

ORIGINAL RESEARCH

Infectious Disease

Updated estimates of sepsis hospitalizations at United States academic medical centers

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Abstract

Objective: Sepsis is a major public health problem. Understanding the epidemiology of sepsis subtypes is important to quantify the magnitude of the problem and identify targets for system wide treatment strategies. We sought to describe the current national epidemiology of community-acquired (CAS), hospital-acquired (HAS) and healthcare-associated sepsis (HCAS) hospitalizations among academic medical centers in the United States using current discharge diagnosis taxonomies.

Methods: Retrospective analysis of patient discharge data from the Vizient Clinical Data Base/Resource Manager. We identified sepsis hospitalizations using four ICD-10 coding strategies: (1) “Martin” sepsis codes (21 ICD-10 codes), (2) “Angus” sepsis codes (ICD-10 infection + ICD-10 organ dysfunction), (3) Medicare “SEP-1” codes (28 ICD-10 codes), and (4) “explicit sepsis” codes (ICD-10 R65.20 and R65.21). Using present-on-admission flags for each diagnosis, we also distinguished: (1) community-acquired sepsis (CAS), (2) hospital-acquired sepsis (HAS), and (3) healthcare associated sepsis (HCAS).

Results: Among 22,655,240 hospitalizations, the number and incidence of sepsis hospitalizations were: (1) Martin ($n = 1,718,257$, 75.8 per 1000 hospitalizations), (2) Angus ($n = 2,749,163$, 121.3 per 1000), (3) SEP-1 ($n = 1,624,909$, 71.7 per 1000), and (4) explicit sepsis ($n = 655,853$, 28.9 per 1000). CAS was the most common sepsis subtype. HAS exhibited higher adjusted mortality than CAS. ICU admission was highest for HAS (Martin, 1.5%; Angus, 1.5%; SEP-1, 1.6%; Explicit, 1.9%).

Conclusions: These results illustrate the prevalence of sepsis at US academic medical centers using the most current sepsis classification taxonomies and discharge diagnosis codes. These results highlight important considerations when using hospital discharge data to characterize the epidemiology of sepsis.

KEYWORDS

administrative data, discharge diagnoses, epidemiology, sepsis

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1 | INTRODUCTION

1.1 | Background

Sepsis is a life-threatening syndrome of a dysregulated response to infection complicated by organ dysfunction.^{1,2} The public health burden of sepsis is enormous. In 2017, there were an estimated 48.9 million sepsis cases and 11 million sepsis deaths worldwide.³ Sepsis care is multidisciplinary, involving care delivered in emergency departments (EDs), ICUs, and hospital wards.^{4,5}

1.2 | Importance

Characterizing the burden of sepsis is challenging. Hospital data and discharge diagnosis taxonomies (such as those by Martin et al⁶ and Angus et al⁷) have been widely used to characterize the national incidence of sepsis. However, updated identification strategies have been proposed to match evolving conceptual frameworks for sepsis. For example, the Centers for Medicare and Medicaid Services have promulgated the SEP-1 definitions to identify sepsis cases for hospital quality assessment.⁸ Other authors have proposed a narrower set of discharge diagnoses more specifically associated with the updated clinical construct of sepsis.⁹ Prior taxonomies were based on International Classification of Diseases (ICD)-9 diagnosis codes; there have been few updates using the more current ICD-10 discharge diagnosis codes, which were widely implemented in the United States in October 2015.

In addition, there is ongoing awareness of different sepsis phenotypes with potentially different epidemiology, course and outcomes; specifically, community-acquired sepsis (CAS, patients presenting to the hospital with sepsis), hospital-acquired sepsis (HAS, sepsis developing during hospitalization for other conditions), and healthcare associated sepsis (HCAS, sepsis among those with recent exposure to the healthcare setting, such as nursing home patients, chronic hemodialysis patients and those recently discharged from the hospital).¹⁰ Updated estimates comparing and contrasting the most contemporary taxonomies, discharge coding systems and sepsis phenotypes may help to inform the current epidemiology of sepsis and potential strategies for its system wide care.

1.3 | Goals of this investigation

Vizient is a consortium encompassing most of the United States' academic medical centers and their affiliated hospitals. Vizient maintains clinical data base/resource manager (CDB/RM) with data on all hospitalizations at member institutions. We sought to provide an updated description of the demographics, clinical characteristics, incidence, and mortality of sepsis hospitalizations in the Vizient CDB/RM.

