OBSERVATIONAL STUDY

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Evaluating Potential Missed Opportunities to Prevent, Treat, or Diagnose Sepsis: A Population-Based Retrospective Study of Insurance Claims

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IMPORTANCE: Delays in diagnosing sepsis may increase morbidity and mortality, but the frequency of delays is poorly understood.

OBJECTIVES: The aim of this study was to estimate the frequency and duration of diagnostic delays for sepsis and potential risk factors for delay.

DESIGN, SETTING, AND PARTICIPANTS: We conducted a retrospective case-crossover analysis of sepsis cases from 2016 to 2019 using claims from Merative MarketScan. We ascertained the index diagnosis of sepsis and corresponding hospitalization. We analyzed healthcare visits in the 180 days before diagnosis and then compared the observed and expected trends in signs or symptoms of infection, immune or organ dysfunction (e.g., fever, dyspnea) during the 14 days before diagnosis. A bootstrapping approach was used to estimate the frequency and duration of potential diagnostic delays along with possible risk-factors for experiencing a delay.

MAIN OUTCOMES AND MEASURES: The number of patients who experienced a potential diagnostic delay, duration of delay, and number of potential missed opportunities.

RESULTS: We identified a total of 649,756 cases of sepsis from 2016 to 2019 meeting inclusion criteria. There was an increase in visits with signs or symptoms of infection, immune or organ dysfunction just before the index diagnosis of sepsis. We estimated that around 16.57% (95% CI, 16.38–16.78) of patients experienced a potential diagnostic delay, with a mean delay duration of 3.21 days (95% CI, 3.13–3.27) and a median of 2 days. Most delays occurred in outpatient settings. Potential diagnostic delays were more frequent among younger age groups and patients who received antibiotics (odds ratio [OR] 2.58 [95% CI, 2.54–2.62]), or treatments for particular symptoms, including opioids (OR 1.43 [95% CI, 1.40–1.46]) and inhalers (OR 1.37 [95% CI, 1.33–1.40]).

CONCLUSIONS AND RELEVANCE: There may be a substantial number of potential missed opportunities to diagnose sepsis, especially in outpatient settings. Multiple factors might contribute to delays in diagnosing sepsis including commonly prescribed medications for symptoms.

KEYWORDS: delayed diagnosis; diagnosis; diagnostic errors; hospitalization; sepsis

Sepsis is a life-threatening condition and a significant cause of morbidity and mortality (1–4). Globally, approximately 48.9 million cases occur annually, resulting in as many as 11 million deaths (1). In the United States, the estimated incidence of sepsis ranges from 903,000 to 1.7 million cases annually contributing to 174,000 to 270,000 deaths (2). Among hospitalized patients, sepsis is responsible for between 36.9% and 55.9% of inpatient deaths

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KEY POINTS

Question: What is the incidence and typical duration of potential diagnostic delays of sepsis, and what potential risk factors may be associated with experiencing a delay?

Findings: In this case-crossover analysis of excess symptomatic healthcare visits during the 14 days before diagnosis, we estimate that 16.57% of patients experienced a potential delay with a median duration of 2 days. Potential delays were most common in outpatient settings, and treatment for symptoms of sepsis may increase the risk of delay.

Meanings: There may be many opportunities for early recognition and treatment of sepsis, especially in pre-hospital settings, which may reduce morbidity and mortality.

(1–4). Furthermore, sepsis contributes to substantial healthcare expenditures and is a leading cause of inpatient healthcare costs in the United States, amounting to over $38 billion and 9% of total inpatient medical costs (5, 6).

Cases of sepsis are typically caused by infectious diseases. Pneumonia is the most common cause worldwide, accounting for 16.4% of sepsis-related deaths (1). Other infections associated with sepsis include intra-abdominal infections, skin and soft-tissue infections, meningitis, and urinary tract infections (1). Treatment guidelines for sepsis recommend antimicrobials, fluids, source control, and vasopressors, all within hours of diagnosing sepsis (7). A 1-hour delay in administering antibiotics has been linked to increased mortality rates for septic shock (8–11). The timely administration of treatments for sepsis is critical in reducing morbidity and mortality. For instance, multiple studies have shown that early administration of IV fluids (12–15) and vasopressors (16, 17) improves survival. Despite the known importance of early recognition and treatment of sepsis, delays in diagnosis and treatment frequently occur (18).

