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# The Presentation, Pace, and Profile of Infection and Sepsis Patients Hospitalized Through the Emergency Department: An Exploratory Analysis

**OBJECTIVES:** To characterize the signs and symptoms of sepsis, compare them with those from simple infection and other emergent conditions and evaluate their association with hospital outcomes.

**DESIGN, SETTING, PARTICIPANTS, AND INTERVENTION:** A multi-center, retrospective cohort study of 408,377 patients hospitalized through the emergency department from 2012 to 2017 with sepsis, suspected infection, heart failure, or stroke. Infected patients were identified based on Sepsis-3 criteria, whereas noninfected patients were identified through diagnosis codes.

**MEASUREMENTS AND MAIN RESULTS:** Signs and symptoms were identified within physician clinical documentation in the first 24 hours of hospitalization using natural language processing. The time of sign and symptom onset prior to presentation was quantified, and sign and symptom prevalence was assessed. Using multivariable logistic regression, the association of each sign and symptom with four outcomes was evaluated: sepsis versus suspected infection diagnosis, hospital mortality, ICU admission, and time of first antibiotics ( $> 3$  vs  $\leq 3$  hr from presentation). A total of 10,825 signs and symptoms were identified in 6,148,348 clinical documentation fragments. The most common symptoms overall were as follows: dyspnea (35.2%), weakness (27.2%), altered mental status (24.3%), pain (23.9%), cough (19.7%), edema (17.8%), nausea (16.9%), hypertension (15.6%), fever (13.9%), and chest pain (12.1%). Compared with predominant signs and symptoms in heart failure and stroke, those present in infection were heterogeneous. Signs and symptoms indicative of neurologic dysfunction, significant respiratory conditions, and hypotension were strongly associated with sepsis diagnosis, hospital mortality, and intensive care. Fever, present in only a minority of patients, was associated with improved mortality (odds ratio, 0.67, 95% CI, 0.64–0.70;  $p < 0.001$ ). For common symptoms, the peak time of symptom onset before sepsis was 2 days, except for altered mental status, which peaked at 1 day prior to presentation.

**CONCLUSIONS:** The clinical presentation of sepsis was heterogeneous and occurred with rapid onset prior to hospital presentation. These findings have important implications for improving public education, clinical treatment, and quality measures of sepsis care.

**KEY WORDS:** electronic health record; infection; mortality; outcomes; sepsis

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Sepsis is a life-threatening syndrome resulting from a dysregulated host response to severe infection (1, 2). Early identification and treatment of infection in sepsis have been shown to improve mortality (3–7). Consequently,

numerous global, national, and local healthcare programs now focus on accelerating the detection and treatment of sepsis (8–12). Particular attention has been paid to improving public education by highlighting signs and symptoms that should prompt patients to seek medical care (9, 13–16).

Despite this focus, little is actually known about the signs and symptoms preceding sepsis (1, 17–27). For example, how common are specific symptoms present at sepsis onset (21)? How long are these symptoms present before presentation (19)? Do symptoms differ between simple infection and sepsis? And, finally, what signs and symptoms are associated with the worst outcomes (17, 18, 20, 25)? Without this knowledge, public education and early detection efforts may be misdirected and hamper the identification of infected patients at the highest risk of adverse outcomes.

We undertook this study to identify the most common signs and symptoms present in sepsis and suspected infection patients hospitalized from the emergency department (ED). Comparing these signs and symptoms against those of heart failure and stroke patients, we also identified those which were most strongly associated with adverse hospital outcomes. Finally, we quantified symptom duration prior to presentation to understand the pace of prehospital progression from simple to severe infection.

## METHODS

This study was approved by the Kaiser Permanente Northern California (KPNC) Institutional Review Board (number 1432052).

Using electronic health record data, we identified all adult patients (age  $\geq 18$  yr) presenting to the ED and subsequently admitted to one of 21 hospitals within the KPNC integrated healthcare delivery system with sepsis or suspected infection between January 1, 2012, and December 31, 2017. We included only hospitalizations that started at a KPNC hospital, included at least one overnight stay, and were not for labor and delivery (28, 29). We identified sepsis and suspected infection patients using Sepsis-3 international consensus definitions based on the timed dyad criteria of receiving antibiotics and cultures to establish “suspected infection” (1). Among these suspected infection patients, we further identified the mutually exclusive subset of sepsis patients if they had a Sequential Organ Failure Assessment (SOFA) score of greater than or equal to 2 (without consideration

for prehospital SOFA score values indicative of preexisting organ dysfunction) (2, 30). We also identified two comparison cohorts: ED patients admitted with heart failure and stroke who did not meet suspected infection criteria (**Supplement Table 1**, Supplementary Digital Content 1, <http://links.lww.com/CCX/A506>).

