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Application of the Third International Consensus Definitions for Sepsis (Sepsis-3) Classifications in a Population-based Cohort: The REasons for Geographic and Racial Differences in Stroke Study

John P. Donnelly, MSPH^{1,2}, Professor Monika M. Safford, MD³, Nathan I. Shapiro, MD^{4,5}, Professor John W. Baddley, MD⁶, and Professor Henry E. Wang, MD¹

¹Department of Emergency Medicine, University of Alabama School of Medicine, Birmingham AL

²Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham AL

³Department of Medicine, University of Alabama at Birmingham, Birmingham, AL and Department of Medicine, Weill Cornell Medical College, New York, NY

⁴Department of Emergency Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Massachusetts

⁵Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, Boston, Massachusetts

⁶Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham AL

Abstract

BACKGROUND—The Third International Consensus Definitions for Sepsis (Sepsis-3) present clinical criteria for classifying infection patients. Event incidence and long-term outcomes across these classifications are unknown.

METHODS—We conducted a retrospective analysis using data from 30,239 US participants aged 45 years enrolled in the REasons for Geographic and Racial Differences in Stroke (REGARDS)

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Contact: Henry E. Wang, MD, MS, Department of Emergency Medicine, University of Alabama at Birmingham, 619 19th Street South, OHB 251, Birmingham, AL 35249, 205-996-6526 (office), 205-975-4662 (fax), hwang@uabmc.edu.

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CONFLICTS OF INTEREST

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CONTRIBUTORS

HEW and JPD conceived the study. HEW and MMS organized and oversaw data collection. HEW and JPD conducted the analysis, and all authors contributed to review of results. JPD produced an initial draft of the manuscript and all authors contributed to its editorial review and revision. JPD and HEW assume responsibility for the work as a whole.

cohort. We identified hospitalizations over 2003–2012 using three classifications: infection with systemic inflammatory response syndrome (SIRS), elevated sepsis-related organ failure assessment score (SOFA), or elevated “quick” SOFA (qSOFA) score. We examined incidence over the study period, in-hospital mortality, and one-year mortality, providing estimates and 95% confidence intervals (CIs).

FINDINGS—Among 2,593 infection events, there were 1,526 sepsis-SIRS, 1,080 sepsis-SOFA, and 378 sepsis-qSOFA events. Sepsis-SIRS events had the highest incidence (8.2 per 1,000 person-years; 95% CI 7.8–8.7), followed by sepsis-SOFA (5.8; CI 5.4–6.1) and sepsis-qSOFA (2.0; CI 1.8–2.2). In-hospital mortality was higher for sepsis-qSOFA (67/295; 22.7%) than sepsis-SOFA (125/960; 13.0%) and sepsis-SIRS (128/1,392; 9.2%). One-year mortality post-discharge was also highest for sepsis-qSOFA (29.4 per 100 person-years; CI 22.3–38.7) compared to sepsis-SOFA (22.6; CI 19.2–26.6) and sepsis-SIRS (14.7; CI 12.5–17.2).

INTERPRETATION—The examined classifications identified different incidence and mortality. Our findings support the use of the sepsis-SOFA and sepsis-qSOFA classifications for identification of infection patients at elevated risk of poor outcomes. We also demonstrate how these classifications could be used in future epidemiological assessments and studies of patients with infection.

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Keywords

Sepsis; outcomes; critical care

INTRODUCTION

Sepsis, or life-threatening organ dysfunction due to a dysregulated response to infection, is a major public health problem worldwide.^{1–4} While sepsis mortality rates have improved over time, sepsis remains a leading cause of death, with in-hospital mortality estimates ranging from 12% to 26%.^{3–7} Although a widely recognized entity, advances in sepsis clinical care and research have been difficult due to disparate terminology for and approaches to the definition of sepsis and its component elements.⁸

The European Society of Intensive Care Medicine and Society for Critical Care Medicine proposed the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) as a new approach to standardizing sepsis terminology.^{8–11} Previous iterations of the international consensus definitions for sepsis focused on developing and refining a framework for conceptualizing systemic inflammatory response to infection.^{12, 13} For the Sepsis-3 definitions, the task force considered several candidate criteria with a lessened focus on identifying systemic inflammation.¹⁰ Using several large hospital databases, Seymour, et al. examined the ability of three classifications to differentiate high risk infection patients: two or more systemic inflammatory response syndrome (SIRS) criteria

(the previous standard for defining sepsis), two or more sepsis-related organ failure assessment (SOFA) score points, or two or more points on the empirically derived “quick” SOFA (qSOFA) score.⁹ The authors found that an elevated SOFA score was best able to discriminate patients with infection at high risk of in-hospital mortality in the intensive care unit (ICU). In contrast, an elevated qSOFA score (based on respiratory rate, altered mentation, and blood pressure) showed the highest discrimination outside of the ICU. Importantly, these analyses were unable to identify incidence and were not able to assess how SIRS criteria and the revised Sepsis-3 classifications (based on SOFA and qSOFA) performed with regard to long-term outcomes; a population-based cohort is the best design for formulating these estimates.

