Received: 26 July 2024 | Revised: 20 November 2024 | Accepted: 6 December 2024

DOI: 10.1111/acem.15074

Academic Emergency Medicine

ORIGINAL ARTICLE

Factors and outcomes associated with under- and overdiagnosis of sepsis in the first hour of emergency department care

Shivansh R. Pandey MS[1] | Sarah K. S. Knack MD[1] | Brian E. Driver MD[1] | Matthew E. Prekker MD, MPH[1] | Nathaniel Scott MD, MHA[1] | Sarah J. Ringstrom MD[1] | Ellen Maruggi BS[1] | Olivia Kaus BS[1] | Walker Tordsen BS[1] | Michael A. Puskarich MD, MS[1,2]

[1]Department of Emergency Medicine, Hennepin Healthcare, Minneapolis, Minnesota, USA

[2]Department of Emergency Medicine, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence
Michael A. Puskarich, Department of Emergency Medicine, Hennepin Healthcare, Minneapolis, MN 55415, USA.
Email: mike.puskarich@hcmed.org

Abstract

Background: Sepsis remains the leading cause of in-hospital death and one of the costliest inpatient conditions in the United States, while treatment delays worsen outcomes. We sought to determine factors and outcomes associated with a missed emergency physician (EP) diagnosis of sepsis.

Methods: We conducted a secondary analysis of a prospective single-center observational cohort of undifferentiated, critically ill medical patients (September 2020–May 2022). EP gestalt of suspicion for sepsis was measured using a visual analog scale (VAS; 0%–100%) at 15 and 60 min post–patient arrival. The primary outcome was an explicit hospital discharge diagnosis of sepsis that was present on arrival. We calculated test characteristics for clinically relevant subgroups and examined factors associated with initial and persistent missed diagnoses. Associations with process (antibiotics) and clinical (mortality) outcomes were assessed after adjusting for severity.

Results: Among 2484 eligible patients, 275 (11%) met the primary outcome. A VAS score of ≥50 (more likely than not of being septic) at 15 min demonstrated sensitivity 0.83 (95% confidence interval [CI] 0.78–0.87) and specificity 0.85 (95% CI 0.83–0.86). Older age, hypoxia, hypotension, renal insufficiency, leukocytosis, and both high and low temperature were significantly associated with lower accuracy due to reduced specificity, but maintained sensitivity. Of 48 (17%) and 23 (8%) missed cases at 15 and 60 min, elevated lactate, leukocytosis, bandemia, and positive urinalysis were more common in the missed sepsis compared to nonsepsis cases. Missed diagnoses were associated with median (interquartile range) delay of 48 (27–64) min in antibiotic administration but were not independently associated with inpatient mortality as risk ratios remained close to 1 across VAS scores.

Supervising Editor: Richard T Griffey

Conclusions: This prospective single–academic center study identified patient subgroups at risk of impaired diagnostic accuracy of sepsis, with clinicians often overdiagnosing rather than underdiagnosing these groups. Prompt abnormal laboratory test results can "rescue" initial missed diagnoses, serving as potential clinician- and systems-level intervention points to reduce missed diagnoses. Missed diagnoses delayed antibiotics, but not mortality after controlling for severity of illness.

KEYWORDS
diagnosis, gestalt, misdiagnosis, sepsis

INTRODUCTION

Sepsis is a life-threatening, heterogeneous syndrome with a significant medical burden. As the third leading cause of death in U.S. hospitals, sepsis impacts around 1.7 million people annually.[1] Hospitalizations for sepsis are alarmingly common and deadly, with incidences ranging from 28.9 to 121.3 per 1000 hospitalizations[2] and an estimated mortality rate of 26.7%.[3,4] As the most expensive inpatient condition in the United States, sepsis not only affects patients but also places a substantial burden on health care resources.[5]

The diagnosis of sepsis is challenging due to its complex and often nonspecific clinical presentation. Certain groups experience disparities in sepsis management and outcomes.[6,7] Furthermore, sepsis misdiagnosis may be influenced by various clinical characteristics.[8–10] Diagnostic errors in sepsis, including both under- and overdiagnosis, can lead to delayed treatment or unnecessary interventions, adversely affecting patient outcomes. Timely recognition and accurate diagnosis of sepsis are crucial, as studies show a substantial increase in mortality with each hour of delay in administration of antibiotics, potentially as high as 7% per hour,[11] starting as soon as 1 h after recognizing sepsis.[12–18] Practically, however, "sepsis recognition" remains a loose and poorly defined term, often defined retrospectively based on the decision to order blood cultures or antibiotics.[19–21] The lack of a clear definition impedes progress toward improving time to antibiotic administration in the patients who need it most.[22,23] The risks of diagnostic delays, however, must be weighed against both antibiotic stewardship and logistic considerations,[24,25] which have been incompletely addressed to date.

Understanding the factors associated with diagnostic errors in sepsis is essential for improving patient care. Certain demographic and clinical characteristics may increase the risk of missed or delayed diagnosis or overdiagnosis. Our recent study demonstrated physician gestalt at <15 and 60 min after emergency department (ED) arrival outperformed other common screening methods including qSOFA, SIRS, MEWS, SOFA, and a machine learning algorithm in diagnosing sepsis among critically ill, undifferentiated medical patients.[26] Despite significantly outperforming other methods of screening, nine patients were assigned a 0% chance of sepsis who ended up with an explicit sepsis diagnosis. Of these, four had an increased probability at 60 min, prompting us to examine the factors that might aid clinicians from missing cases in a time frame in which timely interventions could still be undertaken.

To better understand the interplay of a missed or overdiagnosed sepsis case with clinical presentation, physician decision making, and outcomes, we conducted a secondary analysis of prospectively collected data set to determine factors associated with reduced accuracy of very early assessment of sepsis. By focusing on the clinical and demographic characteristics of patients who were under- or overdiagnosed, we aimed to assist clinicians by identifying groups at high risk of misdiagnosis and strategies to mitigate that risk. We hypothesized that certain demographic and clinical characteristics would increase the risk of diagnostic errors. In the subset of patients ultimately diagnosed with sepsis, we hypothesized that certain factors might mitigate the risk of a persistently missed diagnosis after an initially incorrect assessment. Finally, we hypothesized that an early missed diagnosis would be associated with both decreased propensity to administer antibiotics and increased risk of death.