We sought to extract patients’ signs and symptoms as recorded in physician clinical documentation captured within the first 24 hours of hospitalization, inclusive of their time in the ED. We focused on four clinical note types (“History and Physical,” “ED Provider,” “ED Progress,” and “Consult History and Physical”) and extracted unstructured text following five note header types (“History of Present Illness,” “Patient Presents With,” “HPI,” “HPI Comments,” and Summary”). We used existing signs and symptoms ontologies generated by Systematized Nomenclature of Medicine and National Cancer Institute to identify relevant terms, based on their implementation within the I2E natural language processing software (Linguamatics I2E 5.4.1R13, Cambridge, UK) (31–36). We iteratively developed documentation queries to account for symptom negation and common text patterns like comma-separated lists. We retained terms from these existing ontologies that may not be commonly thought of as signs and symptoms (e.g., sepsis, liver failure, respiratory failure) because our data were derived from clinician notes (in which signs and symptoms are often aggregated using clinical terminology) rather than directly from patient report. We included hospitalizations in which any signs and symptoms were identified (97.8% of all 417,477 potential hospitalizations).

We grouped the top 1,000 most frequent signs and symptoms terms into 439 distinct groups based on similarity. For example, “dyspnea” included the terms “shortness of breath,” “dyspnea,” “labored breathing,” and “winded.” Similarly, “peripheral edema” included “edema limbs,” “peripheral edema,” “edema of foot,” and “pedal edema.” We quantified the proportion of patients in the four cohorts exhibiting each sign and symptom and identified the most frequent overall signs and symptoms by taking the average prevalence across all four cohorts. We also used I2E queries to establish the time of symptom onset prior to ED arrival, truncating pre-ED onset at 7 days for those with longer intervals (e.g., dyspnea starting 2 wk ago). To compare the acuity of sign and symptom onset, we categorized the onset of symptoms as having occurred in

less than 7 days (acute) versus greater than or equal to 7 days (subacute), with day 0 indicating the date of ED presentation. Pre-ED days of symptom onset data were identified in a subset of all hospitalizations with symptom data available ( $n = 106,416$ ; 26.1%).

We characterized patients' baseline hospitalization characteristics, including measures of acute severity of illness (Laboratory and Physiology Score, Version 2) and chronic comorbid disease burden (Comorbidity Point Score, Version 2) (28, 29, 37). We identified key inpatient adverse outcomes (hospital mortality, the need for ICU admission during hospitalization) to assess their association with specific signs and symptoms (38, 39). We also quantified the time to first antibiotic (grouped as  $\leq$  or  $>3$  hr after ED presentation) as a common sepsis process measure (3, 40). We used multivariable logistic regression to estimate the association between the presence of each symptom and each

outcome, adjusting for the presence or absence of all other signs and symptoms at a hospitalization level.

Data are presented as mean (SD), median (interquartile range), or number (percent). To adjust for multiple comparisons, we considered a  $p$  value less than or equal to 0.001 significant. Adjusted odds ratios (ORs) are also reported with 95% CIs. We used STATA/SE 14.2 (STATA Corp, Cary, NC) and RStudio 1.2.5 (Boston, MA) for statistical analyses.