Using data from one of the largest contemporary population-based longitudinal cohorts in the United States (US), we compared incidence, short-term, and long-term mortality for infection patients meeting the revised Sepsis-3 classifications and the previously established SIRS criteria. We hypothesized that these classifications would identify different populations, show different trends in incidence and outcomes, and have utility for identifying high risk infection patients.

METHODS

Study Design

We performed a retrospective analysis of data collected prospectively in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a longitudinal cohort of community-dwelling adults in the US.¹⁴ REGARDS includes 30,239 adults aged 45 years from the 48 contiguous US states and the District of Columbia. The sampling strategy of REGARDS has been previously described in detail.¹⁴ Briefly, sampling frame was a commercially available list with approximately 95% coverage of US adults and the study oversampled blacks and individuals living in the Southeastern US, with 21% of the cohort originating from the coastal plains of North Carolina, South Carolina and Georgia (the “stroke buckle”), and 35% from the remainder of North Carolina, South Carolina and Georgia plus Tennessee, Mississippi, Alabama, Louisiana and Arkansas (the “stroke belt”). REGARDS is 42% black and 45% male, with 69% of participants >60 years old.

The REGARDS study enrolled participants over 2003–2007, obtaining baseline data using phone interview and an in-person evaluation. Information collected at baseline included medical history, functional status, health behaviors, physical characteristics, physiologic measures, blood/urine specimens, and an inventory of medications. REGARDS then contacted study participants at 6-month intervals by telephone, identifying the date, location, and attributed reason for hospitalizations. The REGARDS study was approved by the institutional review boards of participating institutions, and all participants provided verbal consent before the telephone interview and written informed consent before the in-home study visit.

Identification of Infection and Sepsis Events

We identified reported hospitalizations attributed to a serious infection (we defined serious infection events as admissions to the Emergency Department (ED) or hospital for infection based on the criteria of Angus, et al.).¹ Two trained members of the abstraction team independently reviewed all retrieved medical records to identify characteristics of the hospitalization and confirm the presence of infection as a reason for hospitalization.¹ All discordances were resolved via adjudication by a third physician-reviewer. To identify the presence of clinical criteria, we used the worst physiologic and laboratory measurements observed during the initial 28 hours of hospitalization; we chose this timeframe because of our focus on community-acquired infection and sepsis. Although a prior assessment of the Sepsis-3 classifications indicated that performance may differ for ICU and non-ICU patients, it is possible that we would obtain different results. In addition, as measurement was limited to the first 28 hours of hospitalization, we did not restrict our analyses based on admission destination. Thus, we assessed all classifications among the full population of infection events.

Our approach to classifying infection events involved identifying hospitalizations meeting SIRS criteria, which served as a comparator group, and the revised Sepsis-3 classifications (SOFA and qSOFA). First, we identified hospitalizations for an infection with 2 systemic inflammatory response syndrome (SIRS) criteria (termed “Sepsis-SIRS”), including abnormal temperature ($>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$), heart rate (>90 beats per minute), respiratory rate (>20 breaths per minute or partial $\text{CO}_2 <32$ mmHg), and white blood cell count ($>12,000$ per mm^3 , $<4,000$ per mm^3 , or $>10\%$ immature bands).¹³ We also identified infection events with 2 SOFA score points, according to established criteria (termed “Sepsis-SOFA”).¹⁵ Lastly, we identified infection events with 2 “quick” SOFA (qSOFA) criteria, including altered mentation (Glasgow coma score <14 or non-alert per the Alert, Voice, Pain, Unresponsive scale), systolic blood pressure <100 mmHg, or respiratory rate >22 breaths per minute (termed “Sepsis-qSOFA”).⁹ We also defined hypotension with abnormal lactate as sepsis events with a systolic blood pressure <100 mmHg and lactate >2 mmol per liter.¹⁶ Consistent with prior studies, events with missing values for sepsis criteria factors were considered normal and we utilized a previously introduced naming convention (SIRS, SOFA, and qSOFA).⁹

Internal review of 1,349 hospital records indicated excellent inter-rater agreement for presence of infection ($\text{kappa}=0.92$). We included reported events from February 5, 2003, through December 31, 2012, and all-cause mortality through the end of available follow-up (December 31, 2013).

Participant Baseline and Hospitalization Characteristics

Baseline participant characteristics were determined upon REGARDS enrollment. A detailed description of baseline variable definitions is provided in eTable 1. Briefly, demographic characteristics included age, gender, race, region, and self-reported annual household income and education (years of school). We also identified several health-related factors, including smoking and body mass index (BMI).¹⁷ Chronic medical conditions

included chronic lung disease, diabetes, dyslipidemia, hypertension, myocardial infarction (MI), stroke, and chronic kidney disease (CKD).¹⁸

We also determined destination and length of stay for events resulting in hospital admission (ICU, floor, or other). Infection type was identified based on available clinical documentation in medical records. Participants with events were additionally classified based on admission from or discharge to a nursing, assisted care, or rehabilitation facility. We also determined the availability of lactate measurement in the first 28 hours and whether or not each sepsis case experienced hypotension with abnormal lactate.