METHODS

Study setting

This was a secondary analysis of a single-center prospective study conducted from September 2020 through May 2022 at an urban academic safety net hospital with over 100,000 ED visits annually. This study aimed to assess physicians' clinical judgment in identifying sepsis among patients presenting to an ED resuscitation area. This resuscitation area is a dedicated four-bed unit designed to care for patients with critical illness requiring immediate and aggressive resuscitation due to life-threatening conditions. Patients are triaged to this area based on predefined criteria indicating high acuity. Non–critically ill patients are generally not triaged to this area. However, there may be exceptional cases where critically ill patients are triaged elsewhere due to capacity constraints or operational considerations, though this is uncommon. Based on historical controls from our institution related to the number of

sepsis patients meeting explicit sepsis criteria, we believe this study captured the vast majority of eligible patients.[27] The study enrolled critically ill patients presenting to the ED resuscitation area and recorded the treating physician's real-time gestalt, or clinical judgment, of whether or not the patient had sepsis. The study protocol received approval from the local institutional review board (IRB #20_4848). Owing to the time-sensitive nature and the associated low risk of data collection, the study proceeded under a waiver of informed consent.

Patient population

Consecutive patients aged 18 years and older who were directly triaged to the four-bed ED resuscitation area upon arrival were screened for the study. Exclusion criteria included (1) patients younger than 18 years; (2) patients with nonsepsis diagnoses present on arrival (POA), including trauma, stroke activation, cardiac arrest, active myocardial infarction, or active labor; (3) patients transferred from other hospitals; (4) patients initially assessed in other areas of the ED; (5) patients assessed by nonphysician primary providers; (6) patients in alternate treatment areas; and (7) cases where no research staff were available. Patients evaluated in a clinic and subsequently referred to the ED were eligible if they were triaged directly to the resuscitation area. This approach ensured the accurate capture of early clinical impressions.

Data collection

Treating physicians assessed the likelihood of sepsis in patients using a visual analog scale (VAS) ranging from 0 to 100 in response to the question "What is the likelihood that this patient has sepsis?" The question was presented by trained independent observers through a REDCap survey on an iPad. Assessments were made within 15 min of patient arrival and again at 60 (±15) min after patient arrival. Both senior resident and faculty assessments were captured independently.

To adequately capture the urgency of these high-acuity cases, observers collected critical variables such as vital signs and clinical interventions in real time including timing of initial antibiotics. Nondynamic measures were captured from the electronic medical record by trained abstractors including demographics, including age, gender, ethnicity, race, and laboratory results such as white blood cell count, hemoglobin, creatinine, lactate, and urinalysis. ICD-10 diagnostic codes at hospital discharge marked as POA were extracted from medical records. If vital signs and intervention times were missing, supplemental medical record review was utilized to capture this information. Automated abstraction of hospital mortality from the electronic medical record was performed by linkage of unique encounter numbers. Abstractors were blinded to VAS scores and study hypotheses. Study data were collected and managed using REDCap electronic data capture tools.[28,29]

Outcomes

The primary diagnostic outcome was an "explicit sepsis diagnosis present on arrival," indicated by the presence of an ICD-10 code, as defined by Centers for Medicare & Medicaid Services (CMS), for sepsis assigned at hospital discharge and marked as POA in the medical record.[27,30] These diagnostic codes represent the first step of identifying cases potentially eligible for abstraction for the CMS SEP-1 core measure and are consistent with prior methods of identifying explicit sepsis. For all analyses, we conducted sensitivity analyses replacing the primary outcome with a secondary outcome of implicit sepsis. In this approach, implicit sepsis was defined using previously validated ICD-10 combinations of 49 diagnostic codes for infection, complemented by 28 codes to define organ failure, establishing the presence of severe sepsis or septic shock. This sensitivity analysis is akin to the method used and validated by Angus et al.[31] for ICD-9 diagnostic codes, subsequently adapted to correspond with ICD-10 codes.

The primary clinical outcome was in-hospital mortality. To understand the relationship of gestalt with clinical decisions, we focused on administration of antibiotics, specifically administration of intravenous (IV) antibiotics within 3 h from ED arrival and time to first antibiotic dose in minutes recorded in real time, based on data demonstrating an association of this action with mortality.[32] Associations between fluid administration and mortality are not nearly so robust and were not considered in this analysis.[32]

Definition of missed sepsis diagnosis

To examine the association of early missed sepsis diagnosis with process and clinical outcomes, we first needed to define what constitutes a missed diagnosis as it lacks a consensus definition. We defined an initial missed diagnosis of sepsis as a situation where the treating physician's gestalt assessment at 15 min was less than 50 (less likely than not) in accordance with optimized test characteristics. We additionally defined a "persistently missed" diagnosis as an initial missed diagnosis with a 60-min VAS score of <50, while a "rescue diagnosis" as an initial missed diagnosis with a subsequent VAS score of >50 at 60 min. For this analysis, we chose to focus on the 1-h time point, as the Surviving Sepsis Campaign recommends administering antibiotics ideally within 1 h of diagnosis.[33]

Statistical analysis

We first assessed test characteristics of different VAS cutoffs to predict the primary diagnostic outcome (explicit sepsis) at predefined cutoffs of every 10 units of VAS at both <15 and 60 min (Figure S1). Based on this analysis, we selected a VAS 50 for subsequent analysis based on a combination of nearly optimal Youden index (optimal cutoff, 44) and clinical face validity (sepsis more likely

than not). Test characteristics and area under the receiver operator characteristics curves were then calculated in predefined clinically relevant subgroups and cutoffs, determined by literature review and author consensus. Descriptive statistics were used to summarize the groups described in the methods.

Univariate and multivariate logistic models were used to examine the association between the VAS score and the likelihood to administer antibiotics in the subgroup of patients with sepsis. We constructed multivariate logistic regression models for mortality, using a priori covariates, specifically age, SOFA score, and lactate. Less than 2% of all variables were missing with the exception of total bilirubin. For the purposes of multivariate mortality analyses, normal values were imputed for missing values. We did not include factors that differed between groups in Table 1 such as blood pressure or hypoxia, as they are already included in the SOFA score.

Because assigning a low probability of sepsis to a patient who turned out to have sepsis could arguably result in decreased ED clinical interventions and worse outcomes, we determined the association of the VAS and subsequent mortality among patients with sepsis diagnosis. We fit a generalized linear mixed-effects model using a logit link function with mortality as the dependent variable and fixed effects of VAS, age, initial lactate, and total SOFA score. The VAS was modeled with a nonlinear relationship to the outcome using restricted cubic splines with 3 or 4 knots. We then plotted VAS against estimated mortality. Plots were generated for patients with implicit and explicit sepsis. We also generated identical plots for the outcome of receipt of antibiotics.