## RESULTS

### Baseline Cohort Characteristics

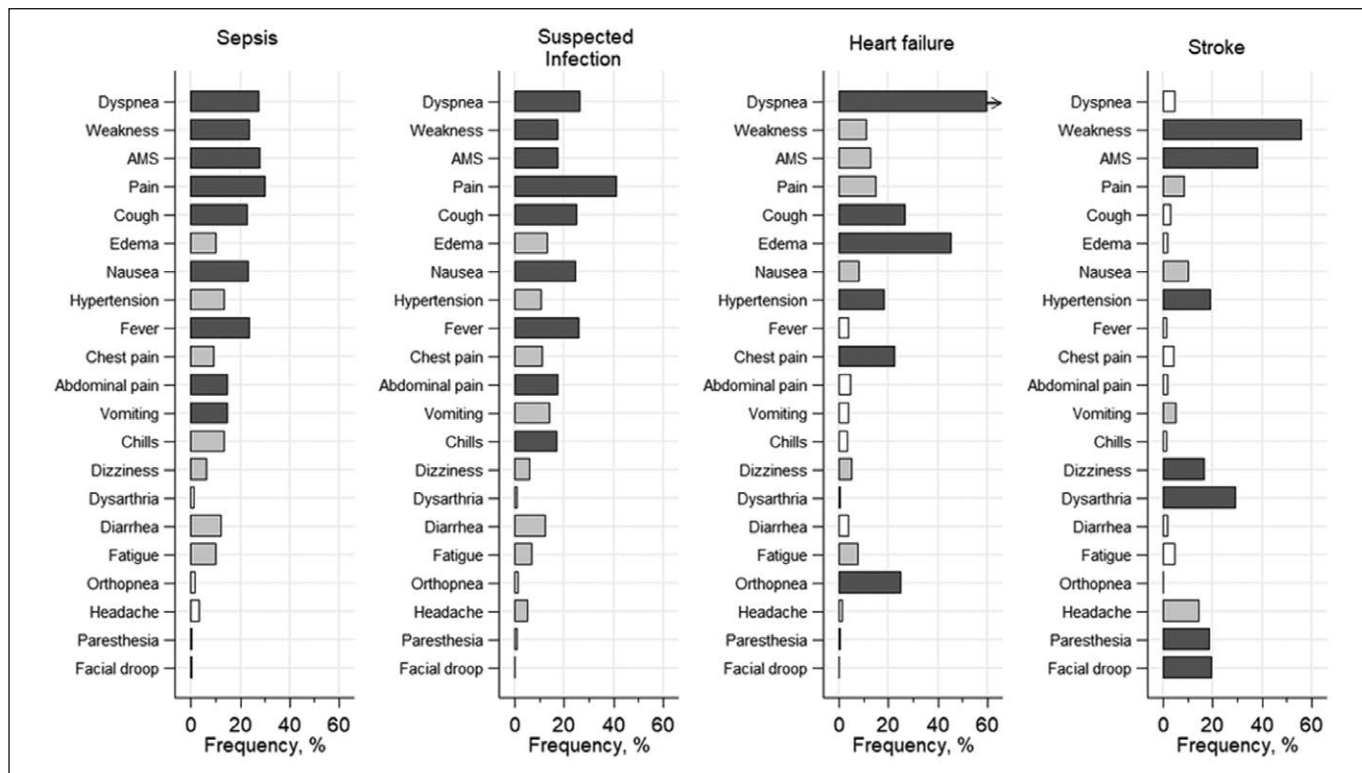
Our study included 408,367 patients admitted from the ED with any sign and symptom identified in physician documentation. Overall, 166,953 (40.9%) had suspected infection, whereas 198,016 (48.5%) had sepsis. We also identified 24,318 patients (6.0%) with

**TABLE 1.**

### Baseline Characteristics of Sepsis, Suspected Infection, Heart Failure, and Stroke Patients Admitted to the Hospital From the Emergency Department

Characteristics	Overall	Sepsis	Suspected Infection	Heart Failure	Stroke
<i>n</i>	408,367	198,016	166,953	24,318	19,080
Age, yr	69 (17)	71 (16)	65 (19)	74 (14)	72 (14)
Male	192,916 (47.2)	101,218 (51.1)	68,832 (41.2)	13,197 (54.3)	9,669 (50.7)
Acute severity of illness (Laboratory and Acute Physiology Score, Version 2)	83 (39)	100 (39)	67 (31)	83 (28)	56 (29)
Comorbid disease burden (Comorbidity Point Score, Version 2)	60 (53)	70 (56)	49 (48)	77 (50)	35 (35)
First hospital unit					
Ward	316,944 (77.6)	139,069 (70.2)	143,678 (86.1)	20,237 (83.2)	13,960 (73.2)
ICU	49,008 (12.0)	37,450 (18.9)	7,122 (4.3)	1,253 (5.2)	3,183 (16.7)
Stepdown	28,134 (6.9)	15,158 (7.7)	8,325 (5.0)	2,793 (11.5)	1,858 (9.7)
Length of stay, d, median (interquartile range)	3.0 (1.8–5.3)	3.7 (2.2–6.5)	2.7 (1.7–4.5)	2.6 (1.7–4.1)	1.9 (1.1–3.8)
Hospital mortality	20,169 (4.9)	16,864 (8.5)	2,195 (1.3)	561 (2.3)	549 (2.9)
Time to first antibiotic after emergency department entry, hr, median (interquartile range)	–	3.2 (1.8–6.9)	3.3 (1.9–6.4)	–	–

Values represent either number (%) or mean (SD), except for length of stay (which is median). Time to antibiotic is not relevant for overall, heart failure, and stroke, as indicated by dashes.



