.51-1.61
Hepatic dysfunction		
Absent	Reference	
Present	1.96	1.92-2.00
Hematologic dysfunction		
Absent	Reference	
Present	1.35	1.33-1.38
Metabolic dysfunction		
Absent	Reference	
Present	1.63	1.61-1.66
Neurologic dysfunction		
Absent	Reference	
Present	1.20	1.17-1.23
Mechanical ventilation use		
Absent	Reference	
Present	1.38	1.35-1.42
Hospital teaching status		
Non-Teaching	Reference	
Teaching	1.19	1.14-1.24
Hospital bed size		
Small	Reference	
Medium	1.03	0.98-1.08
Large	1.13	1.07-1.20
Hospital volume		
Small	Reference	
Medium	0.86	0.83-0.90
Large	0.78	0.73-0.82
Hospital location		
Rural	Reference	
Urban	0.94	0.90-0.99
Hospital region		
Northeast	Reference	
Midwest	0.65	0.61-0.69
South	0.80	0.76-0.84
West	0.77	0.73-0.81
Year of admission		
Each additional year (base 2000)	0.89	0.89-0.89

nonteaching hospitals, although it was somewhat lower in teaching hospitals. The most likely explanation for the observed differences in mortality is variation in severity of illness—a hypothesis supported by our findings of increased organ failures, septic shock, burden of comorbid disease, and receipt of mechanical ventilation in the culture-negative cohort. It is possible that this increased severity of illness may have been manifested at the inception of severe sepsis, prompting clinicians to administer antibiotics early without performing appropriate cultures, leading to culture-negative status. Other possible reasons may include a delay in, or shorter duration of, antibiotic therapy or potentially inappropriate antibiotic therapy for lack of guidance from specific cultures. As inappropriate or inadequate antibiotic therapy has been associated with higher mortality in patients with severe sepsis,[21-23] this could translate into increased mortality seen in the CNSS cohort. It is also plausible that at least a few of the patients with CNSS had culture-negative status, as they had already received antibiotics prior to the episode of severe sepsis. Prior antibiotic exposure can, on one hand, translate into culture-negative status and, on the other hand, could lead to decreased antimicrobial susceptibility and increased mortality.[24] It is also plausible that severe sepsis goes unrecognized in patients with culture-negative status until later in the course of hospitalization, which could therefore contribute to the worse outcomes seen. We were unable to explore this hypothesis for lack of relevant data, but it should be a focus of future research studies.

Our study has several important limitations. We have relied on ICD-9-CM codes to identify patients with severe sepsis. Although our codes to identify severe sepsis are in line with those used in the literature,[2,4,16] it is important to keep in mind their limitations and evolution through the years. Specific codes for severe sepsis and septic shock were introduced in 2002 and 2003, respectively. Observing consistent trends over the years, however, mitigates concerns regarding the impact of ICD-9-CM codes. Although the time frame of the study spans both before and after the Surviving Sepsis Campaign guidelines, but as the management practices for all patients with sepsis (both CNSS and CPSS) should still be similar in each era, it should not have impacted our results. This is also evident from the regression analysis in which the interaction term between the variable for CNSS and the year of admission was not significant ($P = .3$). In addition, when the data were analyzed in two separate eras (2000-2002 and after 2002), CNSS continued to be an independent predictor of mortality in both eras (e-Tables 10, 11). Our data sources did not allow us to capture processes of care and details of the acute illness such as vital signs, laboratory data, drug administration, timeliness of antibiotic therapy, appropriateness of cultures, and timing of source control. If available, inclusion of these variables in our multivariable model would have added to the robustness of our results. Our data sources also may have limited our ability to properly classify infections that may have been diagnosed with newer technologies, such as polymerase chain reaction. If not captured by ICD-9-CM codes, such infections would potentially be misclassified in the CNSS cohort. Similarly, it is also possible that some patients with CNSS may, in fact, have had a noninfectious SIRS and associated organ failure. The NIS database does not have complete data on patient race, which limits our ability to interpret and explore the impact of race on our outcomes. We did, however, perform a sensitivity analysis by including missing values of race as a separate category to evaluate if our missing data handling technique impacted our results; yet we found similar results. In addition, we did not have sufficient information to describe geographic variations in epidemiology and outcomes of CNSS. Further studies specifically looking into this aspect with more granular data are needed. The database also does not provide any information about readmissions. We did, however, determine the similar admissions based on patient, primary payer, and hospital characteristics as potential readmissions and found the same increasing trend of CNSS admissions and their impact on mortality. Patients who die before their cultures have had a chance to become positive can be mislabeled as having a culture-negative status. As the majority of cultures should become positive by day 3,[25] we performed another sensitivity analysis by including only those who survived by day 3 of hospital admission and found having negative culture results was still an independent predictor of mortality. To further explore if acute cardiac dysfunction by itself could explain CNSS-associated increased mortality, we performed another sensitivity analysis by excluding all those with acute cardiac dysfunction and found that culture-negative status continued to be an independent predictor of death. To account for differences in the baseline characteristics of CNSS and CPSS, we generated a propensity score matched cohort (e-Fig 1) and found that having culture-negative status was still an independent predictor of mortality. Thus, although this study has the limitations of any study performed using administrative

data sets, we have shown the robustness of our results by performing multiple sensitivity analyses.

Despite its limitations, our findings indicate that CNSS constitutes a substantial proportion of patients with severe sepsis. Clinicians should be cognizant that patients with CNSS have a greater severity of illness and succumb to their illness more often than their culture-positive counterparts. Our study also provides important directions for future research. Investigators should view persons with CNSS as a distinct cohort of patients who may respond differently to therapeutic interventions. Reasons for the growing incidence and worse associated outcomes of CNSS should be the focus of future studies.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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