OBSERVATIONAL STUDY

OPEN

Clinical Phenotypes of Sepsis in a Cohort of Hospitalized Patients According to Infection Site

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OBJECTIVES: Clinical sepsis phenotypes may be defined by a wide range of characteristics such as site of infection, organ dysfunction patterns, laboratory values, and demographics. There is a paucity of literature regarding the impact of site of infection on the timing and pattern of clinical sepsis markers. This study hypothesizes that important phenotypic variation in clinical markers and outcomes of sepsis exists when stratified by infection site.

DESIGN: Retrospective cohort study.

SETTING: Five hospitals within the Wake Forest Health System from June 2019 to December 2019.

PATIENTS: Six thousand seven hundred fifty-three hospitalized adults with a discharge *International Classification of Diseases*, 10th Revision code for acute infection who met systemic inflammatory response syndrome (SIRS), quick Sepsis-related Organ Failure Assessment (qSOFA), or Sequential Organ Failure Assessment (SOFA) criteria during the index hospitalization.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary outcome of interest was a composite of 30-day mortality or shock. Infection site was determined by a two-reviewer process. Significant demographic, vital sign, and laboratory result differences were seen across all infection sites. For the composite outcome of shock or 30-day mortality, unknown or unspecified infections had the highest proportion (21.34%) and CNS infections had the lowest proportion (8.11%). Respiratory, vascular, and unknown or unspecified infection sites showed a significantly increased adjusted and unadjusted odds of the composite outcome as compared with the other infection sites except CNS. Hospital time prior to SIRS positivity was shortest in unknown or unspecified infections at a median of 0.88 hours (interquartile range [IQR], 0.22–5.05 hr), and hospital time prior to qSOFA and SOFA positivity was shortest in respiratory infections at a median of 54.83 hours (IQR, 9.55–104.67 hr) and 1.88 hours (IQR, 0.47–17.40 hr), respectively.

CONCLUSIONS: Phenotypic variation in illness severity and mortality exists when stratified by infection site. There is a significantly higher adjusted and unadjusted odds of the composite outcome of 30-day mortality or shock in respiratory, vascular, and unknown or unspecified infections as compared with other sites.

KEY WORDS: biological variation; phenotypic variability; sepsis; septic shock; systemic inflammatory response syndrome

Sepsis is a syndrome defined by a dysregulated host response to infection resulting in organ failure and death (1, 2). Because a wide range of infections cause sepsis and a broad spectrum of patients are at risk for sepsis, it is a major threat to global health that contributes to over 5 million deaths annually (3, 4). Bundled protocols are mandated for the initial management of sepsis, however, these are not adapted to unique features of the underlying infection (2,

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KEY POINTS

Question: This study aims to identify meaningful differences in clinical sepsis phenotypes stratified by site of infection.

Findings: Retrospective cohort study of 6,753 hospitalized adults with an *International Classification of Diseases*, 10th Revision code for acute infection meeting any sepsis criteria demonstrating significantly increased adjusted and unadjusted odds of the composite of 30-day mortality or shock in respiratory, vascular, and unknown or unspecified sites of infection as compared with gastrointestinal, genitourinary, skin and soft tissue, and bone/joint infections.

Meaning: Important phenotypic variation in illness severity and mortality exists when stratified by infection site.

5–13). Studies consistently demonstrate variability in the clinical features and outcomes of sepsis. This heterogeneity creates challenges for generalized approaches (8, 14–18). Despite these identified variations in sepsis characteristics such as organ dysfunction patterns, laboratory values, and demographics (16, 19–30), there is a paucity of literature regarding variation of sepsis clinical findings and outcomes by site of infection (31).

Significant research on identifying phenotypic models of sepsis based on biochemical profiles and clinical variables exists, however, few have focused specifically on infection site. Prior studies have employed varied approaches, including machine learning and artificial intelligence modeling, gene expression profiling, transcriptomics, proteomics, and metabolomics. Machine learning and artificial intelligence models cluster patients into groups according to similarities on several variable inputs (16, 19, 21–23, 32). Computing systems can be used to identify patients who fall into these categories, but in clinical practice, the utility of this approach is diminished, as these computer models do not have clear clinical analogs. Genetic, transcriptomic, proteomic, and metabolomics models similarly offer promising models for understanding the biologic basis for differential expression of sepsis syndromes (20, 21, 24, 26–29); however, translation of these novel findings to clinical medicine remains far on the horizon (33).