Prior investigations of diagnostic delays associated with sepsis largely focus on delays within the emergency department and inpatient settings (8, 14, 19). However, multiple investigations have reported that nearly half of all of patients ultimately diagnosed with sepsis had outpatient healthcare encounters the week before hospital admission (20, 21). These visits may represent missed opportunities to diagnose, intervene, and improve outcomes. Patients are more frequently diagnosed in hospital or emergency department settings because the diagnosis of sepsis relies on clinical assessments, imaging, and laboratory tests, some of which may be more difficult to obtain in outpatient clinics in a timely fashion. Despite years of efforts and multiple different campaigns focused on early sepsis recognition in emergency departments and inpatient settings, the case-fatality rate remains greater than 40% for cases diagnosed in hospital settings (22). Accordingly, improving recognition of patients with early or less severe sepsis could reduce sepsis-related mortality.

Given the considerable morbidity and mortality attributable to sepsis and the persistently high mortality rates of the disease among hospitalized patients, this article aims to address two key objectives: 1) to estimate the incidence and duration of potential diagnostic delays associated with sepsis, and 2) to explore the possible risk factors for experiencing a delay in sepsis diagnosis before hospitalization.

METHODS

Study Design

To address the study objectives, we used a type of case-crossover design along with a bootstrapping-based approach previously developed by our research team to study diagnostic delays using observational data sources (23). The approach estimates the expected pattern of healthcare visits for signs or symptoms of sepsis before diagnosis using a "crossover" period before patients develop sepsis. This method has been used to study diagnostic delays for multiple infectious diseases (24–28).

Data Source

We used de-identified longitudinal health insurance claims data from the Merative Marketscan Commercial and Medicare databases from 2016 to 2019 and the Multi-state Medicaid databases from 2016 to 2018. These data contain claims from outpatient, emergency department, and inpatient visits, along with outpatient drug

prescriptions. No institutional review board (IRB) was necessary as this study did not fall under the University of Iowa IRB guidelines for human subjects research.

Study Population

We identified cases of sepsis using a previously validated algorithm found to have high specificity and reasonable sensitivity using combinations of *International Classification of Diseases*, 10th Edition (ICD-10), codes within administrative data (29). Index sepsis events were defined as the initial sepsis diagnosis in each patient. We required this index diagnosis to occur during a hospital stay or an outpatient visit that subsequently resulted in a hospitalization for sepsis within 7 days. Additionally, we required cases to have at least 180 days of continuous enrollment before the index sepsis diagnosis.

Statistical Analyses

To identify potential diagnostic delays, we considered a 14-day window before the index sepsis diagnosis as a potential diagnostic opportunity window, where diagnostic opportunities may occur. A 14-day window was selected as it demonstrated the best statistical fit (**Appendix Fig. 1,** http://links.lww.com/CCX/B488). However, as a sensitivity analysis, a 7-day window was also analyzed. We refer to potential diagnostic opportunities as healthcare visits where clinical evidence (i.e., signs or symptoms) of infection, organ or immune dysfunction was present and a diagnosis of sepsis may have been plausibly made. When sepsis was not diagnosed during a diagnostic opportunity, we refer to this as a potential missed opportunity and the patient is said to have experienced a *potential diagnostic delay*. Note that because our analysis is observational in nature, we acknowledge the events we identify should be considered "potential" missed opportunities.

Figure 1 provides a visualization of our methodological approach. We start by estimating the excess number of visits for signs, symptoms, or symptomatically-similar diagnoses (i.e., diseases or syndromes with similar symptoms to sepsis) of sepsis during the diagnostic opportunity window by implementing a type of case-crossover analysis; **Appendix Table 1** (http://links.lww.com/CCX/B488) lists the ICD-10 codes used to identify these signs and symptoms. The trend in symptomatic visits from 15 to 180 days before diagnosis (i.e., when sepsis is presumed to be absent) is used as a baseline for the expected level of care in absence of sepsis. We fit a model featuring a temporal exponential trend and indicators for weekly periodicity to the daily number of visits with signs and symptoms of sepsis from 15 to 180 days before diagnosis. Next, we extrapolate this trend forward into the diagnostic opportunity window (i.e., 1–14 days before diagnosis). Finally, we estimate the number of potential missed opportunities each day as the difference between the observed and expected trend.

