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ORIGINAL CONTRIBUTION

Most emergency department patients meeting sepsis criteria are not diagnosed with sepsis at discharge

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Abstract

Objectives: Effective sepsis resuscitation depends on useful criteria for prompt identification of eligible patients. These criteria should reliably predict a discharge diagnosis of sepsis, ensuring that interventions are triggered for those who need it while avoiding potentially harmful interventions in those who do not. We sought to determine the proportion of patients meeting sepsis criteria in the emergency department (ED) that was ultimately diagnosed with sepsis and to quantify the subset of nonseptic patients with risk factors for harm from fluid resuscitation.

Methods: This retrospective cohort study of adult ED patients at a tertiary academic medical center included vital signs and laboratory results from the first 6 hours, plus administration of intravenous antibiotics, to determine if patients met 2016 Sepsis-3 consensus criteria. If these patients also had hypotension and lactic acidosis, we categorized them as Sepsis-3 plus shock. We used discharge ICD-9 codes to determine if patients were ultimately diagnosed with sepsis.

Results: Over 8 years, 3,121 ED patients met 2016 Sepsis-3 criteria in the first 6 hours. Of these, only 25% and 48% met explicit and implicit criteria for a discharge diagnosis of sepsis. Of 1,032 patients with Sepsis-3 plus shock, 48% and 62% met explicit and implicit criteria. Overall, 60% to 75% of ED patients meeting Sepsis-3 criteria with or without shock did not receive a sepsis discharge diagnosis. At least one plausible risk factor for harm from large-volume fluid resuscitation was identified among 19% to 36% of patients meeting sepsis criteria in the ED but not ultimately diagnosed with sepsis at discharge.

Conclusions: Most patients meeting sepsis criteria in the ED were not diagnosed with sepsis at discharge. Urgent treatment bundles triggered by consensus criteria in the early phase of ED care may be administered to several patients without sepsis, potentially exposing some to interventions of uncertain benefit and possible harm.

KEYWORDS
core measures, intensive care, resuscitation, sepsis, septic shock

INTRODUCTION

Sepsis contributes to the deaths of approximately 5.3 million hospitalized patients per year worldwide. This is likely an underestimate, as data are lacking for almost 90% of the world population.[1] In the United States, sepsis is the leading cause of death in the intensive care unit and the single most expensive inpatient diagnosis.[2,3] In the decades since Rivers and colleagues[4] described a structured approach to early sepsis resuscitation, substantial scrutiny and tremendous resources have been devoted to early identification of sepsis and prompt action to mitigate deterioration to multiorgan dysfunction and death. Since 2015 the U.S. Centers for Medicare & Medicaid Services (CMS) has indexed the quality of hospital care for sepsis to the SEP-1 core measure, a bundle of interventions intended to be delivered to patients within the first few hours of meeting criteria for severe sepsis or septic shock. These interventions (particularly the prompt administration of antibiotics) have been associated with mortality improvement in both adult and pediatric populations[5,6]

Sepsis is a complex, heterogeneous, and lethal syndrome resulting from a dysregulated host response to infection, for which there is no consistent physical manifestation or unique diagnostic marker.[7] This has led to the development of a series of consensus definitions to identify septic patients as early as possible.[7–9] These criteria generally combine physiologic features of inflammation and/or organ dysfunction with evidence or clinical suspicion of infection. Inevitably these criteria capture a cohort of patients with vital sign or laboratory abnormalities that are not due to infection, leading to diagnostic uncertainty.

To develop sound sepsis policy, criteria to benchmark sepsis incidence have been developed using administrative data, primarily based on formal diagnostic codes. When applied to the same patient population these various techniques yield substantially different point estimates for sepsis incidence and mortality.[10–12] In light of these discrepancies, it is essential to understand the degree to which administrative benchmarking definitions of sepsis—derived with the benefit of hindsight to guide policy development—correspond with consensus definitions, which are ideally applied in real time. Such discrepancies are particularly important given that sepsis resuscitation involves the urgent application of interventions that may harm a subset of patients when applied indiscriminately to those with milder infections or alternative diagnoses. These include invasive procedures, large-volume fluid resuscitation, and broad-spectrum empiric antibiotic therapy.

