Racial disparities in septic shock mortality: a retrospective cohort study

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Summary

Background Patients with septic shock have the highest risk of death from sepsis, however, racial disparities in mortality outcomes in this cohort have not been rigorously investigated. Our objective was to describe the association between race/ethnicity and mortality in patients with septic shock.

Methods Our study is a retrospective cohort study of adult patients in the OneFlorida Data Trust (Florida, United States of America) admitted with septic shock between January 2012 and July 2018. We identified patients as having septic shock if they received vasopressors during their hospital encounter and had either an explicit International Classification of Disease (ICD) code for sepsis, or had an infection ICD code and received intravenous antibiotics. Our primary outcome was 90-day mortality. Our secondary outcome was in-hospital mortality. Multiple logistic regression with Least Absolute Shrinkage and Selection Operator (LASSO) for variable selection was used to assess associations.

Findings There were 13,932 patients with septic shock in our cohort. The mean age was 61 years (SD 16), 68% of the cohort identified as White (n = 9419), 28% identified as Black (n = 3936), 2% (n = 294) identified as Hispanic ethnicity, and 2% as other races not specified in the previous groups (n = 283). In our logistic regression model for 90-day mortality, patients identified as Black had 1.57 times the odds of mortality (95% CI 1.07–2.29, p = 0.02) compared to White patients. Other significant predictors included mechanical ventilation (OR 3.66, 95% CI 3.35–4.00, p < 0.01), liver disease (OR 1.75, 95% CI 1.59–1.93, p < 0.01), laboratory components of the Sequential Organ Failure Assessment score (OR 1.18, 95% CI 1.16–1.21, p < 0.01), lactate (OR 1.10, 95% CI 1.08–1.12, p < 0.01), congestive heart failure (OR 1.19, 95% CI 1.10–1.30, p < 0.01), human immunodeficiency virus (OR 1.35, 95% CI 1.04–1.75, p = 0.03), age (OR 1.04, 95% CI 1.04–1.04, p < 0.01), and the interaction between age and race (OR 0.99, 95% CI 0.99–1.00, p < 0.01). Among younger patients (<45 years), patients identified as Black accounted for a higher proportion of the deaths. Results were similar in the in-hospital mortality model.

Interpretation In this retrospective study of septic shock patients, we found that patients identified as Black had higher odds of mortality compared to patients identified as non-Hispanic White. Our findings suggest that the greatest disparities in mortality are among younger Black patients with septic shock.

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Keywords: Sepsis; Septic shock; Health disparities

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Research in context

Evidence before this study

We searched PubMed and Google Scholar for studies investigating disparities in sepsis incidence, sepsis outcomes, and predictors of sepsis mortality. These searches were supplemented with references identified in papers from the original searches and the authors' knowledge of relevant manuscripts. A review of the literature was completed prior to the study in November of 2019, during the course of writing the initial manuscript (April 2021), and at the time of revision (May 2023). Search terms included "sepsis" AND "disparities", "sepsis incidence" AND "disparities", "sepsis outcomes" AND "disparities", "sepsis mortality" AND "disparities", in addition to synonyms for disparities. Additionally, searches included epidemiologic studies of sepsis, sepsis incidence, and sepsis mortality. Studies were restricted to the United States. There was wide methodologic variation across all studies. Most importantly, at the time of the initial literature search, *none of these studies specifically investigated outcome disparities in the septic shock population,* which was our specific research question. Our study focused on this cohort because *identifying disparities within this population would represent a significant opportunity to address inequalities for this common and deadly condition*. Though others have investigated disparities in outcomes form sepsis, few have investigated outcome disparities specifically among patients with septic shock. Compared to the few studies that have investigated critically ill or septic shock patients, our study is based on more recent data and has more than five times the number of patients compared to some of the limited existing studies of this cohort.

Added value of this study

Our study specifically investigated racial disparities in mortality in the septic shock population and found that Black patients had higher odds of 90-day and in-hospital mortality compared to non-Hispanic White patients. We found an important association between age and outcome disparities. Black patients made up a higher proportion of deaths among patients less than 45 years of age and the interaction between race and age was statistically significant. Our study has several important strengths. Our study used recent data (2012–2018), cutting-edge regression techniques (LASSO), and was able to control for chronic conditions as well as critical aspects of sepsis management (fluid resuscitation, time to antibiotics).

Implications of all the available evidence

Septic shock patients are the subgroup of patients with the highest morbidity and mortality. In this population we found the disparities in outcomes were magnified, not dampened, compared to the undifferentiated sepsis literature. These findings suggest a number of areas in need of further investigation. Future studies should explore time to antibiotic administration, time to source control, time to diagnosis, healthcare bias, hospital type, geographic location, access to care, and disease severity to further elucidate potential causal factors contributing to outcome disparities. Future work should also consider the systemic factors that may influence disparities in health outcomes, including social indicators of health and systemic racism.