Hospitalization Outcomes

For all infection events, we defined in-hospital mortality based on participant vital status upon hospital discharge, as indicated in the medical record. For analyses of 28-day mortality (relative to the event date) and one-year mortality (relative to discharge), we determined all-cause mortality based on information collected as part of REGARDS study procedures. If the participant died, a team of researchers from the REGARDS parent study reviewed death certificates, autopsy reports, and medical records, and interviewed proxies to ascertain the circumstances of the participant's death.

Statistical Analysis

We categorized infection hospitalizations according to previously established criteria (sepsis-SIRS) and the revised Sepsis-3 classifications (sepsis-SOFA and sepsis-qSOFA). As the classifications were not mutually exclusive (events could be included in multiple groups), to compare characteristics, we reported means and standard deviations for continuous variables and percentages with 95% confidence intervals (CIs) estimated by the logit transformation method for categorical variables. We determined the incidence rates (IRs) of infection and events meeting classifications per 1,000 person-years over the study period, censoring on loss to follow-up, death, or on December 31, 2012. To compare temporal trends over two-year intervals, we estimated standardized incidence ratios (SIRs) with 2003–2004 as the reference, using direct standardization to the overall cohort age distribution as a means of accounting for age differences.

To assess infection and sepsis outcomes, we included only the first identified infection event for each participant. We determined in-hospital mortality as well as 28-day mortality relative to the event date and all cause one-year mortality relative to the discharge date. We constructed Kaplan-Meier failure curves to examine differences in time to death across classifications. For 28-day and one-year outcomes, we estimated mortality rates (MRs) per 100 person-years over the study period, censoring on loss to follow-up. In order to determine if mortality differences could be explained by differences in SOFA criteria, we also performed a sensitivity analysis of events meeting sepsis-SIRS and sepsis-qSOFA criteria, stratifying by SOFA score.

We also assessed the ability of previously established (sepsis-SIRS) and revised Sepsis-3 classifications (sepsis-SOFA and sepsis-qSOFA) to identify high risk patients. We constructed logistic regression models for in-hospital mortality adjusted for demographics and comorbidities, adding a dichotomous variable for each classification individually. We

reported odds ratios (ORs) with 95% confidence intervals (CIs), discrimination in the form of areas under the curve (AUCs), the change in AUC, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) indices.^{19, 20} Changes in AUC, NRIs, and IDIs with 95% CIs were estimated using bootstrap resampling with 1,000 replications. We assessed model calibration using Hosmer-Lemeshow goodness of fit tests.²¹ For one-year mortality, we fit Cox proportional hazards models with time to mortality as the outcome. We reported hazards ratios (HRs), C-indices as described by Harrell (transformed Dxy), and extensions of IDI and NRI to survival data as described by Pencina, et al. and Uno, et al.^{19, 22–24} C-indices were estimated using bootstrap resampling with 150 replicates and IDIs/NRIs were estimated using 200 resampling perturbations. We assessed model calibration using Groennesby and Borgan Score tests.²⁵ The proportional hazards assumption was verified using Schoenfeld residuals and interactions with the logarithm of follow-up time.

We conducted all analyses using Stata 13.1 (StataCorp, College Station, Texas) and R 3.1.1 (R foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population and Incidence by Sepsis Classification

Out of 30,239 participants enrolled in REGARDS over 2003–2007, we included 29,692 with follow-up information. Among these participants, we identified 3,413 serious infection events (2,593 first events) over 2003–2012. Measures included in the sepsis classifications were available for a large proportion of infection events (with the exception of Glasgow coma score). (eFigure 1) The majority of events were classified as sepsis-SIRS (1,845/3,413; 54.1%), with lower percentages for sepsis-SOFA (1,332/3,413; 39.0%), non-sepsis infection (1,153/3,413; 33.8%), and sepsis-qSOFA (423/3,413; 12.4%). (Figure 1) Among first infection events, 26.2% (678/2,593) were classified as sepsis-SIRS and sepsis-SOFA, 9.2% (238/2,593) sepsis-SOFA and sepsis-qSOFA, and 10.9% (282/2,593) sepsis-SIRS and sepsis-qSOFA. (eFigure 2) Participants experiencing sepsis-SOFA or sepsis-qSOFA were older at baseline and more likely to be male, have lower education and income, report current smoking, and have a higher burden of comorbidities. (Table 1) There were large increases in age-adjusted incidence for events classified as sepsis-SOFA and sepsis-qSOFA over the study period. (Figure 2)

Hospitalization Characteristics and Outcomes by Classification among First Infection Events