To analyze the frequency and duration of diagnostic delays we estimated the number and percentage of patients who experienced a potential diagnostic delay, the number of potential missed opportunities each patient experienced, the locations where these opportunities occurred, and the duration of diagnostic delay (i.e., time between the earliest missed opportunity and diagnosis). To compute these metrics, we employed the bootstrapping approach described in Miller et al (23) using the uncorrelated algorithm. This approach resamples the data and randomly selects which visits represent a missed opportunity. We generated 100 bootstrapped samples, where each sample of patients was drawn with replacement. We then re-estimated the expected number of missed opportunities for each bootstrapped sample. For each bootstrapped sample, we performed 100 nested trials where we randomly selected which patients represented a diagnostic delay based on the estimated number of missed opportunities for that bootstrapped sample. This resulted in a total of 10,000 trials, for which we computed the delay metrics of interest. Point-estimates (i.e., means) were then computed across trials along with percentile-based 95% bootstrap CIs.

We conducted an exploratory risk-factor analysis, analyzing potential risk factors for delay, using the same bootstrapped samples described above. For each bootstrapped sample, we fit a logistic regression model using the set of patients selected as having a diagnostic delay in that trial. This dichotomous outcome, indicating whether or not the patient experienced a diagnostic delay (i.e., whether or not the patient was selected as having a diagnostic delay), was then regressed on a set of potential risk factors for diagnostic delay. The risk factors evaluated included age, sex, Elixhauser comorbidities, month and year of the index diagnosis,