**Figure 1.** Frequency of the top 30 most common presenting signs and symptoms among patients hospitalized from the emergency department stratified by cohort: sepsis (*left*), suspected infection (*left center*), heart failure (*right center*), and stroke (*right*). Bars are colored by the symptom frequency in the cohort, grouped as: greater than 15% (*dark gray*), 5–15% (*light gray*), and less than 5% (*white*). Dyspnea was present in 81.4% of heart failure patients (*rightward arrow*). Sepsis and suspected infection were defined based on Sepsis-3 specifications. AMS = altered mental status

heart failure and 19,080 (4.7%) with stroke who did not meet suspected infection criteria. **Table 1** displays the baseline characteristics of infected and noninfected patients in our study. Sepsis patients had the highest severity of illness and hospital mortality (8.5%). Sepsis and stroke patients were most frequently directly admitted from the ED to the ICU (18.9% and 16.7%, respectively).

### Signs and Symptoms Between Infected and Noninfected Patients

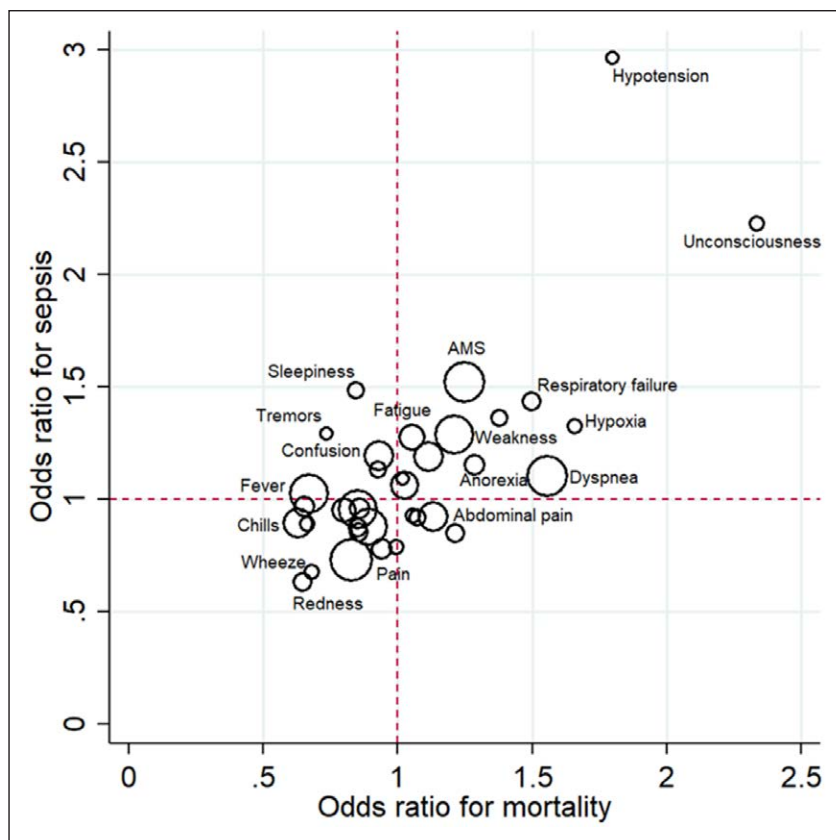
In total, we evaluated 6,148,348 clinical documentation fragments using natural language processing, identifying a total of 10,825 unique nonnegated signs and symptoms. The median number of unique signs or symptoms per hospitalization was 5 (interquartile range, 3–7). Based on the average prevalence across all four cohorts, the most common at ED presentation were as follows: dyspnea (35.2%), weakness (27.2%), altered mental status (24.3%), pain (23.9%), cough (19.7%), edema (17.8%), nausea (16.9%), hypertension (15.6%), fever (13.9%),

and chest pain (12.1%). However, symptom frequency varied considerably among the four cohorts (**Fig. 1**).

Among patients without infection, a few signs and symptoms were highly prevalent. In heart failure, these were dyspnea (81.4%), edema (45.5%), cough (26.8%), orthopnea (25.3%), and chest pain (22.9%). Among stroke patients, they were weakness (56.1%), altered mental status (38.5%), dysarthria (29.4%), facial droop (19.6%), and hypertension (19.2%). In contrast, few signs and symptoms among infected patients were highly prevalent, and many showed similar distribution between sepsis and suspected infection (**Fig. 1**). Overall, the most common in infected patients were pain (35.3%), dyspnea (27.3%), fever (24.9%), cough (24.3%), and nausea (24.3%).