This study aims to characterize clinical phenotypes of sepsis based on infection site. We hypothesize that clinically relevant differences in the manifestations and outcomes of patients hospitalized with sepsis are related to the site of infection.

PATIENTS AND METHODS

Study Design

This is a cohort study of hospital admissions from the emergency department of adults (age ≥ 18) with an *International Classification of Diseases*, 10th Revision (ICD-10) (34) code for acute infection who met any criteria for sepsis within the Wake Forest Health System (Winston-Salem, NC) from June to December 31, 2019 (**eFig. 1**, (http://links.lww.com/CCX/B235).

Adjudication of Infection Site

We reviewed all ICD-10 discharge diagnoses for the entire cohort and included all codes related to infection or sepsis in the analytic dataset. We then grouped site of infection into the following categories: bone or joint, CNS, gastrointestinal, genitourinary, respiratory, skin and soft tissue infection (SSTI), vascular, and unknown or unspecified. Infection site was determined by a blinded two-reviewer process with disputes settled by an additional blind review by the senior reviewer. Manual chart review was performed post hoc on a random subset of 20 subjects within the sample population to assess accuracy in site of infection documentation as compared with ICD-10 coding.

All potential microbial classes of infection, including bacterial, viral, fungal, and parasitic, were included in the study. Noninfectious inflammatory conditions, such as pancreatitis, were only included in the study if there was additional coding information indicating concurrent infection, such as acute pancreatitis with infected necrosis (ICD-10 code K85.92). We excluded admissions with more than one site of infection coded. However, we included admissions in which a single site of infection was coded along with an ICD-10 code indicating a vascular and/or unknown or unspecified site of infection, as these cases were presumed to be related to the single infection site. These cases were not included in the count for vascular or unknown or unspecified sites of infection. A complete list of unknown or unspecified infection sites and the

associated ICD-10 codes collected in this study are included in **eTable 1** (http://links.lww.com/CCX/B235).

Sepsis Definition

Sepsis was defined as meeting systemic inflammatory response syndrome (SIRS) (35), quick Sepsis-related Organ Failure Assessment (qSOFA), or Sequential Organ Failure Assessment (SOFA) (1) criteria during the index hospitalization. A positive score for SIRS or qSOFA required greater than or equal to 2 positive criteria within a 6-hour interval, and the SOFA-based definition required an increase in SOFA score of greater than or equal to 2 from baseline within a 6-hour interval. Septic shock was determined by vasopressor use during an index hospitalization. Eligible antimicrobials were determined by the U.S. Centers for Disease Control and Prevention Hospital Toolkit for Adult Sepsis (36).

Severity of illness was defined by maximum SOFA score during the index hospitalization. Charlson Comorbidity Index (CCI), a validated scale reflecting preexisting comorbidities, was calculated for all patients at the time of admission (37). Culture positivity was determined through review of all available culture data (blood, urine, sputum, wound, bone, etc.) and exclusion of probable contaminants. For known contaminants, two positive cultures in the same patient within 24 hours were treated as a true infection. For laboratory values, the most abnormal value obtained during the index hospitalization is reported.

Outcomes

The primary outcome of interest was a composite of 30-day mortality or shock. Secondary outcomes included hospital time prior to initial sepsis criteria positivity and shock. Additional outcomes of interest included the proportion of patients receiving antimicrobials, culture positivity, and illness severity. Site of infection and culture positivity were time agnostic, whereas sepsis criteria, shock, mortality, and antimicrobial receipt were time dependent.

Human Subjects Research

This study, entitled "The Impact of Antibiotic Choice and Timing on Sepsis Outcomes at Wake Forest Baptist Medical Center," was approved with a waiver of informed consent by the Wake Forest University School of Medicine Institutional Review Board (No. 00054096, approval date December 13, 2018). Funding for the study was obtained from the Wake Forest University School of Medicine Clinical and Translational Science Institute (CTSI), award number UL1TR001420, principal investigators (A.R.S., K.W.T.). Study procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Statistical Analysis

Electronic health record (EHR) data were obtained from the Wake Forest CTSI. Data cleaning and statistical analysis were conducted in R Studio Version 4.0.5 (The R Project for Statistical Computing, Vienna, Austria) and JMP 15.00 (SAS Institute, Cary, NC). Descriptive continuous data are presented as median (interquartile range [IQR]). Statistical tests between sites of infection were performed with the Kruskal-Wallis test for continuous group comparisons, Wald chi-square test for categorical group comparisons, and Steel test for nonparametric pairwise comparisons. We used a p value of 0.05 to define statistical significance.