The Bottom Line

To describe the epidemiology of sepsis hospitalizations in US academic medical centers, the authors performed a retrospective analysis of more than 22 million hospitalizations from the Vizient Clinical Data Base/Resource Manager with 4 International Classification of Diseases (ICD)-10 coding strategies for sepsis; (1) "Martin," (2) "Angus," (3) Medicare "SEP-1," and (4) "explicit sepsis" codes and further categorizing into (1) community-acquired sepsis (CAS), (2) hospital-acquired sepsis (HAS), and (3) healthcare associated sepsis (HCAS). ICU admission was highest for HAS (Martin, 1.5%; Angus, 1.5%; SEP-1, 1.6%; Explicit, 1.9%). These results illustrate the prevalence of sepsis at US academic medical centers and highlight important considerations when using hospital discharge data to characterize the epidemiology of sepsis.

2 | METHODS

2.1 | Study design

We conducted an analysis of hospital discharge data from the Vizient's CDB/RM for hospital discharges between January 1, 2016 and December 31, 2019. We followed the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.¹¹ The institutional review board of the University of Texas Health Science Center at Houston approved the study.

2.2 | Data source

Vizient, Inc. (formerly known as University HealthSystem Consortium) membership includes more than 50% of the nation's acute care providers, which includes 97% of the nation's academic medical centers and more than 20% of ambulatory providers.¹² The Vizient CDB/RM is an analytic platform for performance improvement populated by more than 600 member health systems and community hospitals nationwide. Member hospitals contribute information on each hospitalization including patient demographics, mortality, length of stay, complications, readmissions, diagnoses, procedures, and resource utilization. Vizient uses its own proprietary risk adjustment index or mortality, length of stay, and direct costs.¹³ Hospital demographic data are not available in the data set.

2.3 | Selection of subjects

For this analysis, we included adults (≥ 18 years) hospitalized for sepsis, either through direct admission or admission through the ED. We excluded ED visits that did not result in admission. We excluded

patients <18 years old, incarcerated, under the care of a hospice organization, or transferred from an outside facility. We excluded psychiatric patients because they are often admitted to a dedicated unit for psychiatric care and not typically vulnerable to sepsis. We excluded hospitalizations involving pregnant women because these events are typically associated with childbirth.

2.4 | Identification of sepsis cases

We applied 4 major strategies using ICD-10 discharge diagnoses to identify sepsis hospitalizations. The “Martin” sepsis system included all hospitalizations with 1 of 21 ICD-10 codes⁶ (Appendix S1). The “Angus” method included sepsis cases with the concurrent presence of 1 of 892 ICD-10 codes for infection plus one of 47 ICD-10 codes for organ dysfunction.⁷ As reported by Buchman et al, Medicare “SEP-1” consisted of discharge diagnoses specified by the Centers for Medicare Services “Severe Sepsis and Septic Shock Early Management Bundle” quality measure.^{14–16} We also applied codes for “explicit sepsis” consisting of ICD-10 codes R65.20 or R65.21.^{17,18} The translation of ICD-9 codes to ICD-10 equivalents was completed by study team consensus assisted by publicly available web-based ICD conversion tools.¹⁹

We also defined 3 sepsis subtypes, leveraging Vizient CDB/RM present-on-admission flags and data for source of admission, and readmission. Of note, Vizient includes present-on-admission flags indicating all discharge diagnoses that were present on hospitalization; this information is recorded by hospital coding personnel. Following prior efforts, we defined community-acquired sepsis (CAS) as sepsis hospitalizations where the relevant sepsis discharge diagnoses were present on admission.¹⁰ We defined hospital-acquired sepsis (HAS) as cases where associated sepsis diagnoses were not flagged as present on admission. Last, we defined healthcare-associated sepsis (HCAS) as patients with community-acquired sepsis who were admitted from an inpatient nursing facility, readmitted within the prior 30 days, or with a history of chronic hemodialysis (as determined from ICD10 codes Z992, Z9115, Z4931, Z4901, Z4902, Z4931, Z4932).

2.5 | Clinical characteristics

Demographics included age, sex, and race. For the Angus sepsis cases, we also determined infection and organ dysfunction types. We identified rates of patients admitted to the ICU, length of hospital stays, and length of ICU stay. We also examined hospital mortality for each sepsis subtype.