Sensitivity analyses were conducted to validate the robustness of the results using the alternative implicit definition of sepsis based on ICD-10 codes. Statistical analyses were performed using R Statistical Software (Version 4.3.1, R Foundation for Statistical Computing)[34–37] and STATA (Version 15.1, StataCorp LLC). All tests were two-sided and *p*-values of less than 0.05 were considered statistically significant.

Power and sample size

This study is an exploratory secondary analysis not initially powered to detect differences between subgroups, so in lieu of a post hoc power analysis we describe the original study design. The initial study was designed as follows. Given an unknown distribution of VAS scores and desire to include sufficient numbers of clinically occult cases of sepsis, we initially planned to enroll approximately 2500 patients, anticipating a sepsis prevalence of around 10% to capture approximately 250 patients with sepsis. Based on the observed standard deviation in VAS scores of 30.5, and 275 versus 2209 patients meeting versus not meeting the primary outcome, at an alpha of 0.05, our study had >99%, 95%, and 74% power to detect differences in VAS scores of 10, 7, and 5 between patients with and without explicit sepsis.

RESULTS

A total of 7240 patient encounters were screened from September 2020 through May 2022, and 2484 met eligibility (Figure 1). Explicit sepsis was present in 275 cases (11%), with 48 (17%) initially and 23 (8%) persistently missed cases, with 213 overdiagnosed cases (10%). The demographics and clinical characteristics of the included cohort are summarized in Table 1. Test characteristics at each VAS cutoff for the primary outcome from 10% to 90% at the <15- and 60-min time points are illustrated in Figure S1. A VAS of 50 used for subsequent analyses demonstrated a sensitivity of 0.83 (95% confidence interval [CI] 0.78–0.87) and specificity of 0.85 (95% CI 0.83–0.86). At an alternative cutpoint of 10%, sensitivity increased substantially (0.96, 95% CI 0.93–0.98) but specificity dropped to 0.52 (95% CI 0.50—0.54), demonstrating excellent rule-out characteristics.

The sensitivity and specificity of VAS by clinical subgroups for the primary outcome are illustrated in the forest plots in Figures 2 and 3 at VAS score of >50. Forest plots of other performance metrics are included in Figures S2–S4. Point estimates of sensitivity (indicating missed diagnosis) do not differ significantly by any subgroup. However, overdiagnosis was prevalent in specific subgroups, namely, older patients and those with hypo- and hyperthermia, hypotension, hypoxia, renal insufficiency, and both leukopenia and leukocytosis. Sensitivity analyses using the implicit outcome of sepsis did not substantively change the findings (Figure S11). While overall accuracy of VAS for implicit was modestly lower than explicit sepsis, it was not confined to any specific subgroup, and subgroup patterns were similar to results found with an explicit definition. None of the diagnostic test characteristics differed significantly by sex assigned at birth or self-reported race or ethnicity. Forest plots of performance metrics of VAS by clinical subgroups at 60-min VAS are included in Figures S5–S10.

As shown in Table 1, certain findings are more common in both initial and persistently missed cases of sepsis. Lactate, leukocytosis, bandemia, and positive urinalysis, as well as abdominal and skin examinations, are more common among missed sepsis cases. Compared to rescue diagnoses (Table 2), persistently missed diagnoses tended to have lower WBC counts and were less likely to have a positive urinalysis.

We observed a significant, nearly linear association of both initial and 60-min VAS with likelihood to administer antibiotics within 3 h ($p < 0.0001$) in the entire cohort. In the subgroup of patients with initially missed explicit sepsis, 88% received antibiotics within 3 h. Median (interquartile range [IQR]) time to antibiotic administration was 48 (27–64) min in the misdiagnosis group and 38 (23–58) min in the correctly identified group. In the sensitivity analysis of implicit sepsis, results were similar.

To assess the potential effect of an early (60 min) missed diagnosis on the clinical outcomes in the subgroup of patients with sepsis, unadjusted analyses demonstrated that *higher* clinical suspicion of sepsis was associated with increased mortality and that a missed diagnosis was protective. These results are attributable to a strong

TABLE 1 Demographics and clinical characteristics of the cohort, stratified by presence or absence of explicit sepsis diagnosis and 15-min diagnostic accuracy.

	Presence of explicit sepsis diagnosis		Absence of explicit sepsis diagnosis	
Demographics	**Correct sepsis diagnosis (initial VAS +), *n* = 227**	**Missed sepsis diagnosis (initial VAS −) *n* = 48**	**Sepsis overdiagnosis (initial VAS +) *n* = 333**	**Correct sepsis nondiagnosis (initial VAS −) *n* = 1876**
Age (years)	65 (52–76)	66 (57–71)	62 (50–71)	48 (32–63)
Male sex	128 (56)	30 (63)	196 (59)	1124 (60)
Race				
Asian	6 (3)	0 (0)	11 (3)	34 (2)
Black or African American	59 (26)	13 (27)	118 (35)	692 (37)
Caucasian	123 (54)	25 (52)	143 (43)	721 (38)
Hispanic	8 (4)	2 (4)	12 (4)	119 (6)
Native American or Native Alaskan	19 (8)	3 (6)	17 (5)	94 (5)
Pacific Islander and Native Hawaiian	0 (0)	0 (0)	1 (0)	1 (0)
Other/unknown	12 (5)	5 (10)	31 (9)	215 (11)
Ethnicity				
Hispanic or Latino	9 (4)	2 (4)	12 (4)	127 (7)
Not Hispanic or Latino	204 (90)	40 (83)	287 (86)	1524 (81)
Other	11 (5)	5 (10)	30 (9)	206 (11)
Initial vital signs				
Systolic blood pressure (mm Hg)	115 (95–138)	130 (99–143)	127 (106–147)	137 (121–154)
Heart rate (beats/min)	115 (97–131)	110 (100–129)	100 (85–116)	100 (84–116)
Oxygen saturation	95 (91–97)	96 (92–97)	96 (92–98)	97 (95–99)
Temperature (°C)	37.7 (36.4–38.7)	36.9 (35.8–38.2)	36.7 (36.3–37.3)	36.7 (36.4–36.9)
Laboratory tests				
Creatinine	1.5 (1.0–2.4)	1.7 (1.0–3.1)	1.2 (0.9–1.9)	1.0 (0.8–1.3)
Lactate	3.3 (2.1–5.3)	3.6 (2.2–5.0)	2.5 (1.5–4.3)	2.4 (1.6–4.1)
White blood cells	13.1 (9.2–17.6)	14.6 (11.1–21.0)	9.7 (6.9–13.7)	8.5 (6.5–11.4)
Bands	10.1 (6.4–15.0)	11.2 (8.0–17.5)	6.5 (4.0–10.7)	4.8 (3.2–7.3)
Urinalysis				
Large/moderate leukocytes	80 (40)	9 (21)	26 (11)	55 (8)
Small/trace/none	119 (60)	34 (79)	203 (89)	647 (92)
Clinical signs				
Abdomen tenderness	19 (8)	5 (10)	20 (6)	57 (3)
Skin findings[a]	53 (23)	9 (19)	38 (11)	176 (9)

Note: Data are reported as median (IQR) or *n* (%).