We analyzed hospital time prior to initial sepsis criteria (SIRS, qSOFA, or SOFA) positivity and shock using Cox proportional hazard modeling. Data were right time censored at the end of the index hospitalization for each hospital admission if the event of interest did not occur. We applied logistic regression for the composite outcome of shock or 30-day mortality. Model adjustment accounted for age, sex, body mass index (BMI), race, CCI, hospital time prior to initial antimicrobial receipt, and hospital readmission. The multiple imputation using chained equations (MICE) package in R Studio was used to impute missing data using chained equations and create 10 complete datasets (38). We then applied logistic regression models to each imputed dataset and pooled the coefficients. We used these coefficients to create a heat map of phenotypic variability by site of infection.

RESULTS

A total of 19,536 visits were recorded from June 5, 2019, to December 31, 2019. Six thousand seven hundred fifty-three index admissions met study inclusion

criteria after exclusion of 10,695 admissions without an ICD-10 code for infection, 900 admissions not meeting any sepsis criteria, and 1,188 admissions with ICD-10 codes for multiple sites of infection. Manual chart review performed on a random subset of the sample population showed 95% agreement in site of infection as compared with ICD-10 coding. Pooled Cohen's kappa for reviewer agreement on infection site was 96.58% (95% CI, 95.62–97.53%).

Significant group differences were seen across all demographic and outcome-related variables (**eTable 2**, http://links.lww.com/CCX/B235). Respiratory infections were most common and CNS infections were least common. Patients with genitourinary infections were older and more likely to be female, whereas patients with bone and joint infections were more likely to be male. BMI was highest in the SSTI group at a median of 29.31 kg/m^2 (IQR, 25.80–36.32 kg/m^2). Antimicrobial receipt during the index hospitalization was highest for genitourinary infections (97.10%) and lowest for gastrointestinal infections (79.63%). Any culture positivity was highest in vascular infections (57.41%) and lowest in gastrointestinal infections (15.02%). The proportion of patients with positive SIRS, qSOFA, and SOFA scores were highest in respiratory infections, at 90.63%, 44.04%, and 85.40%, respectively.

For the composite outcome, unknown or unspecified infections had the highest proportion (21.34 %) and CNS infections had the lowest proportion (8.11%). Thirty-day mortality was highest in unknown or unspecified site of infection (13.91%) and lowest in CNS infections (2.70%). Shock was highest in unknown or unspecified site of infection (16.97%) and lowest genitourinary infections (5.27%) (eTable 2, http://links.lww.com/CCX/B235).

Hospital time prior to positive SIRS, qSOFA, and SOFA criteria, and shock is shown in **Figure 1**; and