Compared to sepsis-SIRS, events classified as sepsis-SOFA and sepsis-qSOFA were more likely to be admitted to the ICU, have sepsis documented as an infection type, and be admitted from or discharged to a nursing facility. (eTable 2) Sepsis-qSOFA events were most likely to have lactate measurements available and experience hypotension with an abnormal lactate. (eTable 2) In-hospital mortality was highest for sepsis-qSOFA and lowest for sepsis-SIRS, but mortality differences were limited to events with at least two SOFA points. (Table 2; eTable 3) The 28-day and one-year mortality rates were also higher for sepsis-SOFA and sepsis-qSOFA. (Figure 3) After adjusting for demographics and comorbidities, we observed

the strongest associations for sepsis-SOFA and sepsis-qSOFA for in-hospital mortality (ORs) and one-year mortality (HRs). (Figure 4)

Identification of High Risk Patients among First Infection Events

For in-hospital mortality, AUCs with dichotomous classification variables included in logistic regression models were substantially higher for sepsis-SOFA and sepsis-qSOFA compared with sepsis-SIRS or the baseline model. (Table 3; eFigure 3) Sepsis-SOFA demonstrated the highest change in discrimination and NRI relative to the baseline model. In analyses of one-year mortality post-discharge, the NRI relative to the baseline model for sepsis-SOFA was higher than sepsis-SIRS or sepsis-qSOFA. All models for in-hospital mortality and one-year mortality (baseline, baseline+sepsis-SIRS, baseline+sepsis-SOFA, and baseline+sepsis-qSOFA) demonstrated good calibration (goodness of fit $p > 0.05$). (eTable 4; eTable 5)

DISCUSSION

We applied the Third International Consensus Definitions for Sepsis (Sepsis-3) classifications and the previously established SIRS criteria to the large, population-based REGARDS cohort. We identified different overlapping groups, with sepsis-SOFA and sepsis-qSOFA occurring disproportionately among older participants with a number of comorbidities. Analyses of in-hospital and one-year mortality support the use of sepsis-SOFA and sepsis-qSOFA as screening tools, showing that these classifications are able to identify patients with infection at high risk of poor outcomes. Overall, our study characterizes the Sepsis-3 classifications across several domains (incidence, short-term, and long-term mortality) and demonstrates how these could be applied in future studies.

Analyses of outcomes in this population-based cohort represent a logical extension of studies performed in administrative databases.⁹ Seymour, et al. conducted a retrospective analysis of patients presenting to a geographically diverse pool of health systems and determined the associations of infection severity classifications with in-hospital mortality.⁹ Our results support this prior effort, as we observed similar discrimination, calibration, and measures of association for models including classification variables in addition to demographics and comorbidities. However, we also demonstrated that classifications based on SOFA and qSOFA criteria were able to identify patients at high risk of one-year mortality following discharge. Taken together, these findings demonstrate the robustness of the proposed classifications, as we arrived at similar conclusions despite using an independent sample with a different study design, employing a different method of event detection, and examining post-discharge outcomes.

Our results also underscore a well-recognized challenge of characterizing sepsis - that different classification methods will provide differing results. A number of prior studies have evaluated methods for identifying high risk infection patients in various settings.^{4, 6, 26-31} Iwashyna, et al. examined the validity of claims-based algorithms for identifying sepsis relative to events defined clinically based on prior international consensus criteria, finding high specificity and positive predictive values with modest sensitivity.²⁶ Gaieski, et al. examined several methods for identifying sepsis in administrative data and found striking

differences the total burden of sepsis and temporal trends in incidence depending on the algorithm.⁶ Our results are broadly consistent with these efforts, showing large differences in patient populations, incidence, and outcomes depending on the classification method employed. However, our study differs notably in that we sought to examine the revised classifications and applied these in a large population-based cohort. Our results highlight variations associated with different methods of classifying infection patients and illustrate how these classifications might be utilized in practice, systems planning, and research. However, it is important to note that sepsis-SOFA and sepsis-qSOFA do not define sepsis, but instead may serve as indicators of an increased risk of death among patients with infection.

Our study builds on prior work in that we evaluated several approaches for applying sepsis classifications that do not rely on administrative claims.²⁹ For instance, we found large increases in incidence for sepsis-SOFA and sepsis-qSOFA over time, but less dramatic changes for sepsis-SIRS or any infection event. It is difficult to draw firm conclusions about temporal trends in the current study due to the manner in which events were ascertained in REGARDS, as observed patterns could be affected by event detection. However, Rhee, et al. observed similar patterns, showing increases in incidence over a 10-year period for identification methods dependent on coding practices as well as steadily increasing use of acute organ dysfunction codes with lower observed clinical thresholds.^{29, 32} Further research is needed to determine how estimates could be impacted by vital sign and laboratory value measurement.