With this background in mind, we identified patients meeting consensus definitions for suspected sepsis while in the emergency department (ED) and determined whether they were assigned a diagnosis of sepsis at hospital discharge. We also assessed for the presence of certain relevant comorbid conditions. The objective of this investigation was to address two important knowledge gaps: 1) the general relationship between sepsis criteria in the ED and discharge diagnosis of sepsis and 2) the proportion of patients without sepsis who were plausibly at risk for harm from mandated resuscitative interventions, in whom clinicians may prefer a more nuanced fluid resuscitation strategy.

METHODS

This was a retrospective observational cohort study of adult patients (age ≥ 18 years) presenting to an urban academic ED in the U.S. upper Midwest with > 100,000 patient visits per year. The study date range—January 2007 to October 2015—reflects the period between adoption of the EPIC electronic medical record by our institution and the transition from ICD-9 to ICD-10 diagnostic codes for the CMS core measure. To identify patients with suspected sepsis presenting to the ED, we used the most recent definition, Sepsis-3, published in 2016.[7] Our search incorporated data from the first 6 hours of vital sign monitoring and laboratory results. We constrained the data to this time frame to decrease heterogeneity and limit the data to results likely to be available in the ED. All ED patients admitted to the hospital who met consensus criteria for sepsis were considered eligible, excluding those with a primary trauma diagnosis and those with missing ICD-9 codes. To identify patients meeting administrative criteria for sepsis at the time of hospital discharge, we used previously published ICD-9–based strategies for chart abstraction.[13,14] We then compared incidence and mortality trends among these groups.

Although it is still commonly used in clinical practice, we did not use the earlier iteration, the 2001 American College of Chest Physicians/Society for Critical Care Medicine definition (ACCP/SCCM 2001, hereafter referred to as Sepsis-2).[9] The Sepsis-2 criteria define sepsis as suspected infection plus the presence of two or more systemic inflammatory response syndrome (SIRS) criteria[8]. Despite the continued use of SIRS criteria in contemporary clinical practice the SIRS-based definition of sepsis is broadly understood to be overly sensitive.[15] For the Sepsis-3 definition, patients were included if they had a Sequential Organ Failure Assessment (SOFA) score of ≥2 and suspected infection, conservatively defined as administration of intravenous (IV) antibiotics within 24 hours of admission, consistent with published methodology.[16] Calculation of the SOFA score also followed published methods, with minor modifications.[17] For laboratory components of the SOFA score (platelet count, creatinine, and total bilirubin) we used the first values obtained in the ED if obtained within 6 hours of presentation. The Glasgow Coma Scale (GCS) score was used as recorded in the medical record. Patients treated with vasopressors met a SOFA score of at least 2, by definition, and were therefore considered to meet Sepsis-3 criteria if they were also given antibiotics within the specified time frame. We ignored the respiratory component of the score. Arterial blood gases were rarely checked in the ED and thus data to reliably calculate a PaO_2/FiO_2 ratio were almost never available; documentation of supplemental oxygen delivery was also highly inconsistent.[18,19] Consistent with clinical practice and prior reports, missing data were assumed to be normal.[20] We further defined a cohort of patients meeting Sepsis-3 criteria plus an initial lactate

level > 2 and any systolic blood pressure < 90 mm Hg, which we referred to as Sepsis-3 plus shock. We considered this combination of variables to be a reasonable trigger for crystalloid resuscitation in the ED setting.

We used previously described explicit and implicit criteria[14] to determine a discharge diagnosis of sepsis from administrative data. Explicit sepsis was defined as the presence of an ICD-9 code for septicemia (038), sepsis (995.91), severe sepsis (995.92), or septic shock (785.52). (These are similar to ICD-10 criteria used by CMS to identify patients for potential abstraction for core measure compliance.) Implicit sepsis was defined as any ICD-9 code indicating infection plus any code indicating organ dysfunction, as previously articulated by Angus and colleagues.[13] We also calculated the proportion of patients with an infection diagnosis according to the Angus definition but without associated organ failure. We excluded all patients with a primary trauma diagnosis from the analysis since prophylactic antibiotics are commonly administered to patients sustaining a traumatic or orthopedic injury.