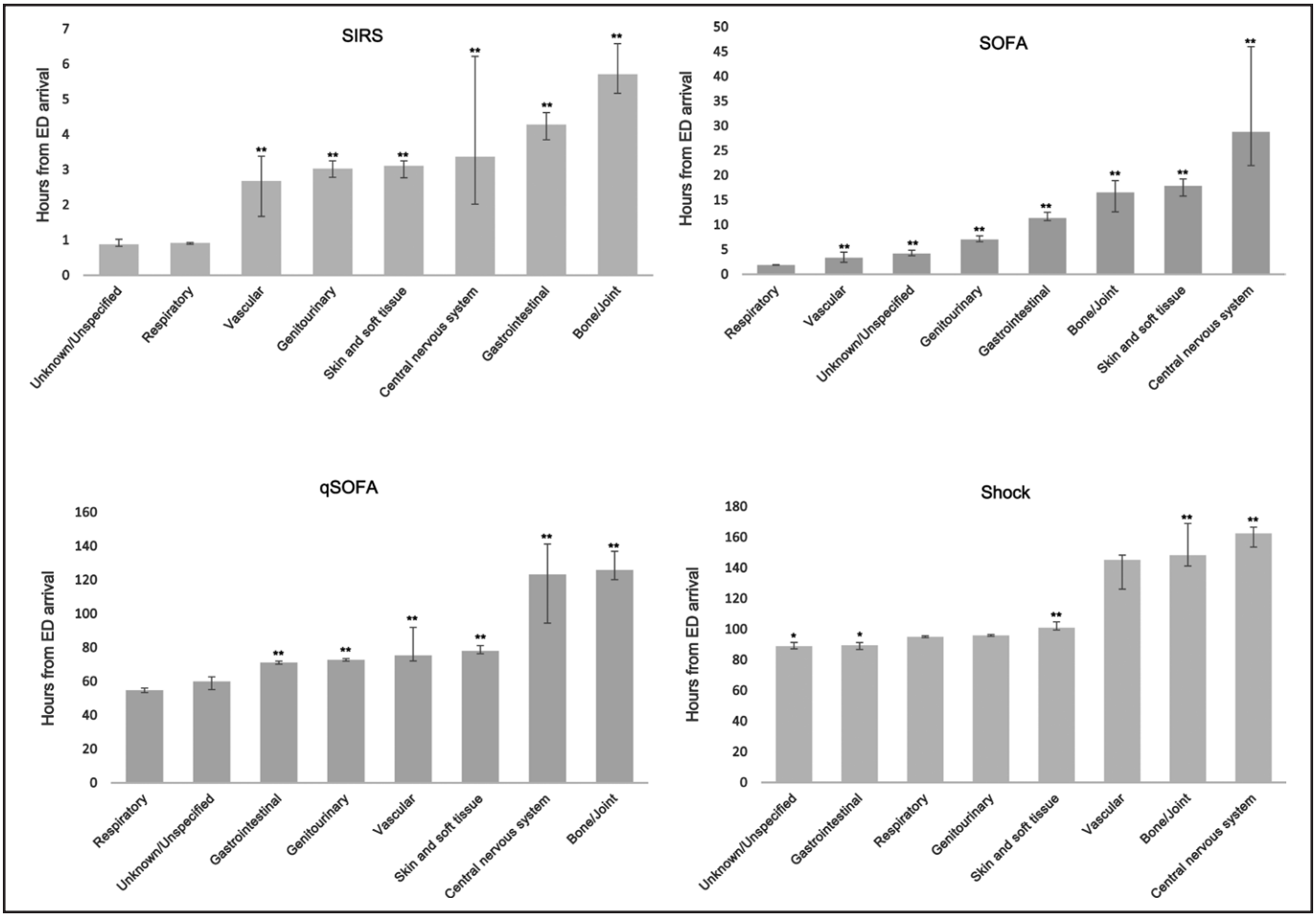

Figure 1. Median hospital time prior to meeting event criteria, by infection site. *Error bars* represent 95% confidence limits. *$p < 0.05$ for lower median pairwise difference (reference, respiratory infection). **$p < 0.05$ for upper median pairwise difference (reference, respiratory infection). ED = emergency department, qSOFA = quick Sepsis-related Organ Failure Assessment, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

eTable 3 (http://links.lww.com/CCX/B235). Hospital time prior to SIRS positivity was shortest in unknown or unspecified infections at a median of 0.88 hours (IQR, 0.22–5.05 hr), and hospital time prior to qSOFA and SOFA positivity was shortest in respiratory infections at a median of 54.83 hours (IQR, 9.55–104.67 hr) and 1.88 hours (IQR, 0.47–17.40 hr), respectively.

The grid heat map shown in **Figure 2** demonstrates clinical variability in demographic, physiometric, and laboratory data by infection site. Respiratory infections were notable for significantly lower Po_2 and higher Pco_2 than other infection sites. Gastrointestinal infections demonstrated significantly higher total bilirubin levels. SSTIs occurred in patients with significantly higher BMI. Bone and joint infections showed significantly higher sedimentation rate. Vascular infections showed significantly lower platelet count and higher international normalized ratio. CNS infections showed significantly lower CCI and significantly lower C-reactive protein levels. No other findings reached statistical significance. Mean values for each variable by infection site are found in **eTable 4** (http://links.lww.com/CCX/B235).

Odds of the meeting the composite outcome and the individual components of the composite were compared with respiratory infection (**Table 1**). Gastrointestinal, bone and joint, genitourinary, and SSTI showed significantly lower adjusted odds for the composite outcome (**Fig. 3**), 30-day mortality and shock as compared with respiratory infections. Unknown or unspecified infections showed a significantly higher adjusted odds of the composite (odds ratio [OR], 1.42 [95% CI, 1.09–1.86]; $p = 0.0090$) and shock (OR, 1.91 [95% CI, 1.43–2.56]; $p < 0.0001$) but