Importantly, our results do not address the feasibility of incorporating the Sepsis-3 classifications in routine clinical care or the potential impact on patient outcomes. Rather, we illustrate that these classifications may have utility in characterizing and identifying high risk infection patients using routine laboratory and vital sign measurements, with fewer components relative to the factors required to define SIRS. Based on the observed event rates, among the US population of black and white adults aged 45 years or older, we would expect more than 400,000 infection events meeting sepsis-SOFA criteria and 100,000 sepsis-qSOFA events annually over a ten year period. These figures would correspond to at least 50,000 sepsis-SOFA deaths and 30,000 sepsis-qSOFA deaths annually. These classifications might also aid future sepsis clinical trials, identifying high risk subgroups. Future studies must evaluate the feasibility and utility of the Sepsis-3 classifications in these contexts.

LIMITATIONS

The main strengths of our study were a large sample size, detailed health information among enrolled participants, complete mortality follow-up over a period of approximately ten years, and systematic abstraction with adjudication for all infection hospitalizations. Despite these strengths, our findings must be interpreted in light of several limitations. We were unable to identify infections occurring during the course of hospitalization and instead focused on events for which infection was a primary reason for admission. Given our focus on community-acquired infection, we also included only vital sign and laboratory measurements within the first 28-hours of hospitalization.

As participants with a first infection hospitalization may have a different risk profile after the event, we limited outcome analyses to the first infection event on record. Due to the manner in which events were detected, it is possible that we may have missed hospitalizations for infection. However, it is unlikely that this would bias results differentially across sepsis criteria and we used standard methods of event ascertainment, chart review, and adjudication. Reporting of laboratory values and vital sign measurement could vary by hospital of presentation. However, the REGARDS cohort is comprised of participants from across the US and includes a diverse sample of hospitals, so we would expect the impact of this limitation to be minimal. Due to the detection method employed and the population studied, our results may not be readily generalizable to other settings.

CONCLUSIONS

We applied classifications from the Third International Consensus Definitions for Sepsis (Sepsis-3) in a national population-based cohort, finding that incidence and outcomes varied widely across event types. The Sepsis-3 classifications have utility for characterizing and identifying infection patients at high risk of poor outcomes up to one year post-discharge. These classifications may also facilitate categorizing patients with infection in future epidemiological assessments and clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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RESEARCH IN CONTEXT

EVIDENCE BEFORE THIS STUDY

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) task force released revised classifications in February, 2016. As part of this initiative, several manuscripts were published that described the conclusions of the task force, assessed the validity of candidate clinical criteria with regard to inpatient outcomes, and presented a revised framework for evaluating sepsis definitions. We searched PubMed up to November 9th, 2016, for papers related to identifying sepsis. We searched for the terms “sepsis” and “validation”, “sepsis” and “definition”, or “sepsis” and “identification.” As a result, we found a wide range of studies pertinent to defining sepsis, but few evaluations of the revised Sepsis-3 classifications. Several recent single-center studies have examined the Sepsis-3 classifications among intensive care unit patients in Brazil and the United States, finding increased mortality among cases meeting the revised criteria. Importantly, these studies had limited sample sizes and lacked robust data on individual patients. All previous validation efforts to date also have not incorporated outcome and baseline data outside of the inpatient setting.

ADDED VALUE OF THIS STUDY

As prior analyses were limited to the inpatient setting, they were not able to provide data on incidence or post-discharge outcomes for the revised classifications. In order to address these limitations, we used data from one of the largest contemporary population-based cohorts in the United States to examine trends in incidence, compare population characteristics and case-fatality across classifications, and determine if the revised classifications have utility for risk stratification among patients surviving to discharge. Our findings demonstrate that the revised classifications identify distinct populations with different incidence, 28-day, and one-year mortality. Compared to infection patients with systemic inflammatory response syndrome (SIRS) or elevated sepsis-related organ failure assessment (SOFA) scores, those with elevated “quick” sepsis-related organ failure assessment (qSOFA) scores experienced the highest in-hospital mortality, 28-day mortality, and one-year mortality post discharge. Models including variables for SOFA and qSOFA classifications demonstrated the greatest improvements in discrimination and reclassification for both in-hospital and one-year mortality.

IMPLICATIONS OF ALL EVIDENCE AVAILABLE

Our work builds on recent efforts, showing that the revised sepsis classifications derived by the Sepsis-3 task force have utility for identifying patients at increased risk of poor outcomes during hospitalization. Importantly, we have demonstrated that, in addition to serving as an in-hospital screening tool, the revised classifications may also be useful for characterizing and identifying patients with infection at increased risk of poor outcomes after discharge. Further study is needed to determine if widespread use of the revised classifications would lead to improved outcomes.

Figure 1.

Study population flowchart

Sepsis classifications not mutually exclusive, events can belong to multiple groups (as indicated by the dotted line). Non-sepsis infections defined as infections not meeting any criteria for sepsis (mutually exclusive from any sepsis events). Sepsis-SIRS defined as infection event meeting ≥ 2 SIRS criteria. Sepsis-SOFA defined as infection event with ≥ 2 SOFA points. Sepsis-qSOFA defined as infection event meeting ≥ 2 qSOFA criteria. “First Events” represent the first event for a given participant (each participant represented once). “Total Events” include recurrent events (each participant can be included multiple times). REGARDS = REasons for Geographic and Racial Differences in Stroke study; SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment; qSOFA = “quick” sepsis-related organ failure assessment; SBP = systolic blood pressure.