**Figure 2** and **Supplemental Table 2** (Supplementary Digital Content 1, <http://links.lww.com/CCX/A506>) display common signs and symptoms (present in ≥ 3% of infection patients) that were most strongly associated with increased odds of meeting sepsis, rather than only suspected infection, criteria. Those associated with sepsis were indicative to neurologic dysfunction (unconsciousness, altered mental status, weakness,





**Figure 2.** Bubble plot of adjusted odds ratios for sepsis versus suspected infection (y-axis) and hospital mortality (x-axis) among common signs and symptoms (sepsis frequency  $\geq 3\%$ ) in infected patients. *Bubble size* is indicative of frequency, ranging from tremor and hypotension (3.0%) to pain (30.2%). Only symptoms with a  $p \leq 0.001$  for at least one outcome are included. *Red dashed lines* indicate odds ratios of 1 for both axes. AMS = altered mental status.

sleepiness, tremors, confusion); significant respiratory disease (respiratory failure, hypoxia, dyspnea); and hypotension. Signs and symptoms associated with decreased odds of sepsis included milder respiratory symptoms (viral upper respiratory tract infection symptoms, cough, sputum production); certain types of pain (generalized, abdominal, chest); and skin changes (wound, redness).

### Sepsis Symptoms Associated With Adverse Outcomes

Many signs and symptoms associated with greater odds of sepsis were also associated with increased hospital mortality (Fig. 2) (**Supplemental Table 3**, **Supplementary Digital Content 1**, <http://links.lww.com/CCX/A506>). These included unconsciousness (adjusted OR, 2.33, 95% CI, 2.18–2.50), hypotension (1.80; 1.67–1.94), hypoxia (1.66; 1.55–1.77), dyspnea (1.56; 1.50–1.62), respiratory failure (1.50;

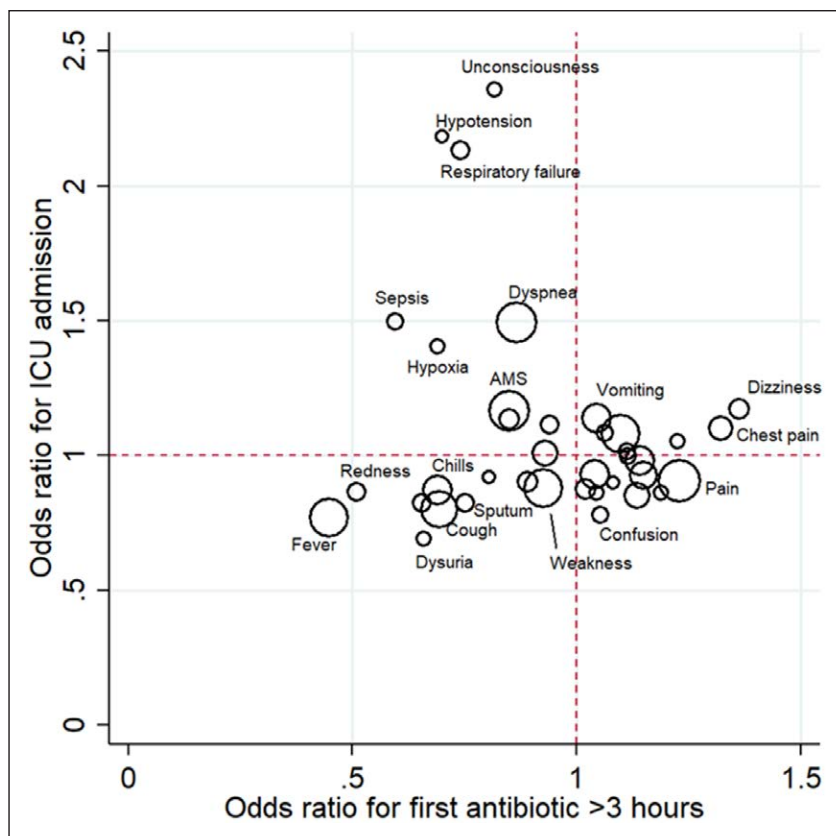
1.41–1.59), sepsis (1.38; 1.29–1.48), and altered mental status (1.25, 1.20–1.30). Similar types of symptoms associated with increased mortality, although less common ( $< 3\%$  prevalence) included the following: cardiovascular collapse (cardiac arrest, shock); altered mentation (gurgling); liver disease (liver failure, jaundice); and significant respiratory disease (pneumothorax, hemoptysis). Signs and symptoms associated with the lowest odds of hospital mortality included urinary symptoms (pyelonephritis, hesitancy, kidney stone, frequency) as well as some localized forms of pain (wrist, eye, pleuritic).