2.6 | Data analysis

We analyzed the data through descriptive techniques. We first determined the number of sepsis hospitalizations based on the 4 sepsis taxonomies, depicting the overlap between sepsis classifications using a proportional Venn diagram. We calculated the incidence of HAS, HCAS, and CAS relative to the total number of hospitalizations in the

dataset. We assessed the demographics and hospital stay characteristics for each sepsis type and subtype. We compared the adjusted odds of mortality between sepsis subtypes using mixed logistic regression models with sepsis type (HAS, HCAS, and CAS) as the main predictor. The mixed logistic regression models included age, sex, race, and Vizient’s predicted mortality as fixed effects and hospital as a random effect. Based on the proprietary All Patients Refined Diagnosis Related Group (APR-DRG, 3M Inc, St. Paul, Minnesota), Vizient’s predicted mortality aggregates acuity data across diagnosis groups to generate global expected mortality estimates for each hospitalization.¹³ We analyzed all data using Stata 16.1 (Stata, Inc, College Station, Texas) and R 4.1.0 (The R Foundation for Statistical Computing Platform, Vienna, Austria).

3 | RESULTS

Among 29,238,212 hospitalizations during 2016–2019, we excluded 6,582,972 observations, leaving 22,655,240 hospitalizations in the analysis (Figure 1). A total of 3,424,339 hospitalizations were identified as sepsis by one of the 4 taxonomies. There was a 4-fold difference in the incidence of sepsis between the taxonomies, with the Angus system providing the highest and Explicit providing the lowest incidence of sepsis: Martin (1,718,257 sepsis, 75.8 sepsis cases per 1000 hospitalizations); Angus (2,749,163, 121.3 per 1000); SEP-1 (1,624,909, 71.7 per 1000); explicit sepsis (655,853, 28.9 per 1000) (Table 1; Figure 1).

The Martin and SEP-1 subsets were nearly overlapping (Figure 2). Explicit sepsis cases were nearly fully nested within Martin and SEP-1 groups. The most common sepsis classification combinations were: (Angus only) 48%, (Martin + Angus + SEP-1 + explicit sepsis) 16%, (Martin only) 14%, (Martin + Angus + SEP-1) 13% (Appendix S2). Only 2.5% fulfilled Martin criteria only, 0.6% fulfilled SEP-1 only, and none were explicit sepsis only.

For all sepsis taxonomies, the prevalence of CAS was approximately 3-fold higher than HCAS, and approximately 6-fold higher than hospital-acquired sepsis. (Table 1, Figure 1) For sepsis cases identified by the Angus system, bloodstream and parasitic, genitourinary and respiratory were the most common infection subtypes across CAS, HAS, and HCAS (Appendix S3). Similarly, renal and cardiovascular organ were the most common organ dysfunctions across the sepsis subtypes.

The mean age of sepsis patients ranged from 62–67 years across the sepsis taxonomies and subtypes (Table 1). There were slightly more male than female sepsis patients. Sepsis patients were approximately 3 times more likely to be white than black. Age, sex, and race distributions were consistent across the sepsis taxonomies and subtypes.

For all sepsis subtypes, ICU admissions were slightly almost 2-fold higher with explicit sepsis than the other taxonomies (Table 2). Hospital lengths of stay were markedly higher for HAS than CAS and HCAS, and were 1–2 days longer with the explicit sepsis taxonomy than the other systems. ICU length of stay was 2-fold higher for HAS than CAS or HCAS, and was consistent across all sepsis taxonomy. Across the sepsis taxonomies, HAS were associated with the highest rates of ICU admission, median length of ICU stay and median hospital stay. Across