[a]Positive skin findings include tender abdomen, skin ulcer presence, or any other skin findings.

association between clinician suspicion and severity of illness. This can also be observed in Table 2, where the persistent missed diagnosis demonstrated a very low mortality rate. After controlling for confounding, an early missed diagnosis of sepsis was not significantly associated with inpatient mortality (as illustrated by point estimates of the risk ratio approaching 1 at all levels of VAS and all 95% CIs of the point estimates crossing 1 [Figure 4]). Sensitivity analyses of implicit sepsis did not substantively affect the findings (Figure S12). Of note, while a missed diagnosis was no longer protective in the adjusted analysis, neither was it associated with increased mortality. In other words, in this analysis and contrary to our study hypothesis, the risk of death was disproportionately attributable to severity of illness rather than an early or persistent missed diagnosis.

DISCUSSION

In this prospective, observational study of nearly 2500 physician–patient encounters involving undifferentiated, critically ill, medical patients triaged to our ED's high-acuity area, we examined the

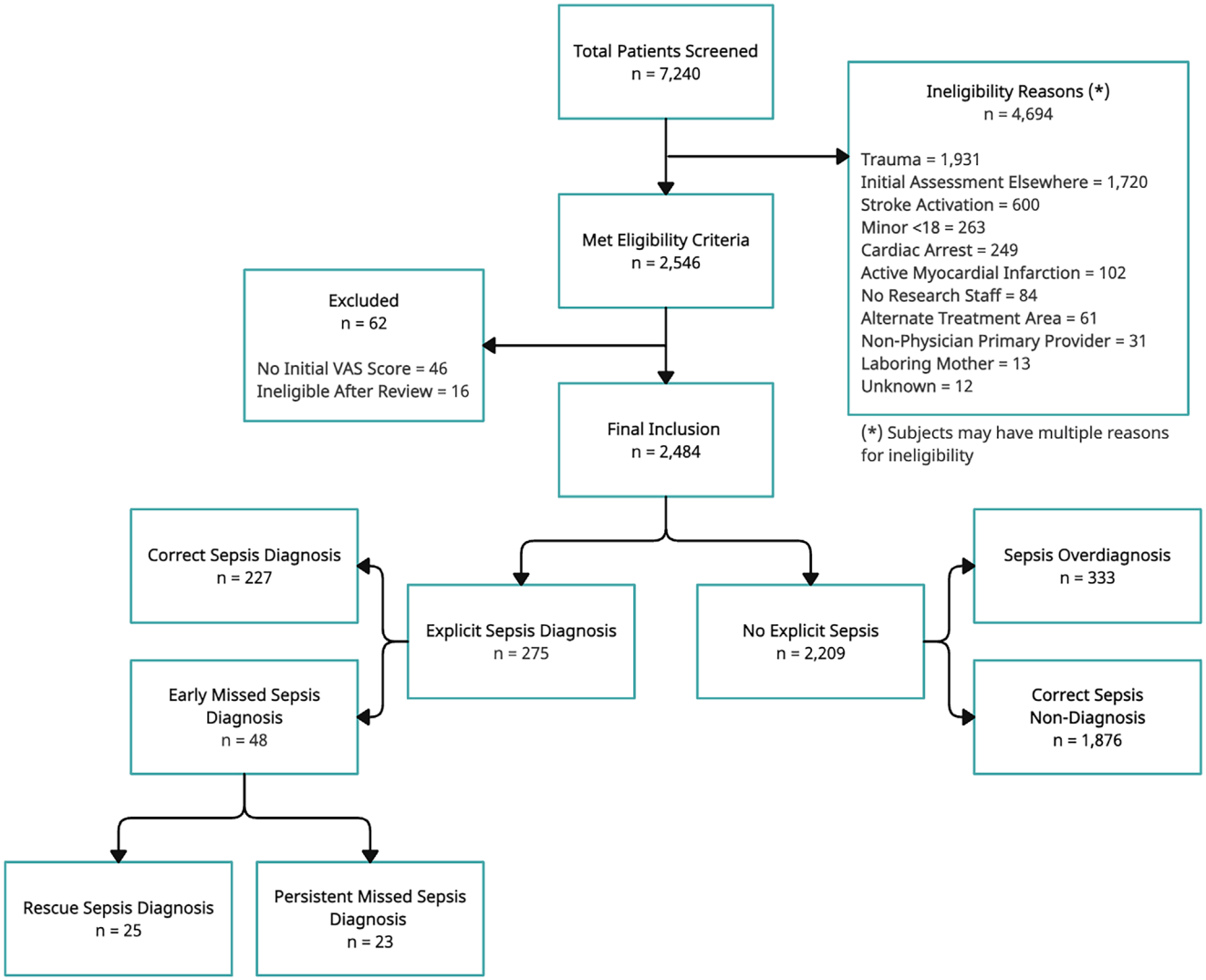

FIGURE 1 Study flow diagram illustrating the flow of participants into this observational research study.

real-time diagnostic accuracy of early physician gestalt and diagnostic decision making. We hypothesized certain subgroups would be more likely to suffer from a missed diagnosis. Contrary to our initial hypothesis, we found relatively stable sensitivity and rates of missed diagnoses across all studied subgroups, though we did observe several cohorts that were more likely to be over- rather than underdiagnosed with sepsis. We do not advocate for decreased vigor in pursuing a sepsis diagnosis in these groups, however, as they tend to also represent the groups most likely to exhibit poor outcomes if a sepsis diagnosis is missed. As such, we instead would caution clinicians to try to avoid early diagnostic closure when arriving as a diagnosis of sepsis, particularly in groups like the elderly or those with abnormal vital signs, as we found these groups were the most likely to have a nonsepsis diagnosis on hospital discharge.