The primary outcome was the proportion of ED patients with suspected sepsis based on consensus criteria who were not ultimately diagnosed with sepsis based on coded diagnosis at discharge. A preplanned secondary outcome was the subset of these ultimately nonseptic patients that was plausibly at risk of harm from the protocolized administration of a rapid weight-based crystalloid bolus. Our predefined risk factors included ICD-9 codes for comorbid systolic heart failure (428.*, 785.51), due to risk of pulmonary edema; cirrhosis (571.*, K74), due to interstitial edema and risk of volume overload; and dialysis-dependent renal failure (585.6), due to risk of volume overload. Morbid obesity (278.01, V85) was also considered a risk factor due to the risk of volume overload in routine clinical practice if actual weight rather than ideal body weight is used for dosing.

We performed data cleaning and analysis using Microsoft Excel and Stata v15.1 (StataCorp, College Station, TX). Our analysis involved simple descriptive statistics. We calculated the frequency of sepsis incidence and mortality for each of the various case definitions, reported as proportions with 95% confidence intervals (CIs) of the point estimates. The study was reviewed by the institutional review board and determined to be exempt under 45 CFR 46.101. Our manuscript was prepared according to published guidelines for the reporting of studies conducted using observational routinely collected health data (RECORD).

RESULTS

During the study period, 4,060 patients received IV antibiotics in the ED and scored at least 2 on the SOFA. We excluded 935 patients with a primary trauma diagnosis and 4 with missing ICD-9 codes. This left for further analysis 3,121 patients meeting our criteria for Sepsis-3 and 1,032 patients meeting our criteria for Sepsis-3 plus shock. The relationships between patients meeting these criteria are summarized in the study flow diagram in Figure 1. Baseline demographics, vital signs, and clinical criteria for the two groups are summarized in Table 1.

Approximately one-quarter of patients meeting Sepsis-3 criteria in the ED were ultimately assigned an explicit sepsis diagnosis at discharge. Approximately twice as many of these patients met implicit sepsis criteria;[13] however, this was still a minority of