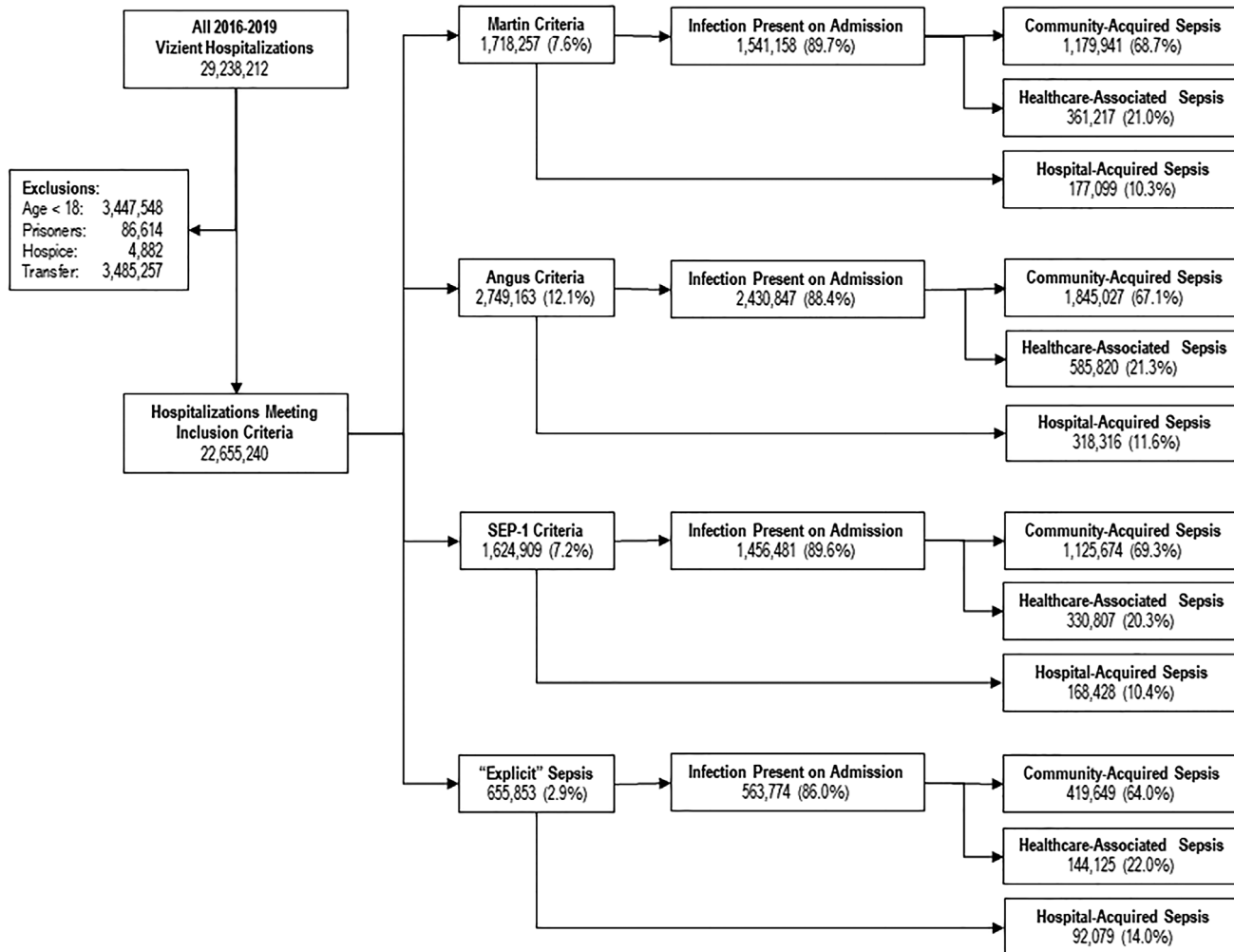


FIGURE 1 Sepsis hospitalizations in the Vizient clinical data base/resource manager, 2016–2019

the sepsis taxonomies, the odds of death were approximately 1.5 times higher for HCAS than CAS, and approximately 3-fold higher for HAS than CAS.

4 | LIMITATIONS

We converted ICD-9 codes to ICD-10 equivalents by study team consensus; there are currently no formally validated strategies for this conversion. Prior efforts to convert ICD-9 to ICD-10 taxonomies followed similar processes.¹⁷ The Vizient data are national in scope but not nationally representative. These data contain only patients from member hospitals (academic medical centers and their affiliated hospitals and other community hospitals). We did not independently validate the present-on-admission flags; however, assignment of present-on-admissions codes is routine in current medical billing practices. We may have also misclassified HCAS patients as CAS patients since Vizient only identifies readmissions to the same facility. We note only 1 prior study has identified CAS, HAS, and HCAS in the Vizient data set.¹⁰

Our study did not differentiate between medical and surgical sepsis. Only discharge diagnoses were available; we did not have access to clinical measures, such as vital signs or laboratory test results. Prior studies have questioned the validity of certain sepsis taxonomies.²⁰ We did not perform an independent validation, which would have required manual review of medical records. Although the 4 described methods provide different estimates, there is currently no gold standard by which to compare the accuracy of the approaches. Additional sepsis identification strategies are possible, such as the system created by the Institute for Health Metrics and Evaluation, which was designed to capture sepsis among the hierarchical structure of the causes of death provided on death certificates.¹⁷ We omitted missing values; we did not use multiple imputation.