We did, however, identify certain characteristics associated with a missed diagnosis of sepsis, namely, higher white blood counts, bands, lactate, and abnormal urinalysis. We interpret these results to indicate that this might be a point of intervention both for individual clinicians and for systems looking to avoid missed sepsis diagnoses. Based on these findings, we would suggest that missed diagnoses may be decreased by prioritization of (a) obtaining these tests as early in the treatment course as feasible and (b) developing methods to alert clinicians as to their results so they are not missed. We also describe, for the first time we are aware, the phenomenon of a "rescue diagnosis" where an initially faulty clinical impression changes from incorrect to correct and demonstrate the clinical findings associated with this change (Table 2). We observe that persistently missed diagnoses tended to have less abnormal lab abnormalities compared to rescue diagnoses, consistent with prior observations regarding the complexity of "vague" presentations, suggesting in some cases that earlier lab values or alerts may be less helpful in preventing missed diagnoses.[38]

We finally examined the association of a missed diagnosis with both clinical actions (administration of IV antibiotics) and outcomes (mortality). Interestingly, while we found that missed diagnoses were associated with delays in antibiotics, contrary to our study

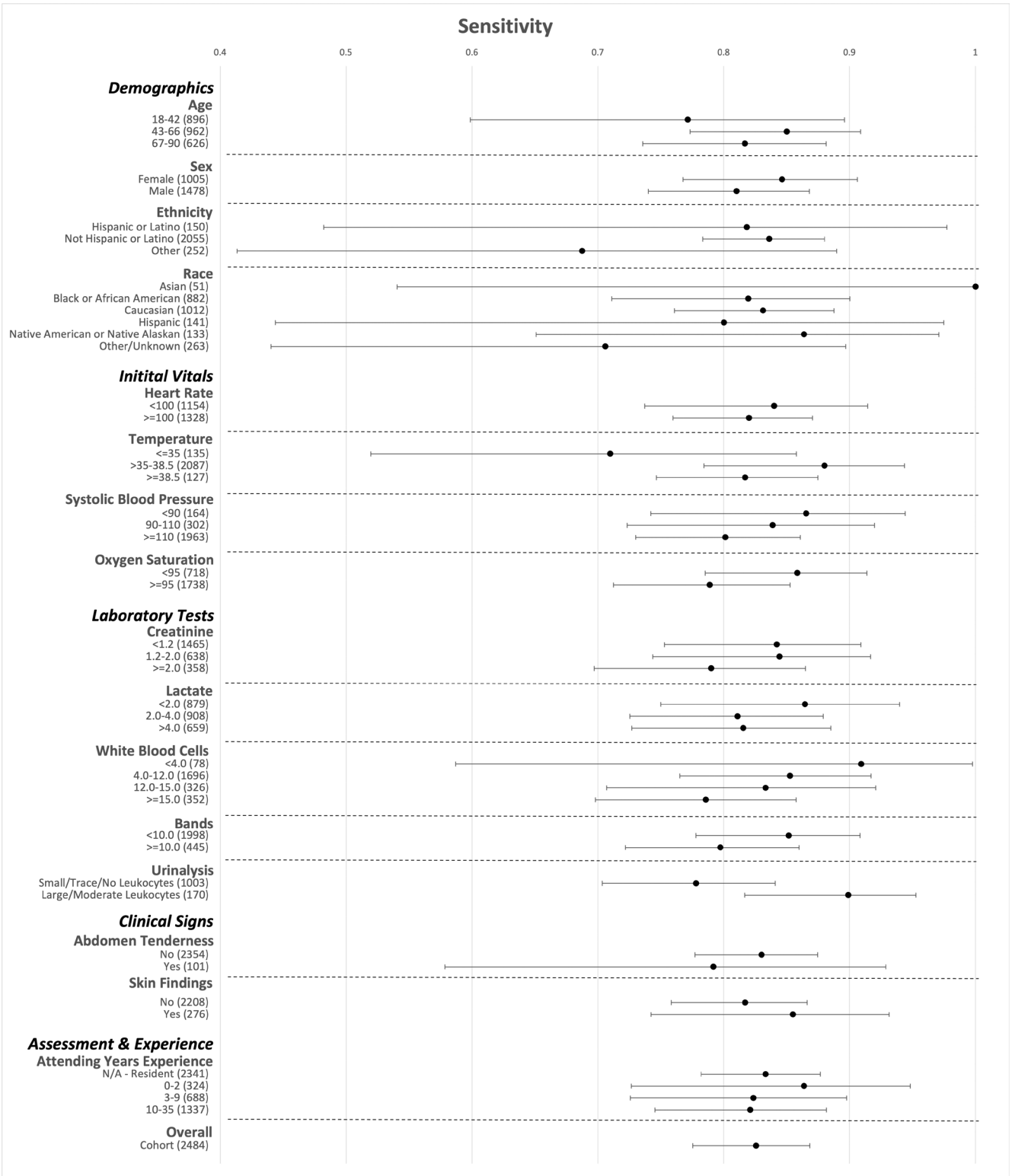

FIGURE 2 Forest plot of the sensitivity of a VAS of 50 (more likely than not) to identify explicit sepsis <15 min from ED arrival within variously defined a priori clinically relevant subgroups. VAS, visual analog scale.

hypothesis these patients did not exhibit higher mortality even after controlling for the observation that missed patients tended to have a lower severity of illness. We interpret these findings to suggest that the major driver of persistently missed diagnosis tends to be diagnostic ambiguity, likely due to a lower severity of illness. These data suggest that, at least in this single-center experience, institutional sepsis mortality is unlikely to be markedly affected by focusing on early missed sepsis diagnosis.