Introduction

Sepsis is a heterogeneous syndrome that affects more than 1.7 million patients in the United States annually and is among the most expensive reasons for inpatient admission, estimated at more than $20 billion annually.[1–3] Sepsis is characterized by life-threatening organ dysfunction that results from a dysregulated response to an infection.[1] Septic shock is the most lethal manifestation of the sepsis syndrome. The metabolic and cardiovascular derangements that define septic shock are associated with a greater than 40% mortality rate.[1,4,5] Sepsis and septic shock have a profound personal and societal cost; however, that burden may not be equally distributed between different racial and ethnic groups.

Several studies demonstrate racial disparities in the incidence of sepsis, with higher rates among Black patients.[6–9] However, evidence conflicts regarding potential disparities in sepsis outcomes among racial and ethnic groups. Some studies demonstrate increased sepsis mortality rates in Black and non-White patients,[6,7] while others have not observed significant differences.[8–10] Wide methodologic variation across studies may contribute to this lack of reproducible results. Importantly, existing studies utilize varying criteria to identify septic patients, include wide periods of time with changing consensus definitions, and inconsistently control for potentially cofounding factors, such as chronic conditions.[6,7,9–11] Sepsis remains a highly heterogeneous disease, and the choice of administrative definition can lead to differences in mortality rate estimates by a factor of 3.5.[12] While recent studies have addressed some of these limitations in undifferentiated sepsis patients,[11] little is known about disparities among the subgroup of septic shock patients, which represent a more homogeneous cohort and exhibit the highest risk of death.

The objective of our study was to describe the association between race/ethnicity and septic shock mortality in a large, recent cohort of septic shock patients, while adjusting for relevant comorbid conditions and severity of illness. To accomplish this, we utilized a large statewide repository of healthcare data from the OneFlorida Data Trust to identify patients hospitalized with septic shock.[13,14] Given existing national data about health outcomes and mortality rates among racial groups, we

hypothesized that non-Hispanic White patients would have lower septic shock mortality rates compared to Black and Hispanic groups. To our knowledge, our study is among the first to examine racial disparities in mortality specifically among septic shock patients.

Methods

Data source and study interval

We conducted a retrospective cohort analysis using data from the OneFlorida Data Trust.[13,14] The OneFlorida Data Trust is a statewide repository of healthcare data curated by the OneFlorida Clinical Research Consortium, a clinical research network of partnered academic institutions and health systems throughout the state of Florida.[15] Data in the OneFlorida Data Trust includes diagnoses, procedures, medications, demographics, and other data elements reported in the Patient-Centered Outcomes Research Institute (PCORI) Common Data Model (CDM), in addition to patient-level electronic health record data from partnered health care systems in the state.[14–16] Data uploaded by partnered institutions is transformed according to the PCORI CDM via the OneFlorida team's custom extract/transform/load (ETL) software.[17] The OneFlorida Clinical Research Consortium is one of eight Clinical Data Research Networks (CDRNs) of the National Patient-Centered Clinical Research Network (PCORnet). PCORnet creates large, representative research networks that incorporates electronic health record data from multiple domains on a national scale for conducting clinical outcomes research.[18] The data curation process across the PCORnet system includes standardized, regular data quality checks, data characterization, and harmonization across sites.[18,19] This process ensures high data quality and fidelity across all sites. The analytic cohort included encounters from January 2012 to July 2018. Our study design and reporting followed STROBE guidelines[20] and was approved by the University of Florida International Review Board (IRB #201802013).

Patient inclusion

We categorized patients as having septic shock if they received vasopressors during their hospital encounter and had either a) an explicit ICD-9 or 10 code for sepsis or septic shock, or b) an ICD-9 or 10 code for infection and received intravenous antibiotics (see Supplementary Table S1 for sepsis ICD codes and Supplementary Tables S2 and S3 for infection ICD codes). We determined vasopressor administration and intravenous antibiotic administration via inpatient medication prescribing records, as reported according to the PCORI CDM. We included patients who received infusions of the following vasopressors: norepinephrine, vasopressin, epinephrine, phenylephrine, dopamine, or dobutamine during the encounter. Supplementary Table S4 includes a list of intravenous antibiotics used for inclusion. We selected these criteria to capture a group of patients consistent with consensus definitions. We considered an infection diagnosis code along with intravenous antibiotic administration representative of presumed infection, and vasopressor dependence as representative of cardiovascular organ dysfunction. These adaptations of consensus criteria are similar to those used by Rhee et al., and others, for retrospective identification of septic patients using electronic health record data.[12,21–25]

Outcome

The primary outcome was 90-day mortality, defined as death within 90 days after hospital triage. Triage was defined by the date and time of the patient's first documented vital signs in their encounter. Date of death was determined by local source data reported from electronic health record systems, and, when possible, confirmed with national death index data, as listed in the PCORI CDM.[16] The secondary outcome was in-hospital death, defined as death during inpatient hospitalization.