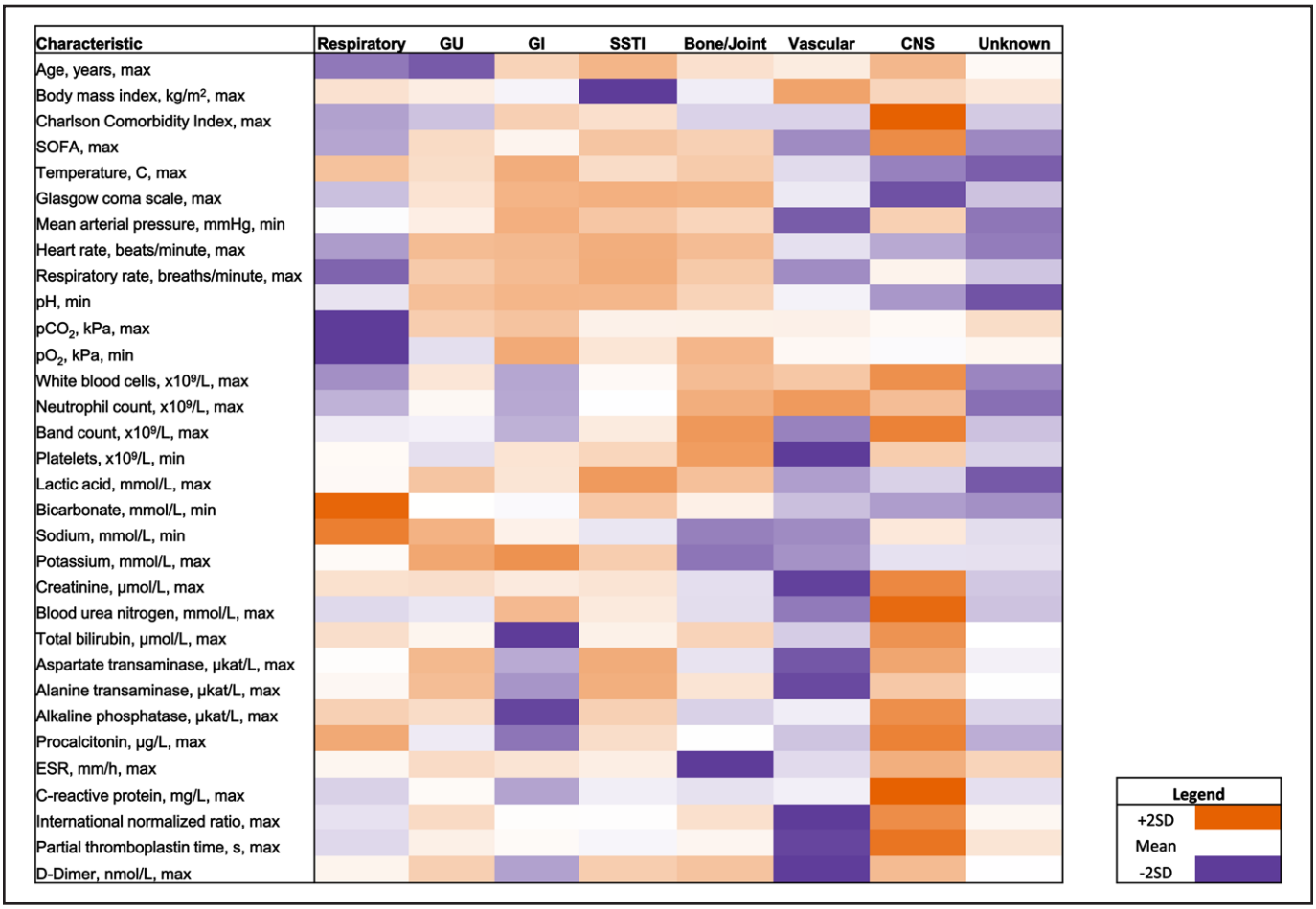

Figure 2. Grid heat map of patient characteristics by site of infection. The heat map is based on parameter estimates derived from logistic regression using the pooled dataset. *Purple coloration* is 2 SDs worse than the grand mean for each variable. *Orange coloration* is 2 SDs better than the grand mean for each variable. *Darker shading* represents greater distance from the mean. Variables are denoted as maximum (max) or minimum (min) indicating that whether highest or lowest value for that variable was used for the analysis. ESR = erythrocyte sedimentation rate, GI = gastrointestinal, GU = genitourinary, SOFA = Sequential Organ Failure Assessment, SSTI = skin and soft tissue infection.