Figure 2.

Incidence of events over study period by sepsis classification

Panel A) Kaplan-Meier failure curves for time to event after study enrollment; Panel B) Age-standardized event incidence by time period. Includes first events only (Total N = 29,692). “All Infections” includes sepsis events as well as non-sepsis events. Sepsis classifications not mutually exclusive, events can belong to multiple groups. Sepsis-SIRS defined as infection event meeting 2 SIRS criteria. Sepsis-SOFA defined as infection event with 2 SOFA points. Sepsis-qSOFA defined as infection event meeting 2 qSOFA criteria. Incidence rates reported provided per 1,000 person years of follow-up. Error bars (Panel B) represent 95% confidence interval limits) and rates for each time period directly standardized to the overall cohort age distribution. SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment; qSOFA = “quick” sepsis-related organ failure assessment; IR = incidence rate; SIR = standardized incidence ratio; CI = confidence interval.

Figure 3.

Kaplan-Meier failure curves for mortality following event by sepsis classification

A) 28-day mortality relative to the date of encounter; B) 1-year mortality relative to discharge date. Includes first infection events only. “All Infections” includes sepsis events and non-sepsis events. Sepsis classifications not mutually exclusive, events can belong to multiple groups. Sepsis-SIRS defined as infection event meeting 2 SIRS criteria. Sepsis-SOFA defined as infection event with 2 SOFA points. Sepsis-qSOFA defined as infection event meeting 2 qSOFA criteria. 28-day mortality (Panel A) includes in-hospital mortality, excludes events with no follow-up after the date of encounter and deaths occurring on the first day of admission (zero follow-up time). One-year mortality (Panel B) excludes in-hospital mortality as well as events with no follow-up after the date of discharge and deaths occurring on the first day of discharge (zero follow-up time). Mortality rates provided per 100 person years. SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment; qSOFA = “quick” sepsis-related organ failure assessment; MR = mortality rate; CI = confidence interval.

Figure 4.

Measures of association for sepsis classification by outcome

Includes first infection events only (Total N = 2,593). Sepsis classifications not mutually exclusive, events can belong to multiple groups. Sepsis-SIRS defined as infection event meeting 2 SIRS criteria. Sepsis-SOFA defined as infection event with 2 SOFA points. Sepsis-qSOFA defined as infection event meeting 2 qSOFA criteria. All models include the events not meeting a given sepsis criteria as the reference group and are adjusted for age, gender, race, hypertension, dyslipidemia, chronic kidney disease, history of stroke, history of myocardial infarction, and diabetes. Error bars represent 95% confidence interval limits. Total N = 2,386 for analysis of one-year mortality, excludes events with in-hospital mortality, no follow-up after the date of encounter, and deaths occurring on the first day of discharge (zero follow-up time). SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment; qSOFA = “quick” sepsis-related organ failure assessment; OR = odds ratio; HR = hazard ratio.