**Figure 3** and **Supplemental Table 3** (**Supplementary Digital Content 1**, <http://links.lww.com/CCX/A506>) display adjusted odds ratios for each common sepsis sign and symptom with ICU admission and first antibiotics given more than 3 hours after presentation. Many symptoms associated with increased sepsis diagnosis and mortality were also associated with increased ICU admission. Fever, identified in clinical documentation among 23.9% of sepsis

patients, was associated with decreased odds of mortality (adjusted OR, 0.67; 95% CI, 0.64–0.70;  $p < 0.001$ ) as were chills (13.9% of patients; 0.63; 0.59–0.67;  $p < 0.001$ ). Fever, based on the first temperature recording in the ED, rather than on clinical documentation, was present in 14.9% of sepsis patients (when defined as  $\geq 100.4^\circ\text{F}$ ) and 29.2% of sepsis patients (defined as  $> 99.0^\circ\text{F}$ ). Fever and chills were both associated with receiving earlier antibiotics, as were other symptoms more clearly indicative of infection (e.g., redness, cough, sputum production, dysuria). Common symptoms associated with later antibiotics included dizziness (1.36; 1.31–1.42), chest pain (1.32; 1.28–1.37), generalized pain (1.23; 1.20–1.26), headache (1.22; 1.16–1.29), and constipation (1.19; 1.13–1.25).

### Duration of Symptoms

In sepsis, the mean time of sign and symptom onset prior to hospitalization was  $4.1 \pm 1.8$  days; however,



**Figure 3.** Bubble plots of adjusted odds ratios for ICU admission ( $y$ -axis) and time to first antibiotic greater than 3 hr ( $x$ -axis) in sepsis for common signs and symptoms (sepsis frequency  $\geq 3\%$ ). *Bubble* size is indicative of frequency, ranging from hypotension (2.9%) to pain (30.3%). Only symptoms with a  $p \leq 0.001$  for at least one outcome are included. *Red dashed lines* indicate odds ratios of 1 for both axes. AMS = altered mental status.

onset time showed a bimodal distribution. For example, a substantial proportion of patients presenting with pain, dyspnea, weakness, cough, and hypertension reported a subacute onset (Fig. 4). In contrast, symptoms with a higher proportion of patients reporting acute onset ( $< 7$  d) included altered mental status (82.8%), fever (85.3%), nausea (84.4%), vomiting (86.8%), and chills (85.8%). Among the top 12 most frequent symptoms, acute symptom onset peaked at 2 days prior to ED presentation, except for altered mental status which peaked at 1 day.