TABLE 1.
Odds Ratios for Composite Outcome by Site (Reference, Respiratory Infection)

Outcome by Site[a]	Unadjusted OR (95% CI)	*p*	Adjusted OR[b] (95% CI)	*p*
Composite				
Bone/joint	0.37 (0.19–0.70)	0.0046	0.48 (0.28–0.81)	0.0066
CNS	0.34 (0.11–1.13)	0.0779	0.58 (0.17–1.95)	0.3825
Gastrointestinal	0.38 (0.28–0.51)	< 0.0001	0.61 (0.47–0.79)	0.0001
Genitourinary	0.56 (0.47–0.67)	< 0.0001	0.51 (0.41–0.63)	< 0.0001
SSTI	0.55 (0.43–0.70)	< 0.0001	0.47 (0.35–0.64)	< 0.0001
Vascular	1.37 (0.88–2.12)	0.1626	1.14 (0.69–1.88)	0.6095
Unknown	1.25 (0.98–1.59)	0.0707	1.42 (1.09–1.86)	0.0090
30-d mortality				
Bone/joint	0.31 (0.16–0.59)	0.0022	0.37 (0.18–0.77)	0.0077
CNS	0.19 (0.03–1.36)	0.0982	0.31 (0.04–2.32)	0.2538
Gastrointestinal	0.34 (0.26–0.46)	< 0.0001	0.55 (0.40–0.76)	0.0003
Genitourinary	0.46 (0.36–0.59)	< 0.0001	0.45 (0.35–0.58)	< 0.0001
SSTI	0.34 (0.24–0.49)	< 0.0001	0.45 (0.30–0.67)	< 0.0001
Vascular	1.17 (0.68–2.01)	0.5735	1.21 (0.68–2.16)	0.5145
Unknown	1.09 (0.81–1.46)	0.5894	1.35 (0.98–1.85)	0.0645
Shock				
Bone/joint	0.53 (0.28–0.98)	0.0440	0.57 (0.30–1.06)	0.0774
CNS	0.43 (0.10–1.79)	0.3460	0.65 (0.15–2.75)	0.5559
Gastrointestinal	0.59 (0.44–0.78)	0.0003	0.70 (0.51–0.94)	0.0177
Genitourinary	0.46 (0.36–0.59)	< 0.0001	0.47 (0.36–0.62)	< 0.0001
SSTI	0.59 (0.43–0.82)	0.0016	0.43 (0.29–0.62)	< 0.0001
Vascular	1.10 (0.60–2.03)	0.7603	0.99 (0.52–1.87)	0.9670
Unknown	1.78 (1.34–2.36)	< 0.0001	1.91 (1.43–2.56)	< 0.0001

OR = odds ratio, SSTI = skin and soft tissue infection, Unknown = unknown or unspecified.

[a]Excludes subjects for whom multiple infection site *International Classification of Diseases*, 10th Revision codes were present, with the exception of "Unknown/unspecified" and "Vascular," which were assigned to the alternate site of infection, if present.

[b]Model adjusted for age, sex, body mass index, race, Charlson Comorbidity Index, time to initial antimicrobial, and hospital readmission.

no difference in 30-day mortality as compared with respiratory infections (Table 1). There was no difference in unadjusted OR for the composite for unknown or unspecified infections as compared with respiratory infections. All unadjusted ORs are shown in **eTable 5** (http://links.lww.com/CCX/B235) and adjusted ORs in **eTable 6** (http://links.lww.com/CCX/B235).

DISCUSSION

The study findings demonstrate important variations in clinical markers and outcomes of sepsis in hospitalized patients when analyzed by site of infection. Respiratory, vascular, and unknown or unspecified sites of infection portend worse outcomes than other sites of infection, with significantly higher adjusted and unadjusted odds of the composite outcome and 30-day mortality (Table 1; and eTables 5 and 6, http://links.lww.com/CCX/B235). Additionally, analysis of hospital time prior to initial sepsis criteria positivity demonstrates that respiratory infections reach SIRS, qSOFA, and SOFA positivity significantly earlier than other sites of infection (Fig. 1). These findings challenge the sepsis paradigm in which all patients and all sources of infection are lumped together in single care bundles.