Table 1

Baseline participant characteristics by sepsis classification

Baseline Characteristic	No Infection	Non-Sepsis Infection	Sepsis Classification		
			Sepsis-SIRS	Sepsis-SOFA	Sepsis-b-SOFA
Total N	27,099	1,031	1,526	1,080	378
Age (years) (Mean/SD)	64.6 (9.4)	66.7 (9.0)	68.1 (9.3)	69.7 (9.1)	70.2 (9.1)
Gender (%; 95% CI)					
Male	44.6 (44.0–45.2)	40.2 (37.2–43.2)	50.9 (48.4–53.4)	59.2 (56.2–62.1)	56.9 (51.8–61.8)
Female	55.4 (54.8–56.0)	59.8 (56.8–62.8)	49.1 (46.6–51.6)	40.8 (37.9–43.8)	43.1 (38.2–48.2)
Race (%; CI)					
White	58.2 (57.6–58.7)	67.8 (64.9–70.6)	66.5 (64.1–68.8)	64.0 (61.1–66.8)	66.9 (62.0–71.5)
Black	41.8 (41.3–42.4)	32.2 (29.4–35.1)	33.5 (31.2–35.9)	36.0 (33.2–38.9)	33.1 (28.5–38.0)
Education (%; CI) *					
<High School	12.3 (11.9–12.7)	12.7 (10.8–14.9)	16.3 (14.5–18.2)	16.6 (14.5–19.0)	17.0 (13.5–21.1)
High School	25.8 (25.3–26.3)	25.6 (23.1–28.4)	27.3 (25.1–29.6)	28.4 (25.8–31.2)	26.0 (21.8–30.7)
Some College	26.6 (26.1–27.1)	29.7 (27.0–32.6)	28.6 (26.4–30.9)	27.2 (24.6–29.9)	32.6 (28.1–37.5)
College or More	35.4 (34.8–35.9)	31.9 (29.2–34.9)	27.8 (25.6–30.1)	27.8 (25.2–30.6)	24.4 (20.3–29.0)
Income (%; CI)					
<\$20k	17.5 (17.1–18.0)	22.8 (20.3–25.5)	23.9 (21.8–26.1)	24.5 (22.1–27.2)	24.9 (20.8–29.5)
\$20–\$34k	23.9 (23.4–24.4)	24.3 (21.8–27.1)	28.6 (26.4–30.9)	28.1 (25.5–30.8)	31.2 (26.7–36.1)
\$35–\$74k	29.9 (29.3–30.4)	27.9 (25.3–30.8)	26.6 (24.4–28.9)	27.8 (25.2–30.5)	24.9 (20.8–29.5)
\$75k	16.3 (15.8–16.7)	12.7 (10.8–14.9)	10.3 (8.9–11.9)	8.9 (7.3–10.7)	9.0 (6.5–12.3)
Not Available	12.5 (12.1–12.8)	12.2 (10.4–14.4)	10.6 (9.2–12.3)	10.7 (9.0–12.7)	10.1 (7.4–13.5)
Region (%; CI)					
Stroke Buckle	20.9 (20.4–21.3)	22.6 (20.1–25.3)	21.0 (19.1–23.2)	21.3 (19.0–23.8)	19.3 (15.6–23.6)
Stroke Belt	34.4 (33.8–35.0)	36.2 (33.3–39.2)	37.9 (35.5–40.3)	37.2 (34.4–40.2)	40.5 (35.6–45.5)
Non-Belt/Buckle	44.7 (44.1–45.3)	41.2 (38.2–44.3)	41.1 (38.6–43.6)	41.5 (38.6–44.5)	40.2 (35.4–45.3)
Smoking (%; CI) **					
Current	14.4 (14.0–14.8)	12.9 (11.0–15.1)	17.3 (15.5–19.3)	16.2 (14.1–18.5)	19.9 (16.2–24.3)

Baseline Characteristic	No Infection	Non-Sepsis Infection	Sepsis Classification		
			Sepsis-SIRS	Sepsis-SOFA	Sepsis-qSOFA
Past	39.7 (39.1–40.3)	44.9 (41.9–48.0)	46.6 (44.1–49.1)	49.3 (46.3–52.3)	49.3 (44.3–54.4)
Never	45.9 (45.3–46.5)	42.2 (39.2–45.2)	36.1 (33.7–38.6)	34.5 (31.7–37.4)	30.8 (26.3–35.6)
BMI Class (%; CI)[†]					
Norm/Under	24.9 (24.4–25.4)	22.8 (20.3–25.4)	23.3 (21.2–25.5)	21.2 (18.9–23.8)	22.2 (18.3–26.8)
Overweight	37.1 (36.5–37.7)	34.9 (32.1–37.9)	33.9 (31.6–36.3)	35.2 (32.4–38.1)	37.1 (32.3–42.2)
Obese	38.0 (37.4–38.6)	42.3 (39.3–45.4)	42.8 (40.3–45.3)	43.6 (40.6–46.6)	40.7 (35.7–45.8)
Chronic Conditions (%; CI)					
Lung Disease	8.5 (8.2–8.8)	14.3 (12.3–16.5)	18.7 (16.9–20.8)	17.4 (15.3–19.8)	18.8 (15.1–23.1)
Chronic Kidney Disease [‡]	10.2 (9.9–10.6)	12.7 (10.8–14.9)	20.1 (18.1–22.1)	31.5 (28.8–34.3)	24.1 (20.0–28.7)
Stroke	6.0 (5.8–6.3)	9.2 (7.6–11.1)	10.4 (8.9–12.0)	12.6 (10.7–14.7)	13.5 (10.4–17.3)
Myocardial Infarction	11.9 (11.5–12.3)	18.5 (16.3–21.0)	19.8 (17.9–21.9)	24.4 (21.9–27.0)	24.6 (20.5–29.2)
Hypertension	58.3 (57.7–58.9)	63.2 (60.2–66.1)	68.3 (66.0–70.6)	74.5 (71.8–77.1)	71.2 (66.4–75.5)
Dyslipidemia	56.6 (56.0–57.2)	61.4 (58.4–64.3)	63.0 (60.6–65.4)	67.3 (64.5–70.1)	63.8 (58.8–68.5)
Diabetes	23.9 (23.4–24.4)	32.2 (29.4–35.1)	34.5 (32.1–36.9)	41.8 (38.8–44.7)	37.8 (33.1–42.9)

Includes first events only (Total N = 29,692). Sepsis classifications not mutually exclusive, events can belong to multiple groups. “Non-Sepsis Infections” defined as infections not meeting any criteria for sepsis (mutually exclusive from sepsis criteria). Confidence intervals estimated using the logit transformation method. Sepsis-SIRS defined as infection event meeting 2 SIRS criteria. Sepsis-SOFA defined as infection event with 2 SOFA points. Sepsis-qSOFA defined as infection event meeting 2 qSOFA criteria.

* 23 missing.

** 114 missing.

[†] 214 missing.

[‡] Chronic kidney disease defined using creatinine values and the CKD-EPI equation. SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment; qSOFA = “quick” sepsis-related organ failure assessment; SD = standard deviation; BMI = body mass index.

Table 2

Mortality by sepsis classification

Classification	In-Hospital Mortality		28-Day Mortality (Time from Event)*				One-Year Mortality (Time from Discharge)**			
	Total Events N	Deaths N (%)	Deaths N (%)	Person Years	MR per 100 py (95% CI)		Deaths N (%)	Person Years	MR per 100 py (95% CI)	
All Infections	2,593	163 (6.3)	167 (6.6)	184	90.7 (77.9–105.6)		238 (10.0)	2,058	111.6 (10.2–13.1)	
Non-Sepsis Infection	916	19 (2.1)	21 (2.3)	68	31.0 (20.2–47.6)		38 (4.3)	796	4.8 (3.5–6.6)	
Sepsis-SIRS	1,392	128 (9.2)	128 (9.6)	96	133.2 (112.0–158.4)		154 (12.5)	1,050	14.7 (12.5–17.2)	
Sepsis-SOFA	960	125 (13.0)	122 (13.4)	64	191.0 (160.0–228.1)		147 (18.1)	650	22.6 (19.2–26.6)	
Sepsis-qSOFA	295	67 (22.7)	62 (22.5)	17	350.4 (273.2–449.5)		51 (23.1)	173	29.4 (22.3–38.7)	

Includes first infection events only. "All Infections" includes sepsis events as well as non-sepsis events. "Non-Sepsis Infections" defined as infections not meeting any criteria for sepsis (mutually exclusive from sepsis groups). Sepsis classifications not mutually exclusive, events can belong to multiple groups. Sepsis-SIRS defined as infection event meeting 2 SIRS criteria. Sepsis-SOFA defined as infection event with 2 SOFA points. Sepsis-qSOFA defined as infection event meeting 2 qSOFA criteria. Rows do not sum to column totals, as events can belong to multiple groups. Mortality rates provided per 100 person years of follow-up relative to the date of encounter or discharge.

* Total N = 2,519, excludes events with no follow-up after the date of encounter and deaths occurring on the day of the encounter (zero follow-up time).

** Total N = 2,386, excludes events with in-hospital mortality, no follow-up after the date of discharge, and deaths occurring on the first day of discharge (zero follow-up time). SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment; qSOFA = "quick" sepsis-related organ failure assessment; MR = mortality rate; PY = person-years; CI = confidence interval.

Table 3

Relative discrimination and reclassification improvement by sepsis classification model

Model	In-Hospital Mortality				One-Year Mortality**			
	AUC	AUC (95% CI) [†]	NRI (95% CI) [†]	IDI (95% CI) [†]	C-Index	NRI (95% CI) [‡]	IDI (95% CI) [‡]	
Baseline Model *	0.664	Ref	Ref	Ref	0.738	Ref	Ref	Ref
Baseline + Sepsis-SIRS	0.721	0.057 (0.029–0.085)	0.530 (0.396–0.664)	0.017 (0.006–0.028)	0.748	0.139 (0.067–0.199)	0.007 (0.002–0.019)	
Baseline + Sepsis-SOFA	0.765	0.101 (0.067–0.136)	0.846 (0.714–0.979)	0.036 (0.020–0.053)	0.763	0.314 (0.245–0.380)	0.023 (0.009–0.040)	
Baseline + Sepsis-qSOFA	0.759	0.095 (0.058–0.132)	0.634 (0.480–0.789)	0.056 (0.026–0.085)	0.749	0.130 (0.070–0.182)	0.022 (0.008–0.041)	

Includes first infection events only (Total N = 2,593). Sepsis classifications not mutually exclusive, events can belong to multiple groups. Sepsis-SIRS defined as infection event meeting 2 SIRS criteria. Sepsis-SOFA defined as infection event with 2 SOFA points. Sepsis-qSOFA defined as infection event meeting 2 qSOFA criteria.

* Includes age, gender, race, hypertension, dyslipidemia, chronic kidney disease, history of stroke, history of myocardial infarction, and diabetes.

** Total N = 2,386, excludes events with in-hospital mortality, no followup after the date of encounter, and deaths occurring on the first day of discharge (zero follow-up time).

[†] Estimated using bootstrap sampling with 1,000 replications.

[‡] Extension of NRI and IDI to survival data (Pencina, et al.) estimated using 200 resampling-perturbations. C-index represents Dxy transformed to Harrell's C for survival data. SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment; qSOFA = "quick" sepsis-related organ failure assessment; AUC = area under the curve; NRI = net reclassification improvement; IDI = integrated discrimination improvement; CI = confidence interval.