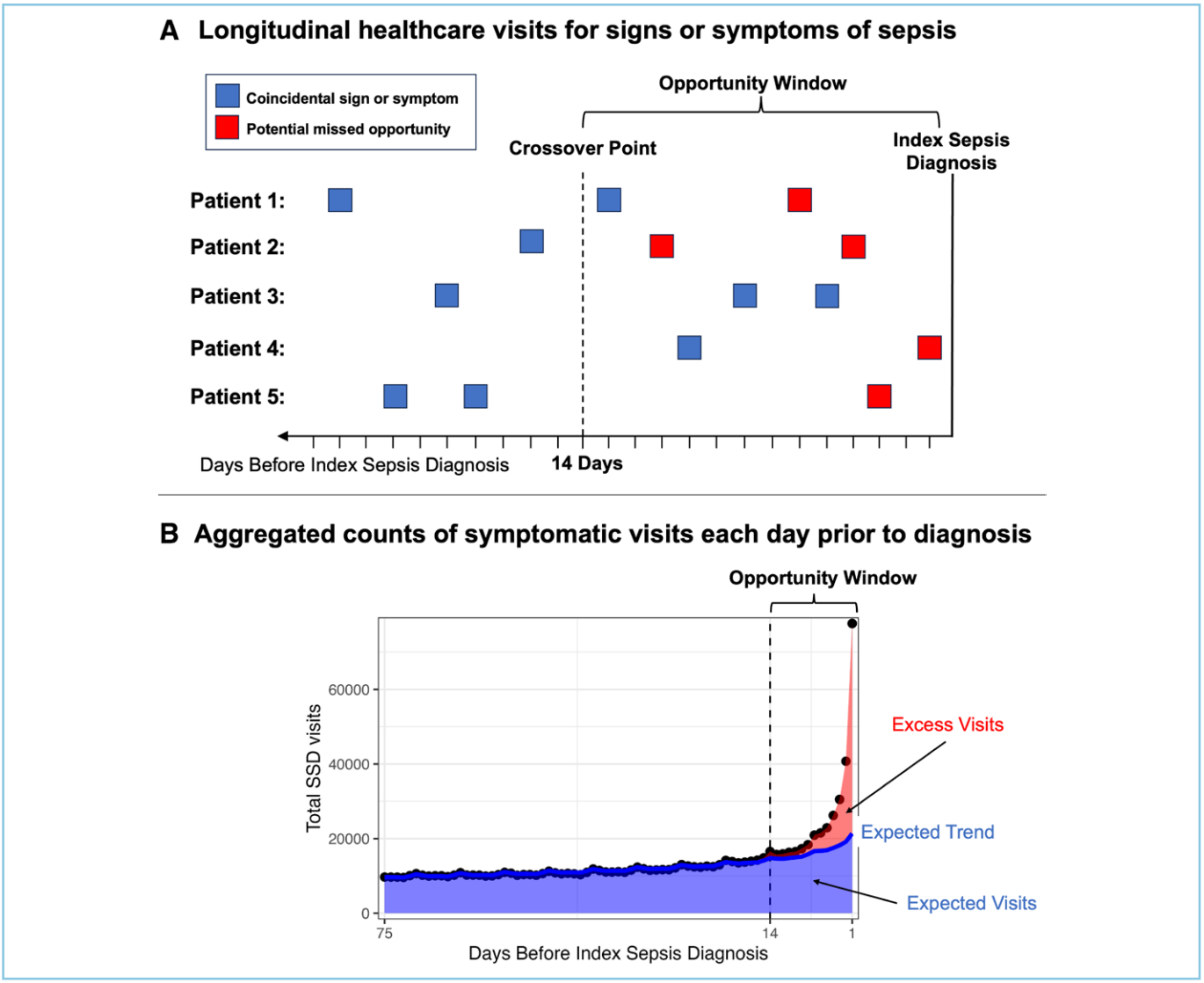

Figure 1. Visual diagram of study methods. **A**, An example of longitudinal patient visits with potential signs or symptoms of sepsis in the time leading up to the sepsis diagnosis. Such "symptomatic" visits may be coincidental (i.e., symptoms unrelated to the eventual sepsis diagnosis) or a potential missed opportunity. Missed opportunities are depicted in red, and coincidental visits are depicted in blue. During the opportunity window, patients 1 and 4 have a symptomatic-visit that is coincidental and another that represents a missed opportunity; patient 2 has two missed opportunities; patient 3 has two coincidental visits; and patient 5 has one missed opportunity. From observational data alone, we cannot directly observe which individual patient visits represent potential missed opportunities vs. coincidental signs or symptoms. In order to estimate statistical measures for the number of potential missed opportunities, we conduct a case-crossover analysis where we compare the observed and expected trends in symptomatic visits. **B**, Depicting how this is done. First, counts of all visits with a potentially symptomatic diagnosis are aggregated across enrollees each day prior to diagnosis (black-dots in B). Second, the trend is estimated during the crossover control-period prior to the opportunity window (blue-line). This trend is then extrapolated into the opportunity window. Third, the excess number of visits during the opportunity window (shaded red region) is computed to estimate the total number of potential missed opportunities each day during the opportunity window. Finally, bootstrapping is used to randomly and repeatedly sample (10,000 times) which visits represent a missed opportunity and the selected visits are used to compute individual delay metrics.

and insurance source (i.e., commercial, Medicare, or Medicaid). Additionally, we considered potential risk factors that might alter the diagnostic process. These include average number of weekly visits before the diagnostic opportunity window; receipt of prednisone or another immunosuppressant before the diagnostic opportunity window; receipt of antibiotics; and symptomatic treatment with opioids or an inhaler during the diagnostic opportunity window. We hypothesized that those receiving treatment of disease process or

symptoms would have higher rates of delay. We also hypothesized that immunosuppressed patients may experience increased delays from presentations with subclinical symptoms.

Sensitivity Analysis

Prior research on diagnostic delays for sepsis has been conducted over a range of time periods (e.g., hours, 7 days, and 30 days) (19, 20) before the index diagnosis. Thus, we also considered a shorter time period of 7 days before diagnosis to identify diagnostic delays, and repeated each of our analyses.

RESULTS

There was a total of 67,728,823 patients enrolled during the study period, of these 840,030 were identified as having sepsis (using the algorithm of Jolley et al (29)) and the final study population included 649,756 cases with 180 days of continuous enrollment before the sepsis diagnosis. **Table 1** summarizes the baseline characteristics of this study population. **Figure 2** depicts the trend in healthcare visits with signs or symptoms of sepsis in the 180 days before the index visit. There is a dramatic increase in visits with signs or symptoms of sepsis just before the index diagnosis, resembling a "hockey-stick" shaped trend. This trend increases most prominently in the 14 days before diagnosis.