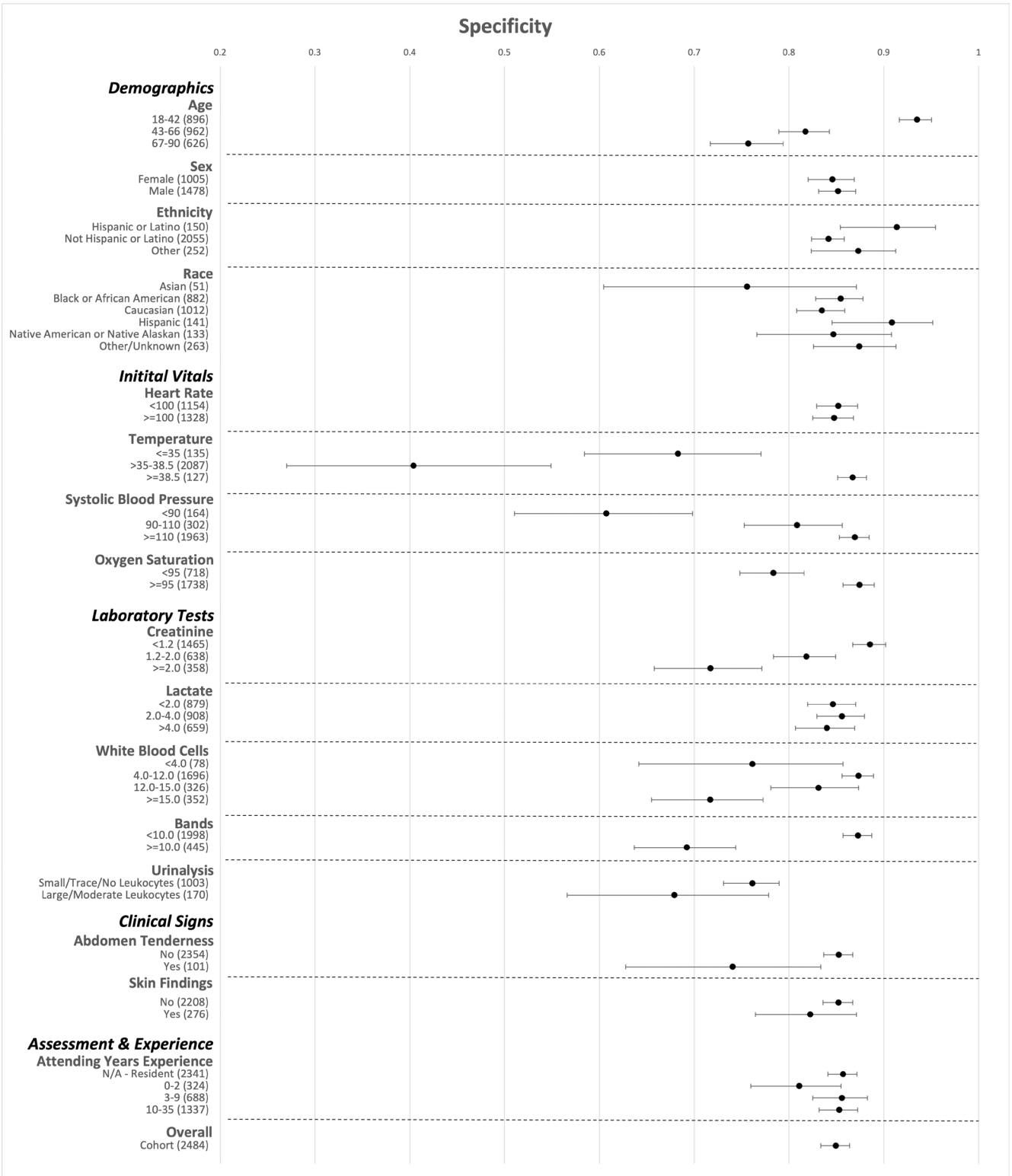

FIGURE 3 Forest plot of the specificity of a VAS of 50 (more likely than not) to identify explicit sepsis <15 min from ED arrival within variously defined a priori clinically relevant subgroups. VAS, visual analog scale.

As mentioned previously, we did not identify any subgroups where clinicians are more likely to miss sepsis. It is worth addressing in light of this observation that racial disparities in sepsis outcomes are well documented,[6,39] and given the time sensitivity of treatment, it might be hypothesized these disparities are driven by diagnostic errors. Like any diagnostic approach based on limited data, early sepsis diagnosis is vulnerable to racial and gender bias[6,7] and may be further exacerbated by task switching.[40] While not a specific focus of our study,

TABLE 2 Characteristics of explicit sepsis patients by diagnosis status.

	Early correct diagnosis (initial VAS score ≥50), *n* = 227	Rescue diagnosis (initial VAS score <50, VAS score at 60 min ≥50), *n* = 25	Persistent missed diagnosis (initial and 60-min VAS score <50), *n* = 23
Initial VAS score	85 (73–100)	24 (16–47)	24 (4–37)
VAS at 60 min	100 (78–100)	82 (65–100)	23 (9–33)
Change in VAS	0 (0–9)	63 (37–72)	0 (−7.5–2.5)
Laboratory tests			
Creatinine	1.5 (1.0–2.4)	1.9 (1.2–3.1)	1.5 (1.0–3.0)
Lactate	3.3 (2.1–5.3)	3.3 (1.9–5.5)	3.7 (2.8–4.9)
% resulted at 15 min	18	36	35
% resulted at 60 min	93	96	100
White blood cells	13.1 (9.2–17.6)	18.9 (11.3–24.6)	13.0 (10.9–17.1)
Bands	10.1 (6.4–15.0)	14.8 (8.5–20.8)	11.0 (6.5–14.8)
% resulted at 15 min	7	8	4
% resulted at 60 min	47	40	48
Urinalysis			
Large/moderate leukocytes	80 (35)	7 (28)	2 (9)
Small/trace/none	119 (52)	17 (68)	17 (74)
% resulted at 15 min	0	0	0
% resulted at 60 min	37	20	17
Antibiotic administration			
Antibiotics within 60 min	164 (72)	19 (76)	12 (52)
Antibiotics within 3 h	212 (93)	24 (96)	18 (78)
Time to antibiotics (min)	38 (23–58)	42 (26–53)	53 (32–136)
Outcome			
Fluid administration	196 (86)	20 (80)	19 (83)
Fluid volume (mL)	2001 (1500–3020)	2004 (1500–2655)	2000 (1000–2444)
Vasopressor administration	77 (34)	8 (32)	7 (30)
Mortality	40 (18)	5 (20)	2 (9)

Note: Data are reported as median (IQR) or *n* (%).
Abbreviation: VAS, visual analog scale.

test characteristics of gestalt did not differ significantly by sex, race, or ethnicity. These data do not support the hypothesis that differences in early diagnostic accuracy are responsible for observed disparities in sepsis outcomes. While diagnostic accuracy did differ by age, this may be attributable to diagnostic complexity as opposed to age-related bias, though we did not specifically examine this possibility.

Importantly from a methodologic perspective, we examined an alternative outcome of implicit rather than explicit sepsis.[27,41,42] While the primary outcome of explicit sepsis is relevant to emergency physicians and health care administrators as it is utilized by the CMS to identify patients potentially eligible for the SEP-1 core measure now part of value based purchasing, patients with an implicit diagnosis of sepsis may also benefit from early intervention. However, test characteristics were only modestly reduced for implicit sepsis with a similar pattern observed among various subgroups, suggesting that our data are robust regardless of the definition.

Relatedly, while the sepsis-3 (and prior) consensus definitions of sepsis[43–45] require a suspicion of infection, what a "suspicion of sepsis" means has been poorly defined in research contexts, and surrogates such as collecting blood cultures or administration of IV antibiotics have often served as proxies. Our findings actually support this surrogate approach, at least in the case of antibiotics. We believe this observation brings the field one step closer to defining a clinical suspicion of sepsis quantitatively, which may be useful in future work.