Sociodemographic variables

We collected data including age at the time of triage (years), biological sex, race and ethnicity, and insurance status. We analyzed race/ethnicity as an aggregate variable, with acknowledgement that race and ethnicity are separate and distinct. We also acknowledge that there are limitations with how race and ethnicity are captured by the electronic health record.[26] We investigated differences between the following broadly categorized race and ethnicity groups: Black, Hispanic, Non-Hispanic White, and Other. For purposes of statistical analysis, the other category was created for those categories with less than 140 patients (1% of the dataset). The other category included patients who self-identified as follows: American Indian or Alaska Native (n = 17), Asian (n = 107), Native Hawaiian or Other Pacific Islander (n = 4), Multiple Race (n = 20), and 135 patients classified as other in the OneFlorida Data Trust. Insurance type was defined as Medicare, Medicaid, Private, Medicare and Private, Other, and Uninsured/Charity. Medicare and private included patients who had Medicare as the primary payer type and private insurance listed as the second payer type. Other insurance included patients with payer type listed as other, or other government (federal/state/local), federal/state/local not specified, or worker's compensation. Patients missing race or insurance data were excluded.

Comorbidities, disease severity, and treatment variables

To account for the impact of comorbid conditions on the primary outcome, we abstracted data for liver disease, hypertension, chronic obstructive pulmonary disease (COPD), End-Stage Renal Disease (ESRD), Human Immunodeficiency Virus infection (HIV), and congestive heart failure (CHF) based on ICD-9 and 10 codes (See Supplementary Table S5). We also collected data on

disease severity and treatments due to potential confounding related to severity of illness and treatment variation. Treatment data included time to antibiotic administration, calculated as time from triage. There were extreme outliers for time to antibiotic administration; the top 5% (n = 721) values were winsorized and the cutoff value was imputed for those encounters.[27]

Organ failure was quantified using the laboratory components of the SOFA score, which we refer to as LabSOFA. LabSOFA combines the values for the components of the SOFA score that are quantified by laboratory values, specifically, the renal, hepatic, and hematologic components. For patients with missing bilirubin, platelet, or creatinine values we imputed the median SOFA score value for each category. Each SOFA score component has a range of 0–4 based on the degree of organ failure, with 0 representing the least amount of organ failure, to 4, representing maximal organ failure.[28] For patients with missing bilirubin, platelet, or creatinine values we imputed the median SOFA score value for each category. Others have previously omitted the neurologic component of the SOFA score and describe similar performance of this modified SOFA score.[29–31] The dataset did not include fraction of inspired oxygen data to calculate respiratory SOFA scores. We therefore captured respiratory dysfunction as a binary variable of mechanical ventilation use. We included initial lactate level, defined as the first lactate measurement during the patient's encounter, as an additional measurement of organ failure and disease severity. 1674 patients were missing a lactate measurement, those we imputed using the random forest algorithm MissForest with 6 iterations,[32] and used the imputed lactate variable for regression modeling.

Univariate and bivariate data analyses

We reported categorical variables as counts and percentages, and continuous variables with mean and standard deviation or median and interquartile ranges (IQR) based on normality.

As race/ethnicity was *a priori* determined to be one of our primary demographic variables of interest, we performed within-group statistical tests to determine how the groups varied with other variables. We used a one-way ANOVA with a Tukey adjustment for the one normal continuous variable (i.e., age), chi-square tests for binary and categorical variables (i.e., sex, race/ethnicity, payer type, comorbidities, and mechanical ventilation), and Kruskal Wallis pairwise Wilcoxon rank sum tests with Bonferroni adjustments for non-normal continuous variables (i.e., initial lactate value, labSOFA score, and time to antibiotics). All tests were performed using an alpha of 0.05 to determine significance, and the largest race/ethnicity pair contributors to the significance were noted.

Regression methods

We used multiple logistic regression to analyze the effects of the sociodemographic factors on 90-day mortality in the cohort of patients with septic shock. We applied LASSO (Least Absolute Shrinkage and Selection Operator) [alpha = 1, nfolds = 10] for variable selection for the multiple logistic regression model. We included the following candidate variables: age, sex, race/ethnicity, comorbidities (liver disease, CHF, hypertension, COPD, ESRD, HIV), labSOFA score, initial lactate measurement, time to antibiotics, and mechanical ventilation use, as well as variable interactions between race/ethnicity and age and race/ethnicity and comorbidities. The LASSO method is a penalized regression method used for variable selection and regularization. The LASSO method considers the entirety of the candidate variables and shrinks the coefficients of some variables to zero, thus removing them from the final model. It allows us to perform a more unbiased variable selection from the candidate variables and reduces overfitting. The dependent variable was 90-day mortality. We checked for multicollinearity using variance inflation factors. All variance inflation factors were less than 2. R Studio (Vienna, Austria) version 12 was used for statistical analyses.[33]

Role of funding source

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Results

Study population

There were 18,197 encounters, corresponding to 15,654 unique patients that received vasopressors and had an explicit diagnosis of sepsis and/or an infection code and received intravenous antibiotics in the OneFlorida Data Trust between January 2012 and July 2018. Only encounters after 2012, after the publication of the 2012 Surviving Sepsis Committee guidelines, were included to reflect recent sepsis management.[34] Of those who met initial inclusion criteria, 188 patients were missing race/ethnicity information and 488 patients were missing insurance or payer data, these patients were subsequently excluded. Additional reasons for exclusion included missing triage time or time of first vital signs, missing antibiotic administration timing data, and missing date of death for patients coded as having died. After the aforementioned exclusions, there were 13,932 patients with septic shock, which represents the cohort used for analysis. Of these 546 patients (3.9%) were classified using only explicit sepsis diagnoses codes plus vasopressor administrator, 3660 patients (26.3%) were classified using only vasopressor administration with infection diagnoses codes plus intravenous antibiotics, and 9726 patients (69.8%) fit both classifications (See Supplementary Figure S1, Flow Diagram of Analytic Cohort).