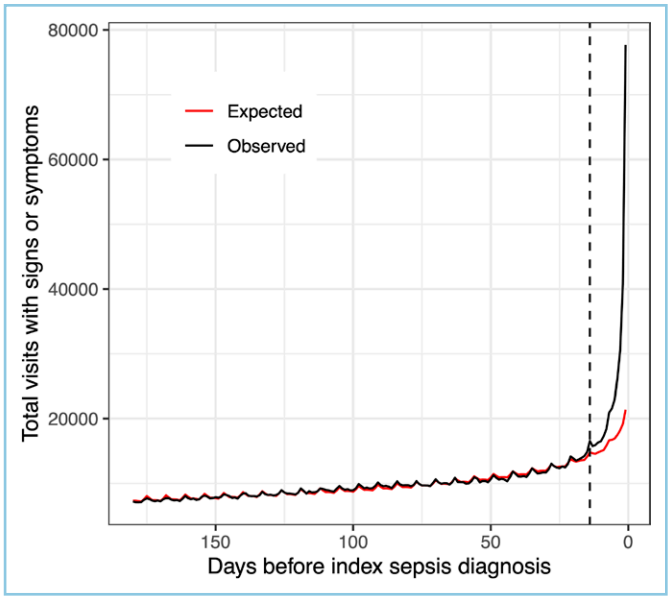

Figure 2. Trend in the number of visits with potential signs, symptoms, or symptomatically similar diagnoses of sepsis over the 180 d prior to the index diagnosis. The observed trend is depicted in black. The expected trend, depicted in red, is estimated based on an exponential model using the observed number of visits from 15 to 180 d prior to diagnosis.

Figure 2 also depicts the estimated expected trend (red line) in visits with signs or symptoms based on the pattern observed from 15 to 180 days before diagnosis. This expected trend reflects the pattern of visits that would be expected to occur in absence of diagnostic delays, assuming that delays lasting beyond 14 days are uncommon. Thus, the difference between the observed (black line) and expected trend (red line) reflects the estimated number of potential missed opportunities each day before diagnosis. **Appendix Figure 2** (http://links.lww.com/CCX/B488) provides a histogram of the estimated number of potential missed opportunities each day during the diagnostic opportunity window.

Table 2 provides summary statistics from the bootstrapping-based approach to estimate individual-level metrics for the frequency and duration of diagnostic delays. We estimated that around 16.57% (95%

TABLE 1.
Baseline Characteristics

Characteristic	*N*	Percent of All Cases
Sex		
Male	285,940	44.0
Female	363,816	56.0
Age group		
<18	48,141	7.4
18–34	71,794	11.0
35–44	57,346	8.8
45–54	95,367	14.7
55–64	159,422	24.5
≥65	217,686	33.5
Insurance type		
Commercial	252,747	38.9
Medicare	130,147	20.0
Medicaid	266,862	41.1
Index diagnosis year		
2016	251,556	38.7
2017	185,394	28.5
2018	143,114	22.0
2019	69,692	10.7

TABLE 2.
Summary Statistics From the Bootstrapping-Based Analysis for the Number of Missed Opportunities and Duration of Diagnostic Delay

Measure	Estimate	95% CI
Patients with a delay		
Number of patients	107,689	106,400–108,999
Percent of all patients	16.57%	16.38–16.78
Duration of diagnostic delays		
Mean	3.21 days	3.13–3.27
Median	2 days	2–2
Number of missed opportunities per patient		
Mean	1.17 visits	1.17–1.17
Median	1 visit	1–1

CI, 16.38–16.78) of patients experienced a potential diagnostic delay. Among those patients who experienced a delay, the mean duration was 3.21 days (95% CI, 3.13–3.27) and the median was 2 days. **Appendix Table 2** (http://links.lww.com/CCX/B488) provides a distribution for the duration of diagnostic delays. Around 70% of all delays lasted 3 days or less, and around 90% were 7 days or less. Most patients who experienced a diagnostic delay only had one healthcare visit representing a potential missed opportunity. On average, patients who experienced a diagnostic delay had around 1.17 (95% CI, 1.17–1.17) visits representing a missed opportunity (Table 2). **Appendix Table 3** (http://links.lww.com/CCX/B488) describes the distribution for the number of missed opportunities that patients experienced. Less than 14% of patients who experienced a potential diagnostic delay had more than 1 visit representing a missed opportunity.

Table 3 summarizes the types of signs, symptoms, or symptomatically-similar-diagnoses that were present during visits representing missed diagnostic opportunities from the bootstrapping analysis. The most common type of symptom was pain, occurring across 26.94% (95% CI, 26.71–27.23) of missed diagnostic opportunities, followed by pulmonary-related symptoms (21.12% [95% CI, 20.88–21.36]), gastrointestinal-related symptoms (19.25% [95% CI, 19.02–19.49]), pulmonary disorders or diseases (14.27% [95% CI, 14.07–14.51]) and cardiovascular-related symptoms (11.46% [95% CI, 11.27–11.67]).