Culture positivity, as shown in eTable 2 (http://links.lww.com/CCX/B235), exposes the limitations of reliance on cultures for diagnosis and management of sepsis. For example, less than 20% of respiratory

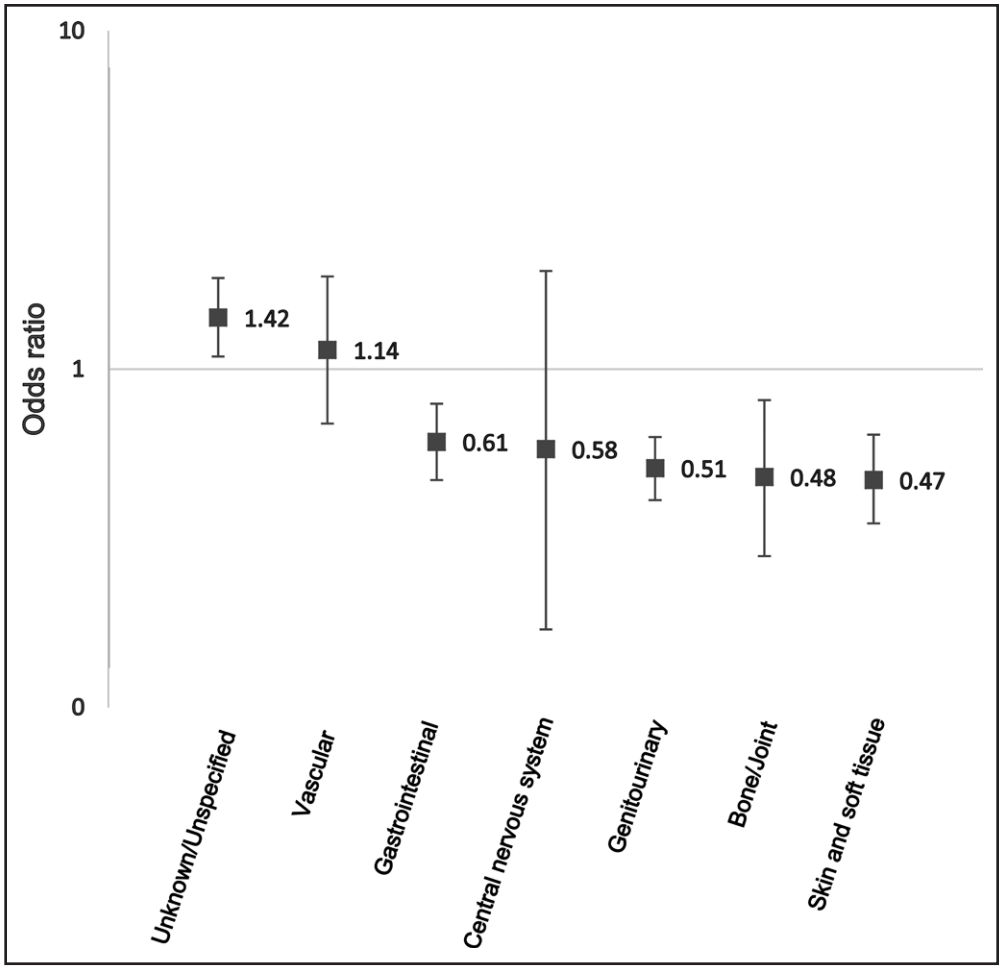

Figure 3. Adjusted odds ratios for the composite outcome by single infection site (reference, respiratory infection). Odds ratio less than 1 is consistent with lower odds of the outcome of interest as compared with respiratory infection and vice versa for odds ratio greater than 1. Model adjusted for age, sex, body mass index, race, Charlson Comorbidity Index, time to initial antimicrobial receipt, and hospital readmission.

infections were associated with bacterial, fungal, or viral organism identification. Only vascular and genitourinary infections reached a threshold of any culture positivity greater than 50%. These findings suggest that continued efforts at improving detection of infectious organisms in the clinical setting is necessary.

The grid heat map shown in Figure 2 displays the heterogeneity of clinical presentation of sepsis by site of infection. Important differences inpatient characteristics, illness severity, and organ systems affected highlight that phenotypic expression of sepsis is, in some way, related to the site of infection. The exact biological mechanism of these differences is poorly understood. Murine models have demonstrated that serum concentration of pro- and anti-inflammatory cytokines such as interleukin (IL)-6, IL-10, and tumor necrosis factor-α varies by method of sepsis induction (i.e., lipopolysaccharide vs cecal ligation) (39–41). Although numerous human studies have assessed the implications of serum concentration of cellular biomarkers in relation to sepsis severity, causative bacterial organism, and molecular genotyping (28, 42–45), there is a paucity of data regarding biomarker expression by site of infection. Further investigation into cellular biomarkers by site of infection might yield interesting findings that aid in our understanding of the cellular mechanisms and clinical manifestations of sepsis.