Of the 13,932 patients with septic shock, the median age was 61 years (SD 16). 68% of the cohort identified as White (n = 9419), 28% identified as Black (n = 3936), and 4% (n = 577) identified as Hispanic or other races. The most common payer types were Medicare plus private insurance (41%, n = 5753), Medicaid (21%, n = 2893), and Medicare (16%, n = 2275). The most common comorbid condition was hypertension, which was present in over 70% (n = 9920) of the patients. The next most common comorbidities included CHF, chronic liver disease, and COPD. Table 1 contains other descriptive characteristics of the population.

Category	Overall (n = 13,932)
Age, mean (SD)	
Years	60.9 (15.8)
Sex, % (n)	
Male	54.7 (7617)
Female	45.3 (6315)
Race/Ethnicity, % (n)	
White	67.6 (9419)
Black	28.3 (3936)
Hispanic	2.1 (294)
Other	2.0 (283)
Payer Type, % (n)	
Medicare	16.3 (2275)
Medicaid	20.8 (2893)
Private	14.2 (1986)
Medicare + Private	41.3 (5753)
Other	4.0 (558)
Uninsured/Charity	3.4 (467)
Liver Disease, % (n)	
Yes	22.9 (3197)
No	77.1 (10,735)
CHF, % (n)	
Yes	34.8 (4852)
No	65.2 (9080)
Hypertension, % (n)	
Yes	71.2 (9920)
No	28.8 (4012)
COPD, % (n)	
Yes	20.7 (2884)
No	79.3 (11,048)
ESRD, % (n)	
Yes	12.0 (1666)
No	88.0 (12,266)
HIV Infection, % (n)	
Yes	2.4 (333)
No	97.6 (13,599)

CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; ESRD: End-Stage Renal Disease; HIV: Human Immunodeficiency Virus.

Table 1: **Demographic and health characteristics.**

Outcomes

Overall 90-day mortality was 32% (n = 4437). Nearly 60% (n = 8155) of this cohort of septic shock patients required mechanical ventilation. The median time to antibiotics was slightly under 4 h with a wide IQR (See Table 2). However, there were significant differences in time to antibiotic administration by race/ethnicity, with White patients having the most prompt time to antibiotic administration (See Table 3, Supplementary Table S6). The median initial lactate was 2 [IQR 1.9–3.4]. LabSOFA was used as a marker of illness severity. The median initial values are reported in Table 2. A secondary outcome was in-hospital mortality.

Demographic and clinical data by race and ethnicity

The frequencies and distributions of key demographic and clinical data by race and ethnicity are reported in Table 3. Compared to White patients, Black patients were younger, were more likely to have Medicaid and less likely to have private insurance. Significance of these relationships and their corresponding test of significance are available in supplementary information (Supplementary Table S6).

Black patients accounted for a higher proportion of the deaths among younger patients, those less than 45 years of age. For the 35–44 year old age group (n = 1016), 42% of deaths (n = 211) occurred in Black patients (n = 88), though they only accounted for approximately one-third of the overall population. In older age groups, the proportion of deaths by race and ethnicity were more representative of the overall cohort (See Fig. 1).

Category	Overall (n = 13,932)
Mechanical Ventilation, % (n)	
Yes	58.5 (8155)
No	41.5 (5777)
Initial Lactate Value, median [IQR]	
mmol/L	1.9 [1.9–3.4]
LabSOFA, median [IQR]	
Total LabSOFA	1.0 [0–3.0]
Renal SOFA	1.0 [0–1.0]
Hepatic SOFA	0.0 [0–0]
Coagulation SOFA	0.0 [0–0]
Time to Antibiotics, median [IQR]	
Minutes	237.5 [70.0–2076.0]
Ninety Day Outcome % (n)	
Death	31.8 (4437)
Survival	68.2 (9495)

[IQR]: Interquartile Range; SOFA: Sequential Organ Failure Assessment Score.

Table 2: **Illness severity and management.**

Category	White	Black	Hispanic	Other
Age, mean (SD)				
Years	61.9 (15.3)	59.0 (16.5)	55.5 (17.3)	59.7 (16.4)
Sex, % (n)				
Male	55.6 (5412)	52.0 (2112)	64.9 (211)	57.8 (171)
Female	44.4 (4327)	48.0 (1948)	35.1 (114)	42.2 (125)
Payer Type, % (n)				
Medicare	17.7 (1670)	13.5 (530)	12.2 (36)	13.8 (39)
Medicaid	18.1 (1701)	27.0 (1061)	25.9 (76)	19.4 (55)
Private	15.6 (1467)	9.5 (373)	21.2 (62)	29.7 (84)
Medicare + Private	41.8 (3934)	41.9 (1650)	31.3 (92)	27.2 (77)
Other	3.9 (368)	4.3 (170)	3.4 (10)	3.5 (10)
Uninsured/Charity	3.0 (279)	3.9 (152)	6.1 (18)	6.4 (18)
Liver Disease, % (n)				
Yes	24.0 (2333)	20.7 (840)	25.2 (82)	24.7 (73)
No	76.0 (7406)	79.3 (3220)	74.8 (243)	75.3 (223)
CHF, % (n)				
Yes	33.7 (3283)	36.7 (1492)	27.4 (89)	30.7 (91)
No	66.3 (6456)	63.3 (2568)	72.6 (236)	69.3 (205)
Hypertension, % (n)				
Yes	67.9 (6615)	77.6 (3151)	62.8 (204)	62.8 (186)
No	32.1 (3124)	22.4 (909)	37.2 (121)	37.2 (110)
COPD, % (n)				
Yes	22.7 (2214)	16.0 (648)	12.9 (42)	14.5 (43)
No	77.3 (7525)	84.0 (3412)	87.1 (283)	85.5 (253)
ESRD, % (n)				
Yes	8.4 (820)	20.0 (810)	9.2 (30)	10.1 (30)
No	91.6 (8919)	80.0 (3250)	90.8 (295)	89.9 (266)
HIV Infection, % (n)				
Yes	0.8 (79)	6.4 (258)	2.8 (9)	0.0 (0)
No	99.2 (9660)	93.6 (3802)	97.2 (316)	100.0 (296)
Mechanical Ventilation, % (n)				
Yes	58.0 (5464)	59.6 (2345)	55.4 (163)	64.7 (183)
No	42.0 (3955)	40.4 (1591)	44.6 (131)	35.3 (100)
Initial Lactate Value values, median [IQR]				
mmol/L	1.8 [1.1–2.7]	2.1 [1.4–3.6]	2.0 [1.3–3.3]	1.9 [1.2–3.2]
LabSOFA, median [IQR]				
Total LabSOFA	1.0 [0–3.0]	1.0 [1.0–3.0]	1.0 [0–3.0]	1.0 [0–3.0]
Renal SOFA	1.0 [0–1.0]	1.0 [0–2.0]	0.0 [0–1.0]	0.0 [0–1.0]
Hepatic SOFA	0.0 [0–0]	0.0 [0–0]	0.0 [0–0]	0.0 [0–0]
Coagulation SOFA	0.0 [0–1.0]	0.0 [0–1.0]	0.0 [0–1.0]	0.0 [0–1.0]
Time to Antibiotics, median [IQR]				
Minutes	227.0 [66.0–1871.0]	256.5 [77.0–2326.0]	419.0 [86.5–3602.5]	366.0 [104.5–3167.0]

SD: Standard Deviation; [IQR]: Interquartile Range; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; ESRD: End-Stage Renal Disease; HIV: Human Immunodeficiency Virus; SOFA: Sequential Organ Failure Assessment Score.

Table 3: **Bivariate comparison of selected variables by race/ethnicity.**

Multivariable logistic regression results

The final logistic regression model for 90-day mortality after LASSO for variable selection included age, race/ethnicity, labSOFA, initial lactate, mechanical ventilation use, the interaction between race and age, and the following comorbidities: liver disease, hypertension, COPD, CHF, ESRD, and HIV.

The three highest odds ratios for 90-day mortality were mechanical ventilation use, history of liver disease, and Black race. Patients who required mechanical ventilation had 3.66 times the odds of mortality compared to those that did not (95% CI 3.35–4.00, $p < 0.001$). Compared to White patients, Black patients had 1.57 times the odds of mortality (95% CI 1.07–2.29,