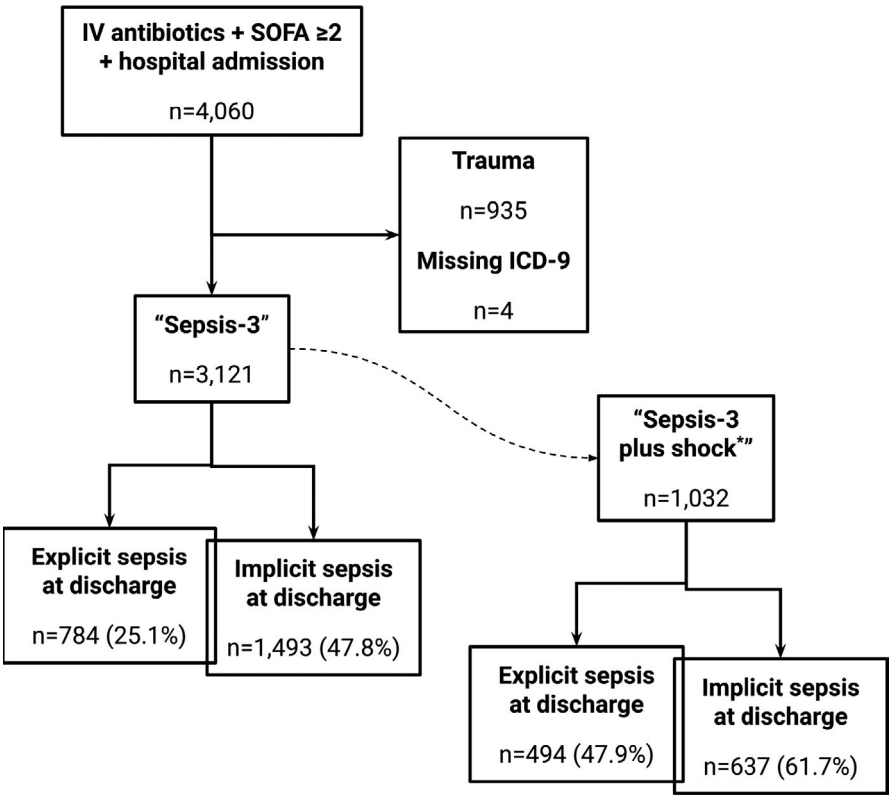

FIGURE 1 Study flow diagram. *Defined as any systolic blood pressure < 90 mm Hg and first lactate > 2 mmol/L. Lower box overlap signifies that patients may meet both criteria

TABLE 1 Characteristics of patients meeting Sepsis-3 criteria

Criterion	Subset meeting only Sepsis-3 criteria	Subset meeting Sepsis-3 criteria plus shock[a]
Sample size (*n*)	3,121	1,032
Age (y), mean (±SD)	59 (±17.5)	60 (±17)
Female sex, *n* (%)	1,141 (36.6)	376 (36.4)
Race, *n* (%)		
American Indian/Alaskan Native	184 (6.0)	55 (5.5)
Asian/Pacific Islander	127 (4.1)	50 (4.8)
Black/African American	843 (27.5)	234 (23.3)
White	1,655 (54.0)	593 (59.0)
Other/multiracial/declined	82 (2.7)	100 (9.7
Ethnicity, *n* (%)		
Hispanic	176 (5.7)	49 (4.9)
Initial vital signs, median (IQR)		
Heart rate (beats/min)	98 (83, 115), {0}	109 (92, 125), {0}
Respirations (breaths/min)	19 (16, 24), {0}	21 (17, 27), {0}
Systolic blood pressure (mm Hg)	126 (107, 149), {0}	111 (87, 137), {0}
Temperature, °F	98.4 (97.3, 100.0), {17}	98.3 (96.8, 100.2), {7}
SpO_2 (%)	96 (93, 99), {16}	96 (92, 98), {7}
Laboratory results,[b] median (IQR)		
Leukocyte count ($\times 10^9$/L)	11.5 (7.9, 16.3) {8}	13.6 (8.7, 19.6), {1}
Platelet count ($\times 10^9$/L)	204 (138, 279) {12}	214 (146, 291), {6}
Serum creatinine (mg/dL)	1.6 (0.9, 3.1), {17}	1.4 (0.9, 2.6), 9}
Total bilirubin (mg/dL)	0.6 (0.3, 1.3), {811}	0.6 (0.4, 1.3), {133}
Venous lactate (mmol/L)	2.0 (1.3, 3.6), {1,442}	3.4 (2.5, 5.5) {0}
GCS, median (IQR)	14 (11, 15) {385}	14 (9, 15)

Abbreviations: IQR, interquartile range; GCS, Glasgow Coma Scale score; SpO_2, peripheral oxygen saturation.

[a]Defined as Sepsis-3 criteria plus first systolic blood pressure < 90 mm Hg and first lactate > 2 mmol/L.

[b]Within 6 hours of presentation {number of missing data elements}.

patients. Notably, 69% of patients meeting Sepsis-3 criteria received a discharge diagnosis of sepsis without organ failure. This implies that approximately 30% of patients with suspected sepsis who were consequently treated with early antibiotics were later determined to have had a noninfectious cause of their physiologic derangement or organ failure. In other words, their AKI or hypoxemia, etc., were ultimately judged not to have been related to their presenting infection. Among these, the most common noninfectious diagnoses included poisoning/overdose, inhalation pneumonitis, acute respiratory failure (due to a combination of asthma, COPD, and/or heart failure), diabetic ketoacidosis, and acute renal failure. Mortality among patients meeting sepsis consensus criteria in the ED was 8.7% for Sepsis-3 and 15.6% for Sepsis-3 plus shock. ICU lengths of stay were short in both cohorts, presumably due to early deaths. These data are presented in Table 2. Approximately 39% and 31% of patients with suspected sepsis or septic shock who were not ultimately diagnosed with sepsis at discharge had at least one prespecified risk factor for potential harm from large-volume fluid resuscitation. These data are outlined in Table 3 and Figure 2.