Finally, it is worth discussing the association of a missed diagnosis with mortality. In the unadjusted analysis, mortality was positively associated with accurate clinical diagnosis—in other words, a missed diagnosis was protective against death. However, this observation stems from the fact that physicians were more likely to diagnose sepsis in more critically ill patients. After controlling for age, SOFA, and lactate, there was no significant association between early sepsis missed diagnosis and mortality, and

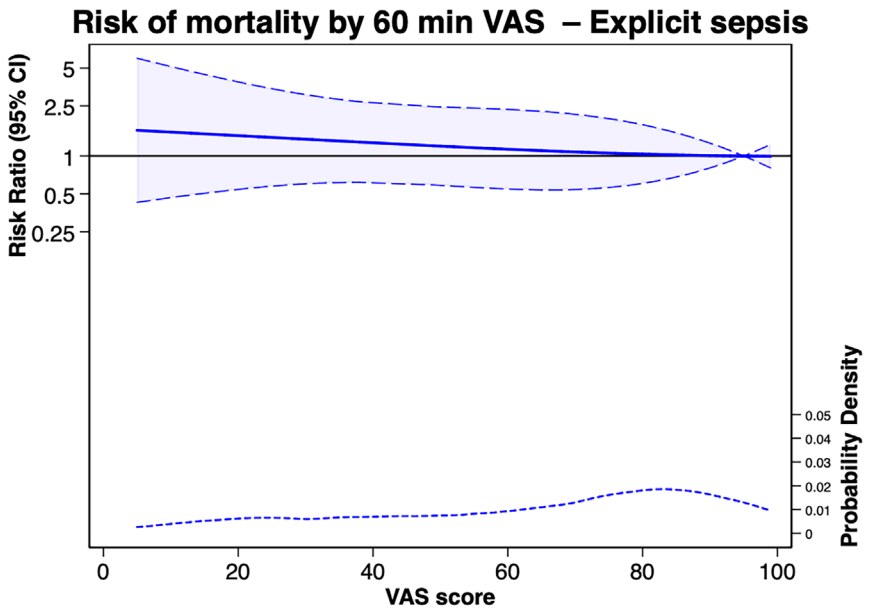

FIGURE 4 Risk ratio for mortality as a function of VAS among patients diagnosed with sepsis after controlling for age, SOFA score, and initial lactate. VAS, visual analog scale.

we observed a nearly linear risk ratio of 1 across the entire range of VAS. This could be interpreted to suggest that delays in antibiotics are more common in less severely ill patients and that a very early (<60 min) accurate diagnosis is less critical and less likely to provide clinical benefit in this cohort. Alternatively, it remains possible that a negative association between diagnosis and outcomes exists, though we were unable to detect it due to sample size. Finally, it remains likely that a missed diagnosis in the first hour does not adversely affect outcomes only in the event that the correct diagnosis is still made in an as yet undefined period of follow-up, which we did not assess. We cannot differentiate these possibilities given our study design, and this remains an area for future investigation.

LIMITATIONS

These findings were generated in a single academic medical center in a resuscitation area with a high physician-to-patient staffing ratio, and the results may not be generalizable to other practice settings or groups. Relatedly, this study observed an 11% prevalence of the primary diagnostic outcome and would be expected to differ in other clinical settings. From a practicality standpoint, and to minimize interruptions in clinical care and potential Hawthorne effects, we only assessed only a single question leading to a point measurement of physician gestalt, and we can only hypothesize regarding the true in situ decision-making process. While we utilized two separate definitions of sepsis in this study, it is conceivable alternative definitions would yield different results. It is also possible that patients excluded due to conditions such as stroke, myocardial infarction, or trauma could have concomitant sepsis as a primary condition, which might influence the prevalence and outcomes observed in this study. While we focused our analysis on a VAS score of 50, it is plausible an alternative cutpoint, such as 10%, which demonstrated very strong rule-out characteristics, would be a better threshold to utilize to quantify diagnosis. This would require a quantification of risk/benefit assessment and other approaches that remain outside the scope of this study and methodology, however. Finally, as discussed above, given the observed association of gestalt with process but not clinical outcomes, there remain several alternative plausible explanations for why we did not observe an association of very early missed diagnosis with outcomes.

CONCLUSIONS

Depending on the threshold selected, gestalt may serve as an excellent rule-in or rule-out test for sepsis. Misattribution is more common in patients with increased age and severity, but tends toward over rather than underdiagnosis. An early missed diagnosis is associated with longer time to antibiotics but not mortality after controlling for severity of illness.

AUTHOR CONTRIBUTIONS

Drafting of the manuscript: Shivansh R. Pandey, Michael A. Puskarich. Conception and study design: Sarah K.S. Knack, Brian E. Driver, Nathaniel Scott, Michael A. Puskarich. Acquisition of the data: Shivansh R. Pandey, Brian E. Driver, Matthew E. Prekker, Nathaniel Scott, Ellen Maruggi, Olivia Kaus, Walker Tordsen, Michael A. Puskarich. Analysis of the data: Shivansh R. Pandey, Sarah K.S. Knack, Brian E. Driver, Michael A. Puskarich. Interpretation of the data: Shivansh R. Pandey, Sarah K.S. Knack, Brian E. Driver, Matthew E. Prekker, Nathaniel Scott, Sarah J. Ringstrom, Michael A. Puskarich. Critical revisions of the manuscript: all authors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Shivansh R. Pandey https://orcid.org/0009-0005-4987-0351
Sarah K. S. Knack https://orcid.org/0000-0002-4220-0866
Brian E. Driver https://orcid.org/0000-0002-7141-0256
Matthew E. Prekker https://orcid.org/0000-0002-3969-3022
Nathaniel Scott https://orcid.org/0000-0003-0103-4045