5 | DISCUSSION

The results of this study provide updated perspectives of sepsis hospitalizations among United States academic medical centers and their affiliated hospitals populating the national Vizient CDB/RM. Our anal-

TABLE 1 Incidence rates and patient characteristics of sepsis hospitalizations in the Vizient clinical data base/resource manager, 2016–2019

Measure	Martin sepsis (N = 1,718,257; incidence: 75.8 per 1000 hospitalizations)			Angus sepsis (N = 2,749,163; incidence: 121.3 per 1000 hospitalizations)			SEP-1 sepsis (N = 1,624,909; incidence: 71.7 per 1000 hospitalizations)			“Explicit” sepsis (N = 655,853; incidence: 28.9 per 1000 hospitalizations)		
	CAS (n = 1,179,941)	HCAS (n = 361,217)	HAS (n = 177,099)	CAS (n = 1,845,027)	HCAS (n = 585,820)	HAS (n = 318,316)	CAS (n = 1,125,674)	HCAS (n = 330,807)	HAS (n = 168,428)	CAS (n = 419,649)	HCAS (n = 144,125)	HAS (n = 92,079)
Incidence (per 1000 hospitalizations)	52.1	15.9	7.8	81.4	25.9	14.1	49.7	14.6	7.4	18.5	6.4	4.1
Age, mean (SD)	62.4 (18.3)	65.0 (17.6)	62.2 (17.2)	66.2 (16.9)	67.1 (16.4)	63.8 (16.9)	62.5 (18.4)	65.6 (17.4)	62.5 (17.2)	65.1 (17.1)	67.5 (16.3)	63.7 (16.3)
Sex												
Male, No. (%)	608,152 (51.5)	190,172 (52.6)	96,052 (54.2)	933,508 (50.6)	297,601 (50.8)	168,491 (52.9)	579,717 (51.5)	173,089 (52.3)	90,933 (54.0)	221,188 (52.7)	75,936 (52.7)	50,693 (55.1)
Female, No. (%)	571,738 (48.5)	171,043 (47.4)	81,037 (45.8)	911,422 (49.4)	288,205 (49.2)	149,800 (47.1)	545,911 (48.5)	157,716 (47.7)	77,485 (46.0)	198,438 (47.3)	68,187 (47.3)	41,381 (44.9)
Race												
White, No. (%)	783,971 (66.4)	238,534 (66.0)	113,542 (64.1)	1,240,393 (67.2)	395,855 (67.6)	209,503 (65.8)	748,851 (66.5)	218,631 (66.1)	107,800 (64.0)	282,180 (67.2)	95,394 (66.2)	59,415 (64.5)
Black, No. (%)	222,474 (18.9)	75,159 (20.8)	36,755 (20.8)	370,862 (20.1)	120,549 (20.6)	65,011 (20.4)	209,923 (18.6)	68,194 (20.6)	34,984 (20.8)	76,045 (18.1)	29,391 (20.4)	18,759 (20.4)
Asian, No. (%)	35,561 (3.0)	10,319 (2.9)	5626 (3.2)	47,187 (2.6)	13,978 (2.4)	9228 (2.9)	34,442 (3.1)	9628 (2.9)	5370 (3.2)	13,970 (3.3)	4466 (3.1)	2967 (3.2)
Other/unknown No. (%)	137,935 (11.7)	37,205 (10.3)	21,176 (12.0)	186,585 (10.1)	55,438 (9.5)	34,574 (10.9)	132,458 (11.8)	34,354 (10.4)	20,274 (12.0)	47,454 (11.3)	14,874 (10.3)	10,938 (11.9)

Abbreviations: CAS, community-acquired sepsis; HCAS, healthcare associated sepsis; HAS, hospital-acquired sepsis.