To assess for potential changes in coding practices, we accounted for the number of Sepsis-3 cases, number of cases admitted to the ICU, and ICU length of stay as a function of time. None of these analyses revealed a significant linear association between any of these variables and year of the encounter (2007–2015).

DISCUSSION

Our data imply that a majority of ED patients meeting Sepsis-3 criteria for suspected sepsis were not ultimately diagnosed with sepsis at discharge. This includes a subset of patients with compelling evidence of septic shock. A substantial portion of these ultimately nonseptic patients could have been exposed to mandated interventions

TABLE 2 Relationship between suspected sepsis in the ED and coded diagnosis at hospital discharge, plus certain clinical outcomes

Criterion	Sepsis-3	Sepsis-3 + shock[a]
Sample size (*n*)	3,121	1,032
Explicit criteria for sepsis, % (95% CI)	25.1 (23.6–6.7)	47.9 (44.8–50.9)
Implicit criteria for sepsis, % (95% CI)	47.8 (46.1–49.6)	61.7 (58.7–64.6)
Infection without ICD-9 coded organ failure, % (95% CI)	69.3 (67.7–70.9)	71.4 (68.5–74.1)
Outcomes		
ICU length of stay (days), median (IQR)	0.6 (0, 3.1)	0 (0, 1.8)
Hospital LOS (days), median (IQR)	5 (3, 10)	4 (2, 8)
Mortality, % (95% CI)	271 (8.7)	163 (15.6)

Abbreviations: IQR, interquartile range; ICU, intensive care unit; LOS, length of stay.

[a]Defined as Sepsis-3 criteria plus any systolic blood pressure < 90 mm Hg *and* first lactate > 2 mmol/L.

TABLE 3 Distribution of potential risk factors for harm among patients with an explicit diagnosis of sepsis at discharge

	Sepsis-3 (*n* = 3,121)		Sepsis-3 + shock[a] (*n* = 1,032)	
Criterion	No explicit sepsis diagnosis at discharge (*n* = 2,337)	Explicit sepsis diagnosis at discharge (*n* = 784)	No explicit sepsis diagnosis at discharge (*n* = 538)	Explicit sepsis diagnosis at discharge (*n* = 494)
At least one risk factor for harm, *n* (%)	902 (38.6)	215 (27.4)	165 (30.7)	111 (22.5)
Specific risk factors, *n* (%)				
CHF	381 (16.4)	112 (14.3)	96 (17.8)	63 (12.7)
ESRD on dialysis	389 (16.6)	95 (12.1)	32 (5.9)	35 (7.1)
Cirrhosis	165 (7.1)	18 (2.3)	31 (5.8)	11 (2.2)
Morbid obesity	91 (3.9)	11 (1.4)	21 (3.9)	15 (3.0)

Abbreviations: CHF, congestive heart failure (including cardiogenic shock); ESRD, end-stage renal disease.

[a]Defined as Sepsis-3 criteria plus any systolic blood pressure < 90 mm Hg *and* first lactate > 2 mmol/L.

with the potential to cause harm. These findings have implications for clinical care, regulatory policy, and trial design.

Among our patients, the Sepsis-3 consensus criteria were a relatively poor predictor of sepsis discharge diagnosis. This discrepancy between clinical criteria for suspected sepsis and administrative diagnosis of sepsis at discharge was poor regardless of whether sepsis was ultimately defined using explicit or implicit criteria. This finding has precedent in other clinical settings.[11] Overall, 60% to 75% of patients meeting our criteria for sepsis or septic shock in the ED did not receive a diagnostic code that would have made them potentially eligible for the CMS SEP-1 core measure. In other words, contemporary criteria used to direct resuscitative interventions to patients expected to receive a sepsis diagnosis at discharge appear quite likely to affect an even larger cohort of patients that will not meet discharge sepsis criteria. These patients thus receive interventions intended to achieve compliance with a quality metric for which they are, based on these data, unlikely to qualify.