We analyzed the healthcare settings where potential diagnostic opportunities were most likely to occur. **Appendix Table 4** (http://links.lww.com/CCX/B488) summarizes the total number of diagnostic opportunities by type of healthcare setting including the number and percentage of these opportunities that were missed. Overall, the majority of missed opportunities occurred in outpatient visits at hospital-based clinics (33.93%), followed by office/clinic visits (21.53%), other outpatient clinics (19.85%), and emergency departments (17.90%). We also estimated the percentage of diagnostic opportunities that were missed. This value can be loosely interpreted as the likelihood of receiving an incorrect diagnosis when a patient presented with symptoms of sepsis. We computed this value as the total number of missed opportunities (i.e., patient presented to a healthcare setting with symptoms of sepsis but was not diagnosed) divided by the total number of diagnostic opportunities (i.e., total number of missed opportunities plus the number of index visits). Other unspecified outpatient settings had the highest likelihood of a visit resulting in a missed opportunity (54.22%) followed by nursing facilities (36.47%), office/clinic visits (34.17%) and hospital-based clinics (31.26%), while inpatient settings had the lowest likelihood (0.73%).

Appendix Table 5 (http://links.lww.com/CCX/B488) depicts the results of the sensitivity analysis using a 7-day opportunity window to identify diagnostic delays. Overall, the results were generally consistent when a 7-day window was used. By shrinking the diagnostic opportunity window from 14 to 7 days, the percentage of patients estimated to experience a potential delay dropped slightly (16.57% to 14.66%), as did the mean/median duration of delays (3.21/2 to 2.28/1.92). However, based on root-mean-square error (RMSE), the 7-day opportunity window did not appear to fit the observed visit trend as well as the 14-day window (Appendix Fig. 1, http://links.lww.com/CCX/B488). Furthermore, based on Appendix Figure 1 (http://links.lww.com/CCX/B488), the expected trend that was estimated using a 7-day window would imply that a small number of missed opportunities occurred between 7 and 14 days.

As an exploratory analysis, we analyzed potential risk factors for diagnostic delay. **Table 4** presents the results of this regression analysis. We found the likelihood of

TABLE 3.
Types of Signs, Symptoms, or Symptomatically Similar Diagnoses That Were Recorded During Visits Selected as Missed Opportunities in the Bootstrapping-Based Analysis

Sign, Symptom, or Symptomatically Similar Diagnosis	Percent of Missed Opportunities (95% CI)
Pain[a]	26.94 (26.71–27.23)
Pulmonary-related sign or symptom	21.12 (20.88–21.36)
Gastrointestinal-related sign or symptom	19.25 (19.02–19.49)
Pulmonary disorder or disease	14.27 (14.07–14.51)
Cardiovascular-related sign or symptom	11.46 (11.27–11.67)
Respiratory infection	10.39 (10.19–10.56)
Fever	9.70 (9.54–9.89)
Nervous system-related sign or symptom	9.23 (9.07–9.41)
Fluid or electrolyte disorder or disease	8.34 (8.18–8.50)
Cardiovascular disorder or disease	7.90 (7.72–8.08)
Weakness or fatigue	7.23 (7.07–7.38)
Skin infection	6.77 (6.62–6.92)
Gastrointestinal disorder or disease	5.40 (5.27–5.52)
Hematologic disorder or disease	3.68 (3.58–3.79)
Genitourinary disorder or disease	3.68 (3.56–3.79)
Musculoskeletal-related sign or symptom	3.61 (3.50–3.72)
Musculoskeletal disorder or disease	3.33 (3.22–3.44)
Genitourinary-related sign or symptom	3.21 (3.11–3.32)
Unspecified infection	3.12 (3.01–3.22)
Nervous system disorder or disease	2.11 (2.02–2.19)
Genitourinary infection	1.84 (1.76–1.92)
Gastrointestinal infection	1.68 (1.60–1.75)
Unspecified pain	1.28 (1.21–1.35)
Abnormal laboratory result	0.77 (0.73–0.83)
Endocrine disorder or disease	0.56 (0.52–0.60)
Systemic inflammatory response syndrome (noninfectious)	0.24 (0.21–0.27)
Musculoskeletal infection	0.20 (0.17–0.23)
Cardiovascular infection	0.07 (0.05–0.09)
Screening or observation for infection	0.05 (0.04–0.07)

[a]Visits for pain were aggregated across organ systems and pain sites; thus, *International Classification of Diseases*, 10th Edition, codes for pain were nonmutually exclusive with other sign, symptom, or symptomatically similar diagnosis categories.

potential diagnostic delays tended to be greater among age groups where sepsis is less common. The odds ratio for experiencing a missed opportunity for patients less than18 vs. patients ≥65 was 1.53 (95% CI, 1.48–1.58). The odds of a missed opportunity decreased with older age groups. Patients who had a greater healthcare visit frequency before developing sepsis were more likely to experience a delay; for every unit increase in the average number of weekly visits, the odds of experiencing a delay increased by a factor of 1.04 (OR 1.04 [95% CI, 1.04–1.05]). Although not statistically significant, patients with a history of immunosuppression medication were slightly less likely to experience a delay (OR 0.97 [95% CI, 0.94–1.00]). Patients who received an

TABLE 4.
Logistic Regression Results for Risk Factor Analysis

Risk Factor	OR	95% CI
Age		
<18	1.53	1.48–1.58
18–34	1.12	1.09–1.15
35–44	1.10	1.07–1.14
45–54	1.05	1.02–1.08
55–64	0.99	0.96–1.01
≥65	Ref	Ref
Female sex	0.98	0.96–0.99
Insurance type		
Commercial	Ref	Ref
Medicare	0.82	0.80–0.85
Medicaid	0.75	0.74–0.77
Characteristics before opportunity window		
Average visits per week	1.04	1.04–1.05
Prednisone or other Immunosuppressant	0.97	0.94–1.00
Treatments during opportunity window		
Antibiotic	2.58	2.54–2.62
Opioid	1.43	1.40–1.46
Inhaler	1.37	1.33–1.40

See **Appendix Table 6** (http://links.lww.com/CCX/B488) for additional results.

antibiotic before the sepsis diagnosis were more likely to experience a delay (OR 2.58 [95% CI 2.54–2.62]). Patients who received a treatment for symptoms of sepsis during the diagnostic opportunity window, when sepsis is believed to be present, were at a greater risk for delay compared with patients who did not; the odds ratio was 1.43 (95% CI, 1.40–1.46) for opioids, and 1.37 (95% CI, 1.33–1.40) for an inhaler.

DISCUSSION

We found a substantial proportion of patients diagnosed with sepsis (almost 17%) have at least one potential missed diagnostic opportunity before their hospital admission where sepsis was the diagnosis. Around 13.6% of patients experienced two or more potential missed opportunities. The vast majority of these opportunities occurred within 7 days before diagnosis. The mean and median duration of delays were 3.2 and 2 days, respectively. The risk for a diagnostic delay increased if patients were prescribed an antibiotic, an inhaler, or an opioid during the days before their admission for sepsis. Finally, diagnostic delays for sepsis were more common among younger populations.

Diagnostic delays are increasingly recognized as an important contributor to morbidity and mortality (30). Outcomes related to sepsis likely depend on the timing of diagnosis and treatment. Failure to treat cases of sepsis in a timely fashion with antibiotics, fluid resuscitation, and vasopressor support is associated with worse clinical outcomes (31–36) and even short delays may increase mortality (11, 37, 38). While a relatively recent meta-analyses regarding sepsis-treatment approaches questioned the importance of the timely administration of antibiotics, the study authors acknowledged methodologic weaknesses associated with their study that may undermine these findings (9, 39).

Our results are consistent with prior studies of the pre-hospitalization period. Reviews of observational trials have shown that around 10–53% of patients had a healthcare encounter in the days before sepsis admission (40). In Medicare populations, as many as 60% who were hospitalized with sepsis had a healthcare claim before admission, with the majority of visits occurring on the day before hospitalization (41). In addition, prior work has described the escalating frequency and intensity of visits, especially outpatient encounters, leading up to hospital admission (20).

Our bootstrapping-based approach also allows us to explore potential risk factors for diagnostic delays. For example, we found that some individual-level characteristics were associated with diagnostic delays. Delays were more common in younger adults compared with older adults. We hypothesize that younger patients were more likely to be missed because healthcare providers may have a higher threshold for considering sepsis in younger patients.