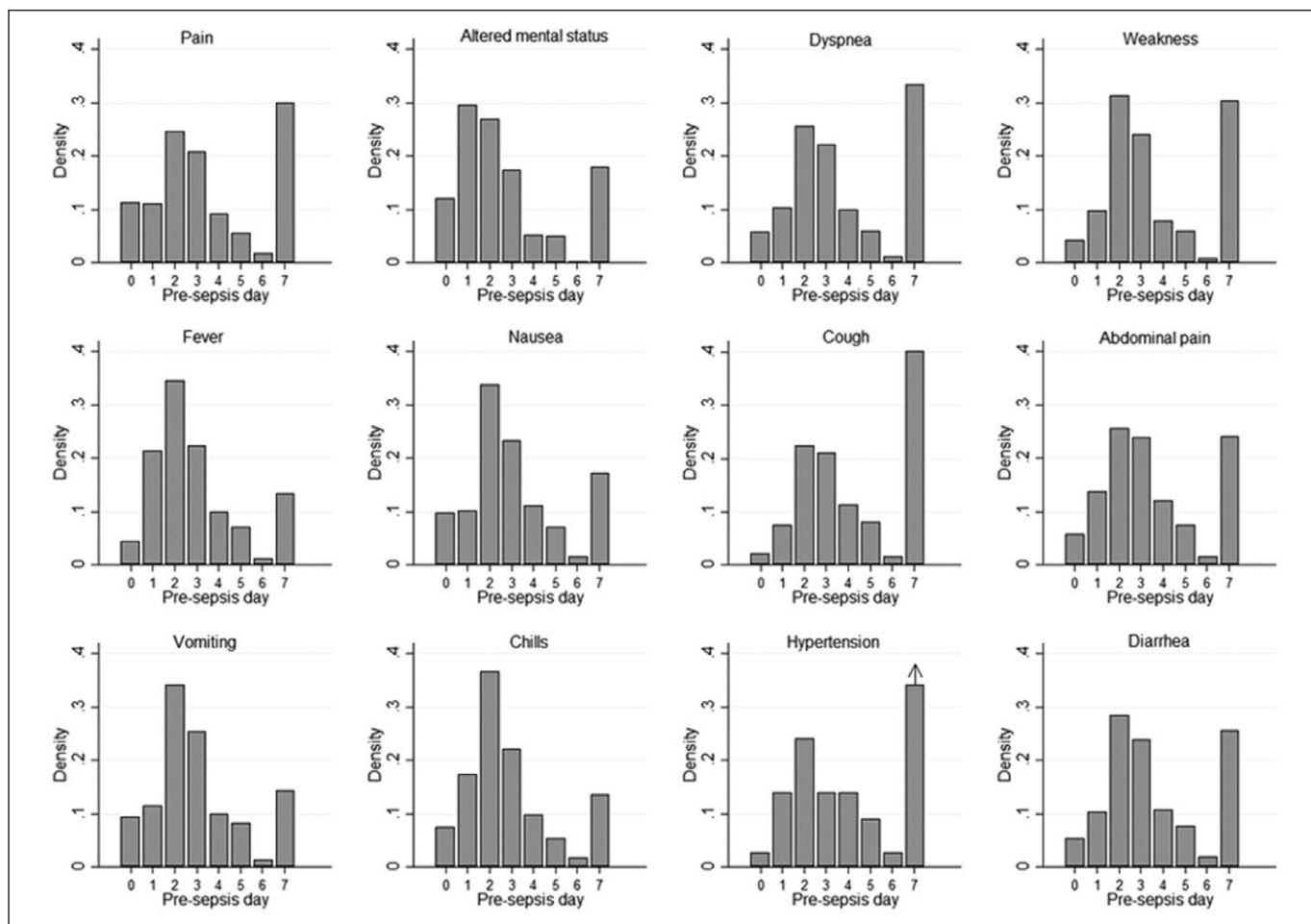
## DISCUSSION

Sepsis is the single most expensive cause of hospitalization in the United States and contributes to one in every two to three hospital deaths (41, 42). It contributes to as many as 11 million deaths worldwide each year (10, 43). Despite this staggering impact, the profile of sepsis presentation—its associated signs, symptoms,

and pace of onset—remains poorly characterized (1, 17–26). Uncertainty about the presentation of sepsis negatively impacts efforts to improve public awareness, clinical treatment pathways, and population health (26, 27, 44, 45). In this exploratory study, we therefore evaluated a large, contemporary sample of patients hospitalized through the ED to characterize the presentation of sepsis. Our findings have several important implications for sepsis identification and treatment.

First, our data highlight the often described, but poorly characterized, challenge of identifying and treating sepsis patients because of heterogeneity in clinical presentation (40, 46). Compared with heart failure and stroke, which showed similarly predominant symptoms between patients, infectious patients presented with symptoms were diverse and nonspecific. Our data confirm that symptoms not typically considered strongly indicative of infection were actually some of the most prevalent symptoms in sepsis: pain, altered mental status, and weakness. Common symptoms in sepsis also overlapped with predominant symptoms in other conditions like heart failure and stroke. For example, dyspnea, present in 81.4% of heart failure patients, and cough were also common in infection as was weakness, present in 56.1% of stroke patients.

The heterogeneity of sepsis presentation also impacted the timing of clinical treatments. Despite being the most common symptom present in sepsis patients, pain was associated with significantly later antibiotic administration. On the other hand, traditional symptoms indicative of infection like fevers, chills, respiratory symptoms, and redness were associated with earlier antibiotics as well as lower hospital mortality. Prior smaller studies have found that diffuse, nonspecific symptoms in sepsis are associated with decreased recognition of sepsis as well as later treatment with antibiotics (17, 21). In some cases, these symptoms were also associated with worsened outcomes which could have resulted from poor early identification of sepsis (17).



**Figure 4.** Histogram of reported time of symptom onset prior to sepsis presentation for the top 12 most common signs and symptoms in sepsis. Time of symptom onset is defined as acute ( $< 7$  d) or subacute ( $\geq 7$  d, truncated at 7 d), with day 0 representing the day of emergency department (ED) presentation. The frequency of subacute hypertension was 78.3%. The peak duration of acute symptom onset was 2 d for all symptoms, except altered mental status which had peak symptoms onset of 1 d before ED presentation.

The incongruity between the diversity of symptoms actually present in sepsis and current guidelines for sepsis definition and treatment highlight significant gaps (27). Although the Sepsis-3 international consensus definitions note that sepsis can present with “a constellation of clinical signs and symptoms” that make “diagnosis difficult, even for experienced clinicians,” no specific recommendations guide clinicians’ early sepsis recognition prior to initiating actions like ordering cultures or administering antibiotics (1). Current publicly reported metrics like the Center for Medicare and Medicaid Services SEP-1 program also fail to account for the clear impact that heterogeneity in clinical presentation has on timed quality metrics of treatment (11). The Surviving Sepsis Guidelines enumerate a broader range of diagnostic criteria that moderately improve the concordance between what is publicized and what is actually prevalent in sepsis (8).