REFERENCES

1. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *JAMA*. 2017;318(13):1241-1249.
2. Chan HK, Khose S, Chavez S, Patel B, Wang HE. Updated estimates of sepsis hospitalizations at United States academic medical centers. *J Am Coll Emerg Physicians Open*. 2022;3(4):e12782.
3. Skei NV, Nilsen TIL, Mohus RM, et al. Trends in mortality after a sepsis hospitalization: a nationwide prospective registry study from 2008 to 2021. *Infection*. 2023;51(6):1773-1786.
4. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1552-1562.
5. Liang L, Moore B, Soni A. National Inpatient Hospital Costs: The Most expensive conditions by payer, 2017. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Agency for Healthcare Research and Quality; 2020.
6. DiMeglio M, Dubensky J, Schadt S, Potdar R, Laudanski K. Factors underlying racial disparities in sepsis management. *Healthcare (Basel)*. 2018;6(4):1-12. doi:10.3390/healthcare6040133
7. Madsen TE, Napoli AM. The DISPARITY-II study: delays to antibiotic administration in women with severe sepsis or septic shock. *Acad Emerg Med*. 2014;21(12):1499-1502.
8. Clifford KM, Dy-Boarman EA, Haase KK, Maxvill K, Pass SE, Alvarez CA. Challenges with diagnosing and managing sepsis in older adults. *Expert Rev Anti-Infect Ther*. 2016;14(2):231-241.
9. Duncan CF, Youngstein T, Kirrane MD, Lonsdale DO. Diagnostic challenges in sepsis. *Curr Infect Dis Rep*. 2021;23(12):22.
10. Capp R, Horton CL, Takhar SS, et al. Predictors of patients who present to the emergency department with sepsis and progress to septic shock between 4 and 48 hours of emergency department arrival. *Crit Care Med*. 2015;43(5):983-988.
11. Huang J, Yang JT, Liu JC. The association between mortality and door-to-antibiotic time: a systematic review and meta-analysis. *Postgrad Med J*. 2023;99(1175):1000-1007.
12. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med*. 2017;196(7):856-863.
13. Arulappen AL, Danial M, Ng LW, Teoh JC. The impact of antibiotics administration on mortality for time in sepsis and septic shock patients including possible reasons for delayed administration in Malaysia. *Antibiotics (Basel)*. 2022;11(9):1-8. doi:10.3390/antibiotics11091202
14. Sankar J, Garg M, Ghimire JJ, Sankar MJ, Lodha R, Kabra SK. Delayed administration of antibiotics beyond the first hour of recognition is associated with increased mortality rates in children with sepsis/severe sepsis and septic shock. *J Pediatr*. 2021;233:183-190.
15. Frost R, Newsham H, Parmar S, Gonzalez-Ruiz A. Impact of delayed antimicrobial therapy in septic ITU patients. *Crit Care*. 2010;14(Suppl 2):P20.
16. Graham C, Leung LY, Huang HL, et al. 2300 door-to-antibiotic time on mortality of admitted sepsis patients: systematic review and meta-analysis. *Emerg Med J*. 2023;40(12):865.
17. Keegan J, Wira CR 3rd. Early identification and management of patients with severe sepsis and septic shock in the emergency department. *Emerg Med Clin North Am*. 2014;32(4):759-776.
18. Landry J, Fowler LH. Early identification and management of the septic patient in the emergency department. *Crit Care Nurs Clin North Am*. 2018;30(3):407-414.
19. Gille-Johnson P, Hansson KE, Gårdlund B. Severe sepsis and systemic inflammatory response syndrome in emergency department patients with suspected severe infection. *Scand J Infect Dis*. 2013;45(3):186-193.
20. Stoneking LR, Winkler JP, DeLuca LA, et al. Physician documentation of sepsis syndrome is associated with more aggressive treatment. *West J Emerg Med*. 2015;16(3):401-407.
21. Im Y, Kang D, Ko RE, et al. Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock: a prospective nationwide multicenter cohort study. *Crit Care*. 2022;26(1):19.
22. Barbash IJ, Davis BS, Yabes JG, Seymour CW, Angus DC, Kahn JM. Treatment patterns and clinical outcomes after the introduction of the medicare sepsis performance measure (SEP-1). *Ann Intern Med*. 2021;174(7):927-935.
23. Peach BC, Ng BP. Organizational factors associated with sepsis bundle compliance: a nationwide study. *Health Serv Res*. 2020;55(S1):82-83.
24. Fitzpatrick F, Tarrant C, Hamilton V, Kiernan FM, Jenkins D, Krockow EM. Sepsis and antimicrobial stewardship: two sides of the same coin. *BMJ Qual Saf*. 2019;28(9):758-761.
25. Seok H, Jeon JH, Park DW. Antimicrobial therapy and antimicrobial stewardship in sepsis. *Infect Chemother*. 2020;52(1):19-30.
26. Knack SKS, Scott N, Driver BE, et al. Early physician gestalt versus usual screening tools for the prediction of sepsis in critically ill emergency patients. *Ann Emerg Med*. 2024;84:246-258. doi:10.1016/j.annemergmed.2024.02.009
27. Litell JM, Guirgis F, Driver B, Jones AE, Puskarich MA. Most emergency department patients meeting sepsis criteria are not diagnosed with sepsis at discharge. *Acad Emerg Med*. 2021;28(7):745-752.
28. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
29. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
30. ICD-10-CM/PCS MS-DRGv33 Definitions Manual. Accessed October 21, 2024. https://www.cms.gov/icd10manual/version33-fullcode-cms/fullcode_cms/P0328.html
31. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
32. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017;376(23):2235-2244.
33. Evans L, Rhodes A, Alhazzani W, et al. Executive summary: surviving sepsis campaign: international guidelines for the management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):1974-1982.
34. Wickham H. Reshaping data with the reshape package. *J Stat Softw*. 2007;21:1-20.
35. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag; 2016.

36. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12:1-8.
37. R Core Team. R: A Language and Environment for Statistical Computing. Accessed July 15, 2024. https://www.R-project.org/.
38. Filbin MR, Lynch J, Gillingham TD, et al. Presenting symptoms independently predict mortality in septic shock: importance of a previously unmeasured confounder. *Crit Care Med*. 2018;46(10):1592-1599.
39. Black LP, Hopson C, Puskarich MA, et al. Racial disparities in septic shock mortality: a retrospective cohort study. *Lancet Reg Health Am*. 2024;29:100646.
40. Jin Y, Duan Y, Ding Y, Nagarajan M, Hunte G. The cost of task switching: evidence from emergency departments. https://papers.ssrn.com. Accessed July 15, 2024. doi:10.2139/ssrn.3756677
41. Filbin MR, Arias SA, Camargo CA Jr, Barche A, Pallin DJ. Sepsis visits and antibiotic utilization in U.S. emergency departments*. *Crit Care Med*. 2014;42(3):528-535.
42. Jentzer JC, Lawler PR, Van Houten HK, Yao X, Kashani KB, Dunlay SM. Cardiovascular events among survivors of sepsis hospitalization: a retrospective cohort analysis. *J Am Heart Assoc*. 2023;12(3):e027813.
43. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):775-787.
44. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644-1655.
45. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med*. 2003;31(4):1250-1256.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pandey SR, Knack SKS, Driver BE, et al. Factors and outcomes associated with under- and overdiagnosis of sepsis in the first hour of emergency department care. *Acad Emerg Med*. 2025;32:204-215. doi:10.1111/acem.15074