We also found that treatments targeting specific symptoms were associated with potential delays in diagnosis. Both inhalers and opioids prescribed in visits before an admission for sepsis were associated with delays. These findings highlight the importance of making a diagnosis rather than just treating symptoms. Inhalers and opioids can temporally mask some of the symptoms related to an underlying infection that may

be unrecognized and untreated, contributing to the development of sepsis. Another study found patients with sepsis who initially presented with shortness of breath had higher rates of mortality, and over a third of patients with septic shock present to emergency rooms with vague symptoms (42). Our work stresses the importance of determining the cause of symptoms for which the inhalers or opioids were prescribed.

Another important consideration in our study is the relationship between prior antibiotic use and diagnostic delays. It is critical to understand that identifying an infection alone is insufficient to prevent sepsis-related morbidity and mortality; timely and appropriate treatment must follow. We hypothesize this may be due to the "wrong" antibiotic(s) being prescribed and the resulting delay in waiting for a potential therapeutic effect. Alternatively, even if the "correct" antibiotic(s) were prescribed, the patient might have needed a higher dose or required prompt source control to adequately treat the infection (43–45). The association between prior antibiotics and diagnostic delays has been described for a wide range of infectious diseases (25, 26, 28). Antibiotic prescriptions before sepsis recognition may obscure the clinical presentation, delaying diagnosis and leading to poorer outcomes. Because the early administration of the appropriate antibiotics should improve clinical outcomes for patients with sepsis, future work should aim to identify the particular cases and specific antibiotics associated with diagnostic delays.

While the timely diagnosis and treatment of sepsis is critical for improving outcomes in hospital settings, it is not clear how far into the pre-hospital setting the benefit of early treatment extends (38, 46). However, among hospitalized patients with sepsis who die, a substantial proportion of deaths may not be preventable from improved hospital care alone. For example, Rhee et al estimated that 88% of the deaths from sepsis in a hospital setting could not have been prevented from improving hospital-based care (47). Dramatically reducing the morbidity and mortality attributable to sepsis may require early recognition and treatment of sepsis in the pre-hospitalization period. Indeed, there is evidence that the pre-hospital administration of antibiotics has been associated with lower mortality rates, and lengths of hospital and ICU stays (48).

Our study has several limitations. First, we identified patients with sepsis using administrative codes. Diagnosis codes for sepsis tend to be specific but limited in sensitivity (2). Although we used an approach designed to improve sensitivity and specificity (29), this approach may still miss less severe or difficult to recognize cases. Second, we do not have access to laboratory or x-ray results, and we cannot perform chart reviews. Thus, we cannot apply the standard Sepsis-3 definition and the Sequential Organ Failure Assessment (SOFA) score, which requires access to detailed clinical information that are unavailable in our data. Third, we do not have access to data on patients' race or ethnicity, so we cannot determine if diagnostic delays are associated with race or ethnicity. Fourth, some of the apparent non-symptomatic visits preceding a sepsis diagnosis may represent missed opportunities if symptoms were not recorded. This may lead to underestimates of diagnostic delays. Fifth, the diagnostic opportunity window (i.e., time before diagnosis where delays can occur) is not entirely known. However, we conducted a sensitivity analysis using a 7-day window and results were largely consistent, suggesting most delays occur within the week before diagnosis. Finally, our data are based on claims from medical insurance coverage and does not include individuals without insurance. Thus, our results might not be generalizable to all populations. Because of these limitations, we emphasize that each of our findings should be contextualized as representing "potential" diagnostic delays, Furthermore, future work should aim to replicate these findings using more granular clinic data that can be used to identify cases of sepsis.

Despite the limitations associated with our work, we highlight the substantial number of potential missed opportunities to diagnose sepsis and identified potential risk factors associated with delays. Our findings align with previous smaller studies using electronic healthcare records (49), chart reviews (49), insurance claims (20), and medico-legal data (21) which all consistently show that patients admitted with sepsis often have significant outpatient healthcare interactions before a hospital admission for sepsis. These pre-hospitalization encounters represent the need for increased recognition of developing sepsis and potential opportunities for earlier interventions. In conclusion, our results highlight the need to develop future interventions to decrease diagnostic delays for sepsis (e.g., using electronic medical record-based alerts for high risk patients) as well as the need for clinicians

to consider prior pre-hospital visits when evaluating patients with potential early sepsis-like presentations.

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