Thus, our data provide a novel findings that can help drive improved sepsis recognition by highlighting the common, but underrecognized, symptoms seen in sepsis (pain, neurologic, and abdominal symptoms). Sepsis quality metrics should also consider the impact that heterogeneous patient presentation has on what is currently a single rigid approach to quantifying guideline-adherent care. Finally, the diversity seen in sepsis presentation continues to reinforce the need for objective biomarker criteria for sepsis that can identify and risk-stratify patients with life-threatening disease, even when a clinical diagnosis of sepsis remains uncertain (46).

Second, the heterogeneity of sepsis’ clinical presentation also makes public education challenging. Early identification and treatment of sepsis is key to improving outcomes; however, public awareness of sepsis has been poor, resulting in delays in care (14–16). Public

awareness programs like The Sepsis Alliance's "It's About TIME" campaign focus on improving symptom recognition (47). The TIME acronym highlights Temperature, Infectious symptoms, Mental decline, and feelings of being Extremely ill (severe pain or discomfort). Similar symptoms are represented in Center for Disease Control and Prevention sepsis materials (48). However, numerous online medical resources continue to incorrectly educate patients that sepsis represents "blood poisoning," which could mislead patients seeking to identify worrisome symptoms (27).

Our data strongly support the public education campaign use of mental decline symptoms as a potent risk factor for poor hospital outcomes and one which displayed the shortest time of onset prior to ED presentation. However, in what may be surprising for patients, abnormal temperature was present in only a minority of patients. And, in this case, both fevers and chills associated with lower hospital mortality and ICU admission (8, 17, 18, 21, 49). Thus, careful attention should be paid to how fevers and chills, as well as other symptoms typically thought of as indicative of infection, are communicated in educating the public about sepsis.

Our data also support including significant respiratory symptoms like dyspnea in public education campaigns for sepsis because they were common, and they were strongly associated with increased odds of sepsis, mortality, and ICU admission. Beyond neurologic and respiratory dysfunction, less common symptom groups, including cardiovascular collapse and liver disease, were also strongly associated with adverse outcomes and could improve early recognition by the public. Overall, these findings align well with the three-criteria quick SOFA score, which identify high-risk sepsis inpatients based on hypotension, respiratory failure, and altered mentation (2).

Finally, our data reveal a narrow presepsis time window during which infectious symptoms present and progress toward sepsis. For those with acute symptoms, the peak period of reported symptom onset was between 2 and 3 days prior to ED presentation (22, 26). Given that sepsis represents a progression from a simpler, localized infection into a systemic, life-threatening severe infection, identifying high-risk symptom profiles could offer an opportunity to predict sepsis onset and provide presepsis screening or treatment. As many as 50% of sepsis patients are seen by physicians in the 7 days leading up to hospitalization, with increases

in infectious diagnosis and antibiotic use over that period (50). Together, these findings highlight potential opportunities to mitigate the progression from simple infection into sepsis even before hospital presentation. What is not known, however, is true denominator of patient with similar symptoms who never progress on to sepsis admission.

The major strength of this study is its use of detailed clinical documentation in a large, multicenter population to empirically identify the signs and symptoms present in sepsis and infection and compare them with those in other common conditions. By further evaluating the association between these signs and symptoms and outcomes, this study provides a unique data-driven approach to highlight opportunities to improve public and clinician awareness of sepsis.

The major limitation of the study arises from potential limitations in using natural language processing and existing ontologies which could be vulnerable to mislabeled or miscoded data. Although the natural language processing (NLP) software we used has been widely applied to diverse types of clinical and medical text, our NLP approach was iterative and lacks an overall validation metric in the current study. Thus, further validation of our findings is needed. However, in the example of fever, we found strong concordance between the frequency of reported symptoms and actual temperature readings. Outside of temperature, our findings were also largely consistent with data reported in prior studies of smaller scale (17, 19, 21–26). We also identified certain terms that may not be considered traditional signs and symptoms (e.g., sepsis, liver failure, respiratory failure, pneumothorax) because we used clinician notes rather than patient report. In addition, our approach fails to account for the subjectivity present in clinical decision making and documentation, particularly in the ED. Finally, these data were also drawn from a single integrated healthcare delivery system from the United States which could impact generalizability of our findings, particularly when compared with low- and middle-income settings (12).

## CONCLUSIONS

In conclusion, using clinical documentation from a large, multicenter cohort of patients hospitalized through the ED, we identified key signs and symptoms in infection and sepsis and quantified their association



with adverse hospital outcomes. Our data provide unique insights about patients' clinical presentation that can inform public health campaigns, acute care treatments, quality measures, and risk stratification strategies to mitigate the devastating impact of sepsis.

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