It is important to note that our point estimates almost certainly overestimate the relationship between initial sepsis criteria and final diagnosis because we only included patients admitted to the hospital. It is likely that even more patients met these criteria initially but were ultimately discharged from the ED. This observation may have policy implications for the development of patient care mandates, which frequently rely on initial clinical parameters like vital signs and laboratory results in the ED to identify patients for initiation of treatment protocols.

As an illustration of the implications for management, a substantial portion of patients in our cohort with suspected septic shock on arrival but no sepsis diagnosis at discharge had one or more comorbid conditions that may respond poorly to algorithmically and indiscriminately applied resuscitative interventions. Given the limitations of our data, we did not specifically test for these adverse effects, but rather provide these estimates as a consideration for future work. Current mandates for the initial care of patients meeting consensus criteria for septic shock include an empiric 30 mL/kg crystalloid bolus.[21] The majority of the patients in our study population did not receive a discharge diagnosis of sepsis and a substantial number of those in the Sepsis-3

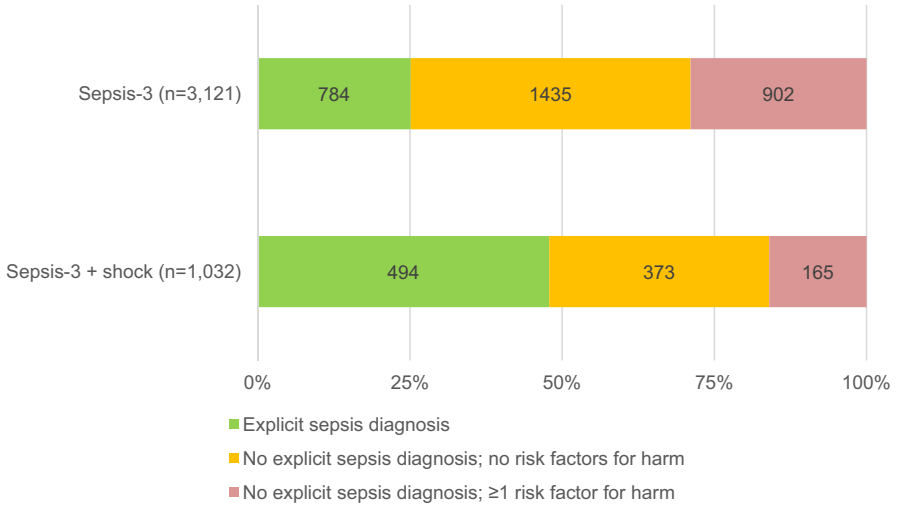

FIGURE 2 Overlap of Sepsis-3 criteria, explicit sepsis diagnosis at discharge, and risk factors for harm

plus shock subset had one or more theoretical risk factors for harm from a rapid crystalloid bolus. An overly sensitive approach to resuscitation would be reasonable if patients reliably exhibited other evidence of sepsis or if they were expected to benefit from these interventions even in its absence. Neither is consistently true. There is uncertainty about the ideal method of fluid resuscitation in early sepsis[22] and whether a universal approach has similar benefits in various sepsis phenotypes.[23] Wholesale compliance with the SEP-1 bundle may not necessarily impact mortality, and individual components may be more or less relevant in different clinical contexts.[24] More pertinent to this analysis, data demonstrating the benefit of fluid administration in low-risk patients without sepsis are generally lacking. Moreover, volume overload is associated with an increased risk of hospitalization, respiratory failure, and death in certain populations.[25–28] Indiscriminate or misguided crystalloid administration cannot be considered a benign therapy.