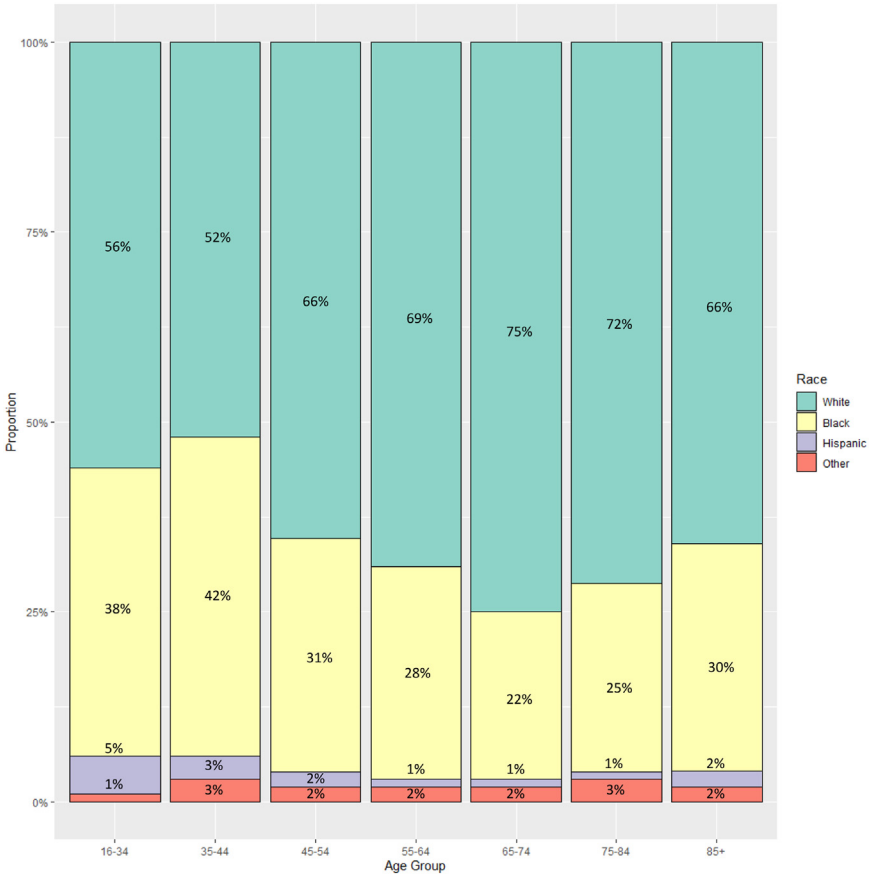

Fig. 1: Race and age of deceased septic shock patients.

p = 0.02). This odds ratio was similar to having a history of liver disease (OR 1.75, 95% CI 1.59–1.93, p < 0.001). The interaction between race/ethnicity and age was also significant. For every one year decrease in age, Black patients experienced a 1.01 increased odds of mortality compared to White patients (95% CI 1.00–1.02, p < 0.01). Holding all other variables constant, the predicted probability of mortality is higher for younger black patients than younger white patients while the relationship is the inverse for older patients (See Supplementary Figure S2). Black patients had higher odds of dying from septic shock and were more likely to die from septic shock at younger ages.

Other significant predictors of increased odds of mortality from septic shock included age, labSOFA, higher initial lactate levels, a history of CHF, and HIV infection (Table 4). For every one year increase in age, the odds of dying from septic shock increased by 4% (95% CI 1.04–1.04, p < 0.001). Each one point increase in labSOFA scores was associated with an increased odds ratio of mortality of 1.18 (95% CI 1.16–1.21, p < 0.001). Increasing initial lactate level was associated with a 10% increased odds of mortality (OR 1.10, 95% CI 1.08–1.12, p < 0.001). Odds ratios for significant comorbid conditions and other variables in the model are included in Table 4.

In hospital mortality logistic regression results

The secondary outcome for this analysis was in hospital mortality, which occurred in 25% of the cohort (n = 3501). For in hospital mortality, similar to 90-day mortality, Black patients who died during their sepsis hospitalization were more likely to be younger. In the 35–44 year old age cohort (n = 1016), Black patients accounted for 47% (n = 87) of the in hospital deaths (n = 187), though they were only 35% of the cohort (n = 355).

The final logistic regression model for in hospital death after LASSO for variable selection included age, sex, race/ethnicity, labSOFA, initial lactate value, mechanical ventilator use, time to antibiotics, the interaction between race and age, a history of liver disease, CHF, COPD, ESRD, HIV, and hypertension. Compared to the 90-day mortality primary outcome model, sex and time to antibiotics were selected by LASSO for the in hospital mortality model, but not the 90-day model. The

Predictor	Coefficient	Odds ratio	95% CI	P-Value
Age	0.04	1.04	(1.04, 1.04)	<0.001
Race/Ethnicity (reference: White)				
Black	0.45	1.57	(1.07, 2.29)	0.02
Hispanic	0.47	1.60	(0.52, 4.64)	0.40
Other	−0.72	0.49	(0.13, 1.65)	0.27
Liver Comorbidity	0.56	1.75	(1.59, 1.93)	<0.001
Hypertension Comorbidity	−0.35	0.70	(0.64, 0.77)	<0.001
COPD Comorbidity	−0.13	0.88	(0.79, 0.97)	0.01
CHF Comorbidity	0.18	1.19	(1.10, 1.30)	<0.001
ESRD Comorbidity	−0.09	0.91	(0.80, 1.03)	0.15
HIV Comorbidity	0.30	1.35	(1.04, 1.75)	0.03
LabSOFA Score	0.17	1.18	(1.16, 1.21)	<0.001
First Lactate Amount	0.10	1.10	(1.08, 1.12)	<0.001
Mechanical Ventilation	1.30	3.66	(3.35, 4.00)	<0.001
Race*Age (reference: White)				
Black	−0.01	0.999	(0.99, 1.00)	<0.01
Hispanic	−0.01	0.99	(0.97, 1.01)	0.14
Other	0.01	1.01	(0.99, 1.03)	0.24

CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; ESRD: End-Stage Renal Disease; HIV: Human Immunodeficiency Virus; SOFA: Sequential Organ Failure Assessment Score.

Table 4: **Regression model for 90-day mortality.**

odds of death for mechanically ventilated patients was higher in the in hospital mortality model. Mechanical ventilation use had an odds ratio of 6.56 (95% CI 5.88–7.34, $p < 0.001$) for in hospital mortality compared to an odds ratio of 3.66 for 90-day mortality (95% CI 3.45–4.00, $p < 0.001$). In the in hospital mortality model, Black race was associated with 1.85 times the odds of mortality compared to White patients (95% CI 1.24–2.76, $p < 0.01$). The interaction between race and age was also significant with the same odds ratio as the 90-day mortality model. For every one year decrease in age, Black patients experienced a 1.01 increased odds of mortality compared to White patients (95% CI 1.00–1.02, $p < 0.01$). Odds ratios for other variables in the model were similar (See Supplementary Table S7). In this model, as well as the 90-day mortality model, Black patients had higher odds of dying from septic shock and were more likely to die younger.