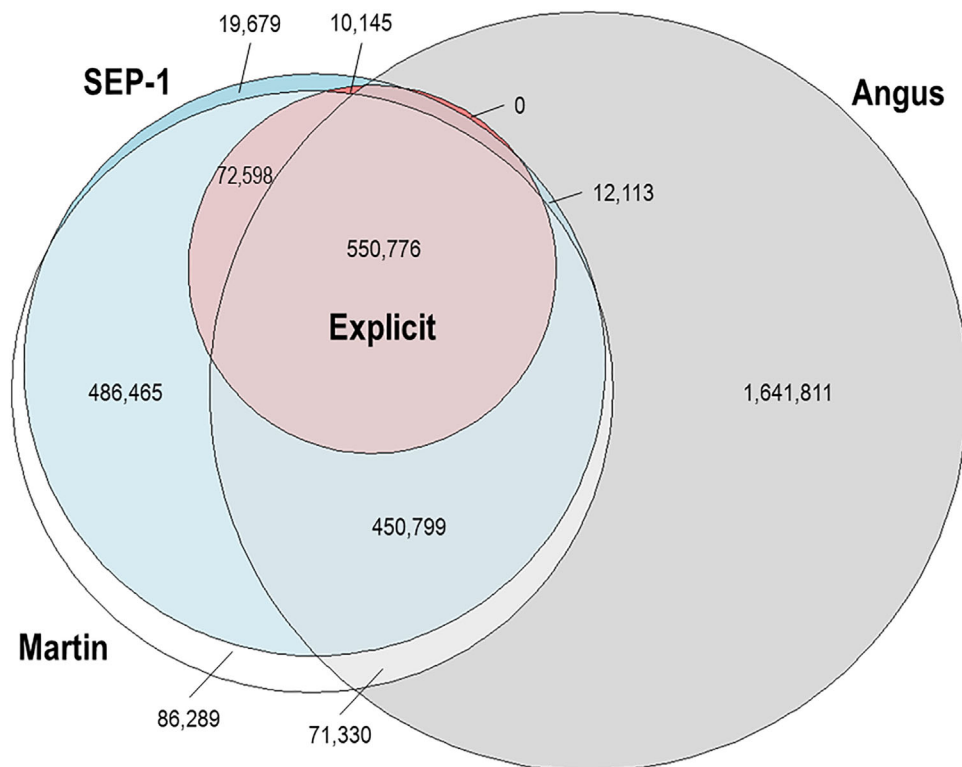


FIGURE 2 Proportional Venn diagram illustrating overlaps between sepsis taxonomies. Frequencies summarized in Appendix S2.

ysis updates prior sepsis rubrics using the newer ICD-10 diagnoses codes as well as newer sepsis diagnosis taxonomies (SEP-1 and explicit sepsis), and offers key insights of the connections between these many systems. We previously illustrated the utility of unique variables in the Vizient data set to identify important sepsis subsets, including CAS, HCAS, and HAS.¹⁰ Our observations add to current knowledge regarding sepsis epidemiology in the United States and provide insights of the methods used for estimating sepsis incidence and outcomes. These results are highly relevant to sepsis care across the spectrum of health care, including the ED, ICU, and hospital ward.

For over 2 decades, hospital discharge data have been used to describe sepsis epidemiology, illuminating its national burden and the characteristics of afflicted patients.^{6,7,21} In the current effort, we illustrated the use of 4 sepsis taxonomies and 3 sepsis subtypes, identifying key observations to inform similar analyses. As expected, the 4 sepsis taxonomies resulted in different sepsis incidence estimates, with the broader Angus criteria capturing a wider number of cases, and the explicit sepsis codes capturing a more select population. As illustrated by the proportional Venn diagram, there are unique patterns of overlap between the 4 taxonomies. Nearly half of sepsis hospitalizations in this series were associated with the Angus system only; this is consistent with broad definitions used by this method and supports sentiment that this approach may be overly sensitive. However, very few cases were associated with only the Martin, SEP-1, or explicit taxonomies. Where precision of case identification is important (eg, assessment of associations with sepsis mortality), the use of multiple taxonomies could offer a viable strategy for sepsis case identification.

There were also some common features observed across the sepsis taxonomies. For example, age, sex, race distribution was similar across the taxonomies. With the exception of the explicit sepsis codes, the Martin, Angus, and SEP-1 codes exhibited similar rates of ICU admission, hospital and ICU lengths of stay, and hospital mortality. