*Brief Report*

# Clinical and Demographic Parameters of Patients Treated Using a Sepsis Protocol

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## ABSTRACT

**Purpose:** The purpose of this study was to investigate potential differences by sex in the demographic and clinical characteristics of patients treated utilizing a sepsis electronic bundle order set. Risk factors for in-hospital mortality were also assessed.

**Methods:** Data on patients in whom the sepsis order set was initiated in the emergency department over a 16-month period were entered into the hospital database. Data were analyzed for differences by sex in demographic and clinical factors, treatment modalities, and in-hospital mortality. The Bonferroni correction was applied to account for multiple comparisons; $\alpha$ was set at 0.006 for sex differences.

**Findings:** A total of 2204 patients were included. Male and female cohorts were similar with regard to a variety of demographic and clinical factors, including age, Emergency Severity Index (ESI) levels 1 and 2, time to disposition, appropriateness of antibiotics, and total fluids given by weight. The ESI is an assessment score ranging from 1 to 5 (1 is emergent). There were modest differences in the source of infection (genitourinary was 4% more common in women; $P = 0.03$) and mode of arrival (men were 4% more likely to arrive by ambulance; $P = 0.03$). These differences did not achieve our predefined $\alpha$ of 0.006 when the Bonferroni correction was applied. Factors associated with in-hospital mortality were advanced age, arrival by ambulance, and an ESI level of 1 or 2 (all, $P < 0.01$).

**Implications:** Women were more likely to have a genitourinary cause of sepsis and less likely to arrive by ambulance. Risk factors of in-hospital mortality were older age, arrival by ambulance, and an ESI level of 1 or 2, but not sex. (*Clin Ther.* 2019;41:1020–1028) © 2019 Published by Elsevier Inc.

**Key words:** sepsis protocol, sex differences.

## INTRODUCTION

Sepsis affects >1.5 million patients each year in the United States,[1] and ~500,000 emergency department (ED) visits in the United States each year are due to suspected severe sepsis, which remains a leading cause of death in industrialized countries.[2–4] Reported mortality varies widely.[5] Sex differences have been found in several studies of sepsis mortality, although with conflicting results.[6] A study from France found that women had higher mortality after the development of nosocomial infections in the intensive care unit (ICU) than did their male counterparts.[7] Other studies have found improved

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rates of survival in women (especially postmenopausal women aged >50 years). Some have attributed these differences in mortality to differing hormone profiles[4,8]: Women tend to have stronger hormonal and cell-mediated immune responses, while septic men have been found to have lower-than-normal testosterone levels.[8]

The contemporary sepsis criteria require the suspected presence of an infectious source, in addition to ≥2 of the criteria that define the systemic inflammatory response syndrome (SIRS)[9]: a temperature of >38°C (100.4°F) or <36°C (96.8°F), a heart rate of >90 bpm, a respiratory rate of >20 breaths per minute, and a white blood cell count of >12 × $10^3$ cells/μL or <4 × $10^3$/μL or >10% immature cells. In October 2015, the Centers for Medicare & Medicaid Services (CMS) introduced a new hospital guideline on the treatment of sepsis.[10] In the hospital network in which the present study was conducted, these guidelines were utilized to create an electronic bundled order set (BOS) for the treatment of patients who meet the criteria for sepsis. The objectives of this retrospective analysis of prospectively collected data were to determine whether there are associations between patient sex and other demographic and clinical characteristics, treatment modalities, and in-hospital mortality, as well as to determine other risk factors for in-hospital mortality in patients who meet the criteria for sepsis and undergo treatment guided by a sepsis BOS.

## MATERIALS AND METHODS

After institutional review board (IRB) approval of the study protocol, this retrospective cohort study was initiated based on a *sepsis BOS*, an electronic medical record order set that was implemented at a health network in Northeastern Pennsylvania on May 1, 2016.

### Data Collection

Data from 3 hospitals were included: 1 suburban trauma center, 1 suburban community hospital, and 1 urban hospital with average ED volumes of 71,000, 58,000, and 32,000 patients/y, respectively. Since May 1, 2016, providers in the EDs at these 3 hospitals have been encouraged to call a *sepsis alert* in patients aged ≥18 years who present with the sepsis criteria to the ED. Sepsis alerts are triggered when the sepsis BOS is initiated. Initiation of the sepsis BOS is done at the discretion of the provider for patients who meet ≥2 manifestations of systemic infection according to the modified SIRS criteria on initial evaluation (see Supplemental Appendix in the online version at https://doi.org/10.1016/j.clinthera.2019.03.016)[11] and/or the presence of a change from baseline in mental status. Nurses were given the SIRS vital-sign criteria to screen patients and alerted providers with a note on the trackboard (electronic board that lists patients in the ED) identifying patients as possible candidates for use of the sepsis BOS.

The sepsis BOS is available through a patient's electronic medical record, is labeled *Sepsis Initiation Order Set*, and includes a sepsis initiation tracking order with the following laboratory tests: complete blood count with differential, comprehensive metabolic panel, three troponins, lactate (initial and at 3hrs), and two sets of blood cultures, prothrombin time with international normalized ratio, activated partial thromboplastin time, urine culture, urine microscopy, as well as an ECG, chest radiography, normal saline IV fluid bolus 30 mL/kg administered over 2 h, and a list of approved antibiotics for suspected source. The antibiotics were chosen based on the 2015 CMS guideline.[10]

For antibiotic therapy to be considered "appropriate and timely," an intravenous dose of monotherapy or appropriate dual antibiotic therapy must have been initiated within 90 min after the sepsis BOS order being placed. The 2015 CMS guideline calls for the fluid bolus and antibiotics to be administered within 3 h; therefore, the guideline in the current study was even more stringent. Emergency Severity Index (ESI) levels were also tracked. The ESI is an ED assessment score ranging from 1 to 5; patients with a lower ESI score are more acutely ill.[12,13]

### Patient Eligibility

Data on patients in whom a sepsis BOS was utilized were contemporaneously entered manually from chart review by process-improvement nurses into a database maintained by the institutional quality-improvement group. A retrospective chart review of discharge diagnoses was utilized to determine source of infection. Eligible patients were aged ≥18 years, presented to 1 of the 3 EDs between May 1, 2016, and August 31, 2017, underwent use of the sepsis BOS, and were admitted to the hospital. Patients aged <18 years, those in whom the sepsis BOS was not utilized, and those who were discharged home from the ED were excluded.

### End Points

The primary objective of the study was to assess for differences in demographic and clinical variables

between sexes. Demographic variables included age, measured in years, and weight, measured in kilograms. Clinical variables included arrival mode, ESI level, total fluids received in the ED, fluids given per weight (mL/kg), appropriate fluids given (defined as receiving 30 mL/kg of body weight), source of infection (captured from the medical record), time to disposition from the ED (measured in minutes), and appropriate antibiotics given as defined earlier. The secondary objective of the study was to determine risk factors for in-hospital mortality. Risk factors assessed were age, sex, arrival mode, ESI level, time to disposition, and appropriate fluids given.

### Statistical Analysis

Categorical variables are described using frequencies and percentages; continuous variables are described using medians and interquartile ranges. The $\chi^2$ test, or Fisher exact test when appropriate, was used to compare categorical variables, and the Mann–Whitney *U* test was used to compare continuous variables between groups. Bivariate analyses were conducted to assess the relationships between sex and other demographic/clinical characteristics, and between the demographic/clinical characteristics and in-hospital mortality. If patient data on any variable included in the bivariate analysis were missing, that patient was excluded from that analysis. When assessing for an association between sex and demographic and clinical characteristics, adjustment for multiple comparisons was done using the Bonferroni correction. A series of logistic regression models were run to assess risk factors for in-hospital mortality. Risk factors included in the analysis were all variables associated with in-hospital mortality at the level of $P \leq 0.02$ in bivariate analysis. If a patient's data on any of the risk factors or on in-hospital mortality were missing, the patient was excluded from the analysis. Assumptions for all statistical tests were checked. All analyses were 2-tailed, and a *P* value of <0.05 was considered statistically significant, unless otherwise stated. Statistical analyses were performed using SAS version 9.3 (SAS, Cary, North Carolina).

## RESULTS

During the 16-month period, the sepsis BOS was utilized in 2204 ED patients; 181 were discharged from the ED after treatment and were excluded from this analysis. incomplete data were likely due to a combination of missing data in the chart (eg, the data were never captured) and/or a failure to transcribe the chart data completely. Demographic and clinical data are presented in Table I. There were few significant differences between the male and female cohorts, but women were significantly less likely to have arrived by ambulance (50.6% vs 55.0%; $P = 0.03$). There were also statistically significant sex differences in age and mode of arrival. The median age of all patients who arrived by ambulance was 74 years, and by car or private vehicle, 60 years ($P < 0.01$). ESI levels were similar by sex. Median age differed between the sexes by only 3 years (Table I).

Women were more likely to have a genitourinary source of infection (14.4% vs 10.4% in men; $P = 0.03$), and men were significantly heavier (P<.05) and received less total fluids ($P < 0.01$). After applying a Bonferroni correction to control for the family-wise error rate when assessing for associations between sex and demographic and clinical characteristics, $\alpha$ was set at 0.006, and the association between sex and infection source was no longer statistically significant. Median time to disposition in all patients was 189 min and was similar between sexes (women, 200 min; men, 177 min). Women received a median amount of total fluids of 2000 mL; men received a similar median amount of 2035 mL ($P < 0.01$). Although statistically significant, this difference is not clinically significant; women received a median amount of fluids by weight of 29.5 mL/kg, and men, 29.3 mL/kg ($P = 0.54$). Data on appropriate antibiotic usage were available from 1513 patients; appropriate antibiotic usage did not differ by sex ($P = 0.11$) (Table II). However, appropriate antibiotic usage did vary by age: The median age of those not given appropriate antibiotics was 56 versus 68 years in those given appropriate antibiotics ($P < 0.01$) (data not shown).

Age was a predictor of in-hospital mortality; in this sample those who died in the hospital had a higher median age (72 vs 67 years; $P < 0.01$). In the current study, sex was not a predictor of in-hospital mortality, although a trend toward greater male mortality was noted; 4.9% of men and 3.3% of women died ($P = 0.07$). Patients who died arrivied by ambulance compared to those who survived (74.7% vs 52.2%, respectively; $P < 0.01$); more patients who survived arrived by car/private vehicle. Arrival mode originally had a category for public transportation, but due to a small sample size, this category was excluded from the

Table I. Demographic and clinical characteristics of patients aged ≥18 years in whom a sepsis bundle order set was activated in the emergency department and who were admitted to the hospital. Data are given as number (%) of patients unless otherwise noted.*

| Factor | Total (n = 2204) | Female (n = 1047) | Male (n = 1157) | Unadjusted *P* | Adjusted *P*† |
|---|---|---|---|---|---|
| Age, median (IQR), y | 67 (54–79) | 65 (52–78) | 68 (56–79) | <0.01 | 0.01 |
| Arrival mode | (n = 2202) | (n = 1047) | (n = 1155) | 0.03 | 0.24 |
| Ambulance | 1165 (52.9) | 530 (50.6) | 635 (55.0) | | |
| Car/private vehicle | 1011 (45.9) | 509 (48.6) | 502 (43.5) | | |
| Hospital transport | 10 (0.5) | 4 (0.4) | 6 (0.5) | | |
| Other | 16 (0.7) | 4 (0.4) | 12 (1.0) | | |
| ESI level | (n = 2202) | (n = 1045) | (n = 1157) | 0.06 | 0.48 |
| 1 (immediate) | 117 (5.3) | 61 (5.8) | 56 (4.8) | | |
| 2 (emergent) | 1620 (73.6) | 743 (71.1) | 877 (75.8) | | |
| 3 (urgent) | 461 (20.9) | 238 (22.8) | 223 (19.3) | | |
| 4 (less urgent) | 4 (0.2) | 3 (0.3) | 1 (0.1) | | |
| Weight | (n = 1247) | (n = 282) | (n = 327) | | |
| Median (IQR), kg | 79.4 (65.8–99.0) | 72.6 (60.8–90.7) | 85.9 (72.4–102.0) | <.05 | |
| Appropriate antibiotics | (n = 1513) | (n = 715) | (n = 798) | | |
| No. (%) | 1397 (92.3) | 652 (91.2) | 745 (93.4) | 0.11 | 0.88 |
| Total fluids | (n = 864) | (n = 410) | (n = 454) | | |
| Median (IQR), cc | 2000 (1533–2586) | 2000 (1500–2418) | 2035 (1716–2721) | <0.01 | <0.01 |
| Fluids given, by weight | (n = 609) | (n = 282) | (n = 327) | | |
| Median (IQR), ccs/kg | 29.4 (20.8–30.0 | 29.5 (23.1–30.0) | 29.3 (20.0–30.0) | 0.54 | 1.00 |
| Time to disposition | (n = 2145) | (n = 1015) | (n = 1130) | | |
| Median (IQR), min/sec | 189 (138–260) /11340 (8280–15,600) | 200 (146–271) /12000 (8760–16,260) | 177 (133–244) /10620 (7980–14640) | <.01 | |
| Infection source | (n = 2202) | (n = 1046) | (n = 1156) | 0.03 | 0.24 |
| Sepsis NOS | 546 (24.8) | 246 (23.5) | 300 (26.0) | | |
| Respiratory infection NOS | 408 (18.5) | 178 (17.0) | 230 (19.9) | | |
| GU | 271 (12.3) | 151 (14.4) | 120 (10.4) | | |
| Skin | 147 (6.7) | 60 (5.7) | 87 (7.5) | | |
| GI | 92 (4.2) | 49 (4.7) | 43 (3.7) | | |
| Viral | 16 (0.7) | 10 (1.0) | 6 (0.5) | | |
| Blood | 13 (0.6) | 6 (0.6) | 7 (0.6) | | |
| Musculoskeletal | 12 (0.5) | 4 (0.4) | 8 (0.7) | | |
| Influenza | 10 (0.5) | 5 (0.5) | 5 (0.4) | | |
| Other | 687 (31.2) | 337 (32.2) | 350 (30.3) | | |
| Appropriate fluids given | (n = 1673) | (n = 799) | (n = 874) | | |
| No. (%) | 993 (59.4) | 480 (60.1) | 513 (58.7) | 0.57 | 1.00 |

cc = cubic centimeters; ESI = Emergency Severity Index; IQR = interquartile range; GI = gastrointestinal; GU = genitourinary; NOS = not otherwise specified.

* Percentages may not add to 100%, due to rounding.

† Adjusted *P* values were calculated using the Bonferroni correction.

analysis. There was a statistically significant association between in-hospital mortality and ESI level ($P < 0.01$). More patients who died had an ESI of 1 compared to patients who survived (12.6% vs 5.0%); the same pattern emerged in patients with an ESI of 2 (75.9% died in the hospital compared to 73.6% who survived). More patients survived who had an ESI of 3 compared to patients who died (21.2% vs 11.5%; respectively). No patients with an ESI of 4 died (Table II).

In the final logistic regression model (adjusted odd ratio [OR]), advanced age, arrival mode of car/private vehicle, and ESI level 1 (immediate) were statistically significant predictors of in-hospital mortality in patients in whom the sepsis BOS was utilized. Increasing age was associated with an increased likelihood of dying in the hospital (OR = 1.019; 95% CI, 1.004−1.034). Patients who arrived by ambulance were almost twice as likely to die in the hospital compared to patients who arrived by car/private vehicle (OR = 1.938). Patients who were classified as having an ESI level of 1 (immediate) had a 2.257-fold greater likelihood of dying in the hospital compared to patients who were classified as having an ESI level of 2 (emergent) (95% CI, 1.141−4.461) (Table III). Patients who were classified as having an ESI level of 3 (urgent) were less likely to have died in the hospital compared to patients with an ESI level of 2 (emergent) ($P < 0.01$).

## DISCUSSION

The current study, which reflects 2015 definitions and treatment of sepsis, demonstrates differences between sexes with respect to infection source and mode of arrival. In-hospital mortality was associated with older age, arrival by ambulance, and higher ESI level, but not with patient sex. More emergent patients, those assessed as ESI 1 or 2, were more likely to die in the hospital than were those assessed as ESA $\leq$3, which appears to demonstrate that this validated scoring system[14] was utilized appropriately by the ED nurses in the hospital network where the study was performed. The 2015 CMS guideline requires hospitals to track their results on various parameters in septic patients, highlighting laboratory tests including blood cultures and lactate level as well as timely administration of antibiotics and a 30 mL/kg bolus.[10] Prior studies have differed from ours in that arrival by emergency medical services was not a predictor of in-hospital mortality.[15,16] In contrast, in the current study, arrival by ambulance was an independent risk factor for in-hospital mortality, perhaps because those arriving by private vehicle were identified and treated more rapidly after the institution of the sepsis BOS and nurses were instructed to notify providers of possible candidates for a sepsis alert. Prior to the 2015 CMS guideline, septic patients arriving by ambulance may have been more rapidly treated than those arriving by private vehicle and therefore, despite feeling ill enough to call an ambulance, these patients were not more likely to die. In the current study, men were more likely to arrive by ambulance but not more likely to die than were women (however, after control for the family-wise error rate, the association between sex and arrival mode was not statistically significant). In addition, men and women had similar times to disposition, suggesting rapid assessment of women despite arriving more frequently by private vehicle compared to men. If this finding was unrelated to severity of illness, and it appears to be, as men and women had similar ESI scores, then this study demonstrates the importance of these types of protocols in treating women, as they may be more likely to drive themselves to the ED and potentially not receive rapid treatment without these types of protocols. In addition, both men and women in the current study had a target of receiving the required fluids and antibiotics within 90 min instead of the 180 min mandated by CMS. This could also have improved outcomes but would likely not have changed the sex difference.

A recent systematic review of data from 8 studies demonstrated reduced survival in women on univariate analysis but stressed that whether there is a true survival benefit (after adjustment for confounding factors) in women over men was unclear.[6] Clinical research studies have failed to show consistent outcomes with respect to sepsis and sex/gender, although studies have highlighted being female as an independent predictor of increased mortality in the ICU setting when admitted for sepsis.[17] In the current study, the prevalence of genitourinary tract sepsis was higher in women. This finding was also true in a series by van Vught et al,[18] although that same study showed that men were more frequently admitted to the ICU and that sex was not associated with a difference in 90-day or 1-year mortality. In contrast, a study from Germany demonstrated increased mortality in women in a mostly surgical ICU cohort with sepsis,[19] but a study from Indonesia, by Wullur et al,[20] demonstrated that female surgical ICU patients were

Table II. Demographic and clinical characteristics of patients aged ≥18 years in whom the sepsis bundle order set was activated in the emergency department and who were admitted to the hospital, by in-hospital mortality. Data presented are number (%) unless otherwise specified.*

| Factor | Survived | Died | *P* |
|---|---|---|---|
| Age | (n = 2009) | (n = 87) | |
| Median (IQR), y | 67 (53–79) | 72 (61–87) | 0.01 |
| Sex | (n = 2009) | (n = 87) | 0.07 |
| Male | 1047 (52.1) | 54 (62.1) | |
| Female | 962 (47.9) | 33 (37.9) | |
| Arrival mode | (n = 2008) | (n = 87) | <0.01 |
| Ambulance | 1048 (52.2) | 65 (74.7) | |
| Car/private vehicle | 937 (46.7) | 21 (24.1) | |
| Hospital transport | 8 (0.4) | 1 (1.2) | |
| Other | 15 (0.8) | 0 | |
| ESI level | (n = 2007) | (n = 87) | <0.01 |
| 1 (immediate) | 100 (5.0) | 11 (12.6) | |
| 2 (emergent) | 1478 (73.6) | 66 (75.9) | |
| 3 (urgent) | 425 (21.2) | 10 (11.5) | |
| 4 (less urgent) | 4 (0.2) | 0 | |
| Appropriate antibiotics | (n = 1443) | (n = 60) | |
| No. (%) | 1331 (92.2) | 56 (93.3) | 1.00 |
| Fluids given per weight | (n = 581) | (n = 23) | |
| Median (IQR), cc/kg | 29.4 (21.0–30.0) | 29.1 (17.2–30.0) | 0.94 |
| Time to disposition, median (IQR) | (n = 1954) | (n = 84) | 0.15 |
| Minutes | 189 (139–260) | 177.5 (125–243.5) | |
| Seconds | 11,340 (8340–15,600) | 10,650 (7500–14,610) | |
| Appropriate fluids given | (n = 1593) | (n = 67) | |
| No. (%) | 950 (59.6) | 35 (52.2) | 0.23 |
| Infection source | (n = 2007) | (n = 87) | – |
| Sepsis, NOS | 503 (25.1) | 22 (25.3) | |
| Respiratory infection, NOS | 370 (18.4) | 23 (26.4) | |
| GU | 258 (12.9) | 6 (6.9) | |
| Skin | 138 (6.9) | 1 (1.2) | |
| GI | 88 (4.4) | 2 (2.3) | |
| Viral | 16 (0.8) | 0 | |
| Blood | 13 (0.7) | 0 | |
| Musculoskeletal | 12 (0.6) | 0 | |
| Influenza | 10 (0.5) | 0 | |
| Other | 599 (29.9) | 33 (37.9) | |

cc = cubic centimeters; ESI = Emergency Severity Index; GI = gastrointestinal; GU = genitourinary; IQR = interquartile range; NOS = not otherwise specified.
† $\chi^2$ test.
§ Wilcoxon rank sum test.
‡ Fisher exact test.
* Percentages might not add to 100%, due to rounding.

Table III. Risk factors associated with in-hospital mortality, by single and multiple logistic regression analysis.

| Factor | Unadjusted OR (95% CI) | Adjusted OR (95% CI)* |
|---|---|---|
| Age | 1.027 (1.013–1.041) | 1.019 (1.004–1.034) |
| Sex | | |
| Male | Ref | Ref |
| Female | 0.665 (0.428–1.035) | 0.692 (0.443–1.083) |
| Arrival mode | | |
| Ambulance | Ref | Ref |
| Car/private vehicle | 0.361 (0.219–0.596) | 0.516 (0.302–0.882) |
| Hospital transport | 2.015 (0.248–16.358) | 2.095 (0.255–17.233) |
| Other | — | — |
| ESI level | | |
| 1 (immediate) | 2.463 (1.261–4.812) | 2.257 (1.141–4.461) |
| 2 (emergent) | Ref | Ref |
| 3 (urgent) | 0.527 (0.269–1.034) | 0.602 (0.305–1.186) |
| 4 (less urgent) | — | — |
| Time to disposition, min | 0.998 (0.995–1.000) | — |
| Appropriate fluids given | 1.351 (0.828–2.204) | — |

ESI = Emergency Severity Index; OR = odds ratio.
*Adjusted OR included age, sex, arrival mode, and ESI level.

more likely to survive when compared to men, with the caveat that studied men had slightly higher APACHE and SOFA scores and a longer length of stay. The effects, if any, of differences in sex and source of infection on mortality are inconsistent and likely vary according to the precise population studied and the standards utilized at different times and different places to define sepsis and appropriate treatment. The possibility of a sex/gender-related bias in the provision of care has been suggested, as one study found that men received more invasive procedures and received an increased level of care despite a higher illness severity in women.[17] Physiologic explanations, mostly related to hormone differences, have been advanced for both sexes with little supporting data.

A recent review, by Weniger, et al,[21] demonstrated a survival benefit in proestrus (menstruating) women with trauma or sepsis. The investigators proposed that estrogens and estrogen-receptor agonists could play a role, but the benefit of the proestrus state was questioned by Adrie et al[22] in a nested case–control comparison in ICU patients with severe sepsis. The study showed that men had a higher overall mortality, but when patients were age-stratified to determine the women's menopausal state, women aged ≤50 years had a similar mortality to men and women aged >50 years, and had a significantly lower mortality when compared to their matched male controls.[22] In an ICU cohort from Italy, Sakr et al[8] demonstrated that female septic patients were significantly older than were their men counterparts and were less likely to have severe sepsis and septic shock. Mortality was similar but in the cohort with severe sepsis, being female was associated with a higher risk for mortality. Conclusions by Sakr et al were called into question by Guidet and Maury,[23] who noted that the female patients in the study were older, which could offer an explanation for their increased mortality. As mentioned previously, male septic patients have been shown to have lower testosterone levels.[8] The role of sex hormones in survival of sepsis has clearly not yet been established. Measuring hormone levels in septic patients could help to determine any potential survival benefits.

Further studies that control for comorbid conditions, source of infection, presence of true infection, lactate level, age, weight, mode of arrival, APACHE and SOFA scores, and pre-versus

postmenopause status and hormone levels would help to determine the true role of sex in sepsis-related mortality. In the current study there was no difference by sex in those in whom the electronic dataset was utilized. A randomized controlled trial would be necessary to ensure a lack of bias in the decision to enroll a patient and whether the recommended treatment protocols are followed.

Limitations of the current study included a lack of certain measures of clinical acuity, including APACHE or SOFA scores. Also incomplete data on some variables that were included influenced the analysis by decreasing the power of the study to detect important differences between groups. In addition, fluid boluses based on weight were recommended at 30 mL/kg, but the final decision on fluid bolus volume was at the discretion of the ED physician. There was no mandatory documentation of reasons for a physician's decision to give more or less than the CMS-recommended dose of intravenous fluid. If a weight-based fluid bolus was ordered, a patient's weight at the time of the ED visit may have been self-reported or obtained from a last documented weight in the electronic medical record, as an ED weight may have been impossible to obtain given patient acuity, ambulatory status, or a limited number of beds with scales. Finally, it must be conceded that even those comparisons achieving statistical significance were quantitatively relatively modest; the clinical significance to the individual clinician with any given patient would be limited.

## CONCLUSION

In this large-scale, domestic ED series utilizing the 2015 definition of sepsis and modern standards of appropriate treatment, older age, arrival by ambulance, and an ESI of 1 or 2 were all associated with higher in-hospital mortality. but there were no differences when the data were analyzed by sex.

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## CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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## APPENDIX A

Table A1. Systemic Inflammatory Response Syndrome (SIRS) criteria

| Category | Criteria |
|---|---|
| Temperature | >100.4°F/>38°C |
| | <96.8°F/>36°C |
| Heart Rate | >90bpm |
| Respiratory Rate | 20 breaths per minute |
| White Blood Cell Count | >12 thousand/$mm^3$ |
| | <4 thousand/$mm^3$ |
| | >10% immature cells |

F=Fahrenheit; C=Celsius; bmp=beats per minute; $mm^3$=millimeters cubed.[9]

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