Early identification of patients with sepsis and septic shock is essential to the prompt initiation of all resuscitative efforts. To that end, it is vital to understand the prevalence of sepsis as early as possible. This would ideally occur in the ED, which is constantly available and is equipped for rapid resuscitation. Consensus criteria drive upfront resuscitative care and allocation of hospital resources, while coded diagnoses at discharge are used retrospectively to develop policy, assess epidemiology, and drive quality improvement efforts. The relationships between these criteria have significant implications for both the design of clinical trials of novel interventions in sepsis and the development of related health policy, such as the CMS SEP-1 core measure. The extent to which these definitions overlap or diverge affects our understanding of sepsis and best practices for management. Further defining the pretest probability thresholds, patient phenotypes, and clinical contexts for which suspected infection should trigger sepsis bundle elements remains an important area of continued investigation. This echoes similar approaches taken for other clinically ambiguous diagnoses targeted with core measures in the ED.[29]

LIMITATIONS

The results of this single-site study may not be generalizable to other health systems or geographic regions—particularly the developing world—and warrant external validation. Our data are subject to human and technological errors and our use of a retrospective data set, which was not originally collected for the purposes of a specific research question, may have compromised our analysis to the extent that it introduced confounding variables or excluded certain essential elements. Final diagnoses and the reference standard were determined using ICD-9 codes, which may contribute misattribution bias. This would have been more likely to occur using implicit rather than explicit codes, which are comparatively unambiguous and are used to determine which patients may be eligible for application of quality measures for sepsis; they are therefore the most relevant to this analysis. CMS abstraction for the SEP-1 core measure is based on ICD-10 codes, which were not in use during the period of our analysis. For our data set we were careful to capture ICD-9 codes that closely parallel the relevant ICD-10 codes. It is also possible that early bundled care of some patients mitigated later organ dysfunction, decreasing the number of implicit sepsis cases identified.

We chose to define suspected infection as administration of any IV antibiotics within 24 hours, which may be too nonspecific, but serves as a reasonable proxy for suspected infection in clinical practice. We applied a conservative standard to only those patients most clearly meeting Sepsis-3 criteria in the ED in an attempt to minimize the effect of fringe or mild cases. Regarding the SOFA score, application in clinical practice is limited by the variables collected; missing variables in our analysis could have influenced the findings. Due to limitations in data quality for the respiratory component in particular, more patients likely qualified for these criteria than we identified. However, we chose to focus on patients clearly meeting Sepsis-3 criteria rather than making risky assumptions given data quality limitations. While it is possible that we misidentified some patients who were intubated due to altered mental status and airway compromise

rather than respiratory failure using this criteria, those patients would likely have qualified for a SOFA score of 2 based on the GCS and neurologic organ failure criteria and would have been included in the cohort either way. We used any elevated SOFA score of at least 2, not necessarily a new or acute change. This may have led to overestimates of patients meeting Sepsis-3 criteria and could have affected the correlation with hospital discharge diagnoses.

The purported risk factors for harm were established a priori and defined by ICD-9 codes alone, and the associated risk is only theoretical. We sought these data largely to determine the general scope of a common clinical dilemma: Do certain septic patients warrant a more judicious approach to crystalloid administration, or is a uniform resuscitative approach to all septic patients of greater net benefit? These factors may or may not translate to actual harm, and in fact some data from other investigators suggest that patients with sepsis and heart failure might not be at risk of harm from early fluid resuscitation.[30] Rather, we view this as thought provoking, recommend additional research toward these risk factors, and await the results of ongoing randomized control trials.

CONCLUSIONS

A substantial majority of patients with suspected sepsis and septic shock based on consensus definitions in the ED are not diagnosed with sepsis at discharge. These data have implications for early sepsis care and the formulation of health policy related to sepsis epidemiology and management. Algorithmically applied volume resuscitation may expose a large subset of patients without sepsis to potential harm.

CONFLICT OF INTEREST

The authors have no potential conflicts to disclose.

AUTHOR CONTRIBUTIONS

Study concept and design: Michael A. Puskarich. Acquisition of the data: Michael A. Puskarich. Analysis and interpretation of the data: Michael A. Puskarich, John M. Litell. Drafting of the manuscript: John M. Litell, Michael A. Puskarich. Critical revision of the manuscript for important intellectual content: all authors. Statistical expertise: Michael A. Puskarich, Brian Driver. Acquisition of funding: n/a.

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