Clearly, the current standardized approach to sepsis diagnosis and therapy poorly accounts for phenotypic variations in clinical presentation, morbidity, and mortality associated with sepsis syndromes. Novel approaches to deriving sepsis phenotypes through machine learning and artificial intelligence (16) promise to aid in our understanding of sepsis. These approaches will provide opportunities for further research into precision therapies based on an individual's phenotypic expression of sepsis. As demonstrated in this study, site of infection plays a role in the clinical manifestation of sepsis syndromes and should be considered as a relevant variable in future studies.

This study has some limitations. First, it was conducted using retrospective EHR data from a single health system in the United States over a relatively short period of time. Infectious agents, sites of infection, and comorbid conditions differ meaningfully at the global level. As such, our study findings may not be applicable to areas with a different infectious profile or different care model as compared with the United

States. Additionally, representation of some sites of infection, specifically CNS infections, was relatively low in the sample, making analysis more challenging. These aforementioned factors may reduce the generalizability of the study.

Next, we relied on ICD-10 coding to determine site of infection. We used a blind two-reviewer process to mitigate selection bias. We also performed manual chart review on a random subset of patients with strong agreement between ICD-10 coding and chart review. However, the inherent potential for over- and under-coding of infection and site of infection remains. Although there is potential for bias in infection site coding, the direction of that bias is unclear and unlikely to affect the overall study results given the large sample size. It might be possible to use natural language processing and/or unstructured EHR data as an adjunct to, or in lieu of, ICD-10 codes, which could be a future consideration for additional study.

The inability to verify true infection and accurate site of infection in all instances is a major limitation associated with use of ICD-10 coding. Notably, there is overlap between infectious and noninfectious inflammatory conditions, such as cholecystitis, pancreatitis, or pneumonitis. Because many noninfectious inflammatory conditions are often treated as infection during a hospitalization, and furthermore, adjudication of infection is difficult to assess, we erred on the side of inclusivity for these conditions. As previously stated, however, we did exclude patients with ICD-10 codes where the conditions were labeled as "chronic" or "without infection." Study findings should be evaluated with this caveat in mind.

This study demonstrates that using culture data or organism positivity to define infection site greatly underestimates the number of documented infections for nearly all sites. Exclusion of culture negative infections would significantly reduce the power of the study and select for a sicker patient population, as sensitivity analysis demonstrated that blood, respiratory, or the composite of any culture positivity is significantly associated with higher odds of the composite outcome. Additional sensitivity analysis showed no change in the overall results for the composite, 30-day mortality or shock when controlling for positive blood culture (**eTable 7**, http://links.lww.com/CCX/B235).

A particular challenge in this study was the presence of multiple infection sites coded during a single encounter. We felt that excluding admissions with multiple sites of infection coded was most in line with the goal of the study, namely to clearly present phenotypes of sepsis by single infection site. We did not include the group for multiple infection sites in the analysis because we felt that this was too broad a category that would not provide relevant clinical information. Analysis of the whole population including all coded sites of infection demonstrated strong concordance with the study population, lending further credibility to our methodology.

We used a broad definition of sepsis to capture a wider range of presentations and outcomes instead of using Sepsis-3 criteria alone (1). We felt that this approach was advantageous as it afforded a larger sample size and did not preselect for higher severity hospital admissions. This approach, however, increased the potential for identifying false positive cases that were temporally disconnected from the infection. This potential for temporal disconnection was an inherent limitation in the study design, as discharge ICD-10 codes for site of infection were not reliably or consistently time-stamped at the time of infection determination.

Last, we relied on structured EHR data obtained retrospectively for the analysis. With collection of EHR data, there is a risk of missing, inaccurate, or incomplete data. Some variables had significant amounts of missing data (**eTable 8**, http://links.lww.com/CCX/B235), and caution must be taken to avoid overinterpretation of aspects of the heat map with a high proportion of missing data. Data was presumed to be missing at random, but specific data may be over-collected in some conditions, such as erythrocyte sedimentation rate in bone/joint infections or Pco_2 and Po_2 in respiratory infections. MICE was performed to account for missing data and robust statistical analysis was employed to mitigate these limitations in data collection.

CONCLUSIONS

Phenotypic variation in clinical sepsis syndromes exists when stratified by infection site. Respiratory, vascular, and unknown or unspecified sites of infection portend worse outcomes than other sites of infection. A one-size-fits-all approach to sepsis diagnosis management lacks sufficient nuance to optimally identify

and treat those patients at highest risk for morbidity and mortality. Heterogeneity in sepsis should be better recognized and further studies are necessary in order to improve prediction algorithms for sepsis, as well as to develop and guide therapeutic choice in early sepsis.

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