Overall, only there were only 936 deaths that occurred after discharge but within 90 days, amounting to 6% of the overall cohort. Nearly 80% of the deaths in this cohort of patients with septic shock occurred in hospital.

Discussion

In this large study of nearly 14,000 patients with septic shock, we found Black patients had 1.57 times the odds of 90-day mortality compared to White patients. Further, we found that Black patients represented a disproportionately higher proportion of deaths among younger patient cohorts (age <45 years). Our results indicate compelling disparities in septic shock mortality among Black patients. To our knowledge, this is one of the first studies investigating racial disparities outcomes in patients with septic shock.

Barnato et al. found higher age and sex-standardized case fatality rates among Black patients admitted to the intensive care unit with sepsis, compared to White patients.[7] This study cohort likely includes a large proportion of septic shock patients, as all were admitted to the intensive care unit. Compared to our study, their data is now more than 20 years old, their initial findings were standardized only for age and sex, and they had limited ability to control for illness severity at presentation and potentially confounding treatment variables. A recent study from Koköfer et al. of intensive care unit patients admitted with sepsis did not find race or ethnicity to be associated with differences in intensive care unit or hospital mortality for patients with sepsis or septic shock.[35] Compared to their study, our study is considerably larger, with more than six times the number of patients with septic shock.

Among undifferentiated sepsis patients, not limited to shock, several studies demonstrate higher sepsis incidence and hospitalization rates among non-White patients, though findings pertaining to mortality differences are inconsistent. Some found higher case fatality rates among Black patients,[6,7,11] where others found similar[8,9] or lower[10] case fatality rates. Disparities in case fatality rates have also be reported among patients who identified as Hispanic,[7,11] Asian or Pacific Islander,[11] and other races.[8] A study in Baltimore City found that neighborhood poverty, lack of insurance, and a lower

education level was associated with undifferentiated sepsis mortality, and after accounting for these factors, race no longer had a statistically significant association with higher mortality rates.[36] Several studies have found longer length of stays among Black patients with sepsis compared to White patients, though they did not find differences in mortality by race or ethnicity.[35,37] Notably, there is significant methodologic heterogeneity among these existing studies.

Several studies reporting disparities in sepsis outcomes had unstable findings in sub-analyses depending on what factors were included as covariates for in the analysis.[7,10,11] Inconsistent results may be confounded by variation in illness severity due to different classification methods used to identify patients with sepsis. Some studies used only explicit ICD codes to identify patients with sepsis, where others utilized modifications of the Angus system, which captures a more broad cohort of patients, including those that may not have been explicitly recognized as septic by providers. Schrader and Lewis found Black patients were assigned lower acuity scores during Emergency Department triage, indicating racial bias in the triage process and symptom underestimation.[38] Similar factors may influence provider recognition and coding of sepsis. In our study, we utilized a clinically-centered definition using a combination of ICD codes and EHR based clinical data (i.e., vasopressor use, intravenous antibiotic administration), similar to the methodology recently employed by Rhee et al. to study sepsis incidence.[21] Rhee et al. found sepsis incidence rates were more stable over time when using a clinical data based definition of sepsis as compared to billing and coding based analyses.[21] Further, data from a wide range of years is used the existing sepsis disparities literature, with some studies including data from as far back as the late 1970s.[8] These studies span a wide range of time in which definitions and management changed significantly. Recognizing the evolution of sepsis recognition and management in recent decades, a strength of this analysis is our ability to focus on more recent data. None of the aforementioned studies specifically investigated disparities within the septic shock population, the group of patients with the highest morbidity and mortality. Our study focused on this cohort because identifying disparities within this population would represent a significant opportunity to address inequalities for this common and deadly condition. In a more critically ill cohort, we found the differences were magnified, not dampened.

We found the greatest inequalities in mortality among younger Black patients. Our findings are consistent with the undifferentiated sepsis literature where nearly all of the existing studies found that Black patients hospitalized with sepsis were younger than White patients.[8–11] Dombrovskiy et al. found half of the Black patients with sepsis were under the age of 65, while only a quarter of White patients fell within that age range.[9] Similar to our results, they found the greatest relative risk for sepsis for Black patients compared to White patients in the 35–44 year old age range.[9] As with our findings, the differences decreased with increasing age.

Our findings provide compelling evidence of racial disparities in septic shock mortality. Given that nearly 80% of the deaths occurred in hospital, and the similarities in the models for in hospital mortality and 90 day mortality, this suggests that in hospital mortality is likely driving much of our findings. Divergence in hospital mortality indicates that disparities related to the inpatient admission are likely associated with our findings. These compelling disparities in outcomes provides information that could be used to target follow-up studies aimed at better understanding care in the inpatient setting. For example, some evidence suggests differences in times to antibiotic administration for patients with pneumonia.[39] Similar to our findings, Madsen et al. found longer unadjusted time to antibiotics in non-White patients compared to White patients, though this difference was no longer significant after adjusting for other factors.[40] Others have found that sepsis was documented less frequently in clinical notes for Black patients compared to White patients.[41] Similarly, disparities in sepsis recognition could lead to delayed treatment and potentially, a modifiable factor contributing to outcome disparities. Future studies could also explore time to antibiotic administration, time to source control, time to diagnosis, healthcare bias, hospital type, geographic location, access to care, and disease severity to further elucidate potential causal factors contributing to outcome disparities.

Though our findings show a compelling need to better understand differences in septic shock outcomes, we advocate for a thoughtful and contextualized interpretation of these findings given the limitations of observational data. Appropriate consideration must be given to the complex factors that influence racial variation in outcomes, including systemic racism. Earlier investigations of disparities in sepsis outcomes have interpreted differences in incidence and mortality rates as evidence of biological or genetic differences in sepsis susceptibility.[6–8] Concluding biologic or genetic differences based on incidence rates standardized for age and sex alone, without consideration of any other factors is problematic. One prior study went as far as proposing that racial variation in age-standardized sepsis mortality rates may be explained by differences in genetic susceptibility due to different environmental selection pressures between individuals of European and African ancestry.[7] These explanations perpetuate myths of racial biology and may reinforce racial stereotypes and racism in healthcare.[42] As Chowkwanyun and Reed contend, proposing a biological explanation for racial differences without appropriate consideration of systemic factors deflects attention from modifiable structural factors,

shifts blame to biology without appropriate contextualization, and potentially undermines the overarching goal of eliminating health disparities, shifting blame to biology.[42] Future work should also consider the systemic factors that may influence disparities in health outcomes, including social indicators of health and systemic racism.

Limitations

This study has several limitations. First, our study is an observational, retrospective study that indicates that Black patients experience an increased burden of septic shock mortality. We acknowledge that race alone does not explain sepsis-related disparities in mortality, though we believe it provides evidence that highlights the importance of increased investment in research into the drivers of health inequality. Race and ethnicity data may have been self-reported or selected based on provider perception at the treating facility. Additionally, race and ethnicity data were grouped for analysis, though there is likely wide ethnic variation within each broad racial group. Further, the OneFlorida Data Trust includes partners throughout Florida, however, at the time of this study, there were more partnered institutions in North and Central Florida than South Florida. This may have resulted in some differences in racial and ethnicity breakdowns that seen in census data, particularly with regards to the Hispanic population. Furthermore, there are significant, demonstrated limitations in capturing ethnicity accurately in electronic medical records, which may have resulted in underidentification of patients who are Hispanic.[26]

Although we were able to control for severity of illness, age, sepsis management, insurance status, and other factors related to septic shock mortality, we were limited in our ability to study factors that may be potential drivers of observed racial differences. Future work that presents septic shock health care disparities within the context of more robust indicators of socioeconomic status, hospital resources, economic inequality, education inequality, geographic distribution of healthcare resources, and racial variation in healthcare expenditures is needed to make meaningful progress on the path towards eliminating health outcome inequities.[42]

Our study quantified organ failure using labSOFA, which enabled our ability to retrospectively assess organ failure within our database. Similar approaches have been used that modify the components of the SOFA score with similar predictive ability for mortality.[30,43,44] Moreover, we found labSOFA to be predictive of mortality despite these limitations. Though we lacked available pulse oximetry data to calculate respiratory SOFA scores, we were able to capture respiratory dysfunction as mechanical ventilation use. In addition, this was a study of septic shock patients, as such, all were on vasopressors and would have had a cardiac SOFA score of at least two or more. However, given our inability to assign specific respiratory and cardiac SOFA scores, this limited our ability to detect patients with respiratory dysfunction that were not mechanically ventilated (i.e., non-invasive ventilation, nasal cannula). This could have led to underestimation of the severity of respiratory or cardiac dysfunction in this cohort, as well as the degree of the association between organ failure severity and mortality. Despite these limitations, in this study of septic shock patients, our method allowed us to account for renal, hematologic, hepatic, and respiratory dysfunction in our model.

Conclusions

In this study, Black patients had considerably higher odds of mortality from septic shock compared to White patients. This was especially pronounced in the younger age cohorts where Black patients had disproportionately higher odds of mortality.

Contributors

Lauren Page Black, MD, MPH: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing–original draft, writing–review & editing.

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Faheem W. Guirgis, MD: conceptualization, funding acquisition, investigation, methodology, supervision, writing–original draft, writing–review & editing.

Directly accessed and verified the underlying data reported in the manuscript: Lauren Page Black, MD, MPH, Charlotte Hopson, MS, and Cynthia Garvan, PhD, MS.

All authors contributed equally to review & editing.

All authors were not precluded from accessing the data for this study and accept responsibility to submit for publication.

Data sharing statement

Raw data used for this study can be obtained for a fee via an application to the OneFlorida Clinical Research Network Data Trust, which can be found at https://onefloridaconsortium.org.

Declaration of interests

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All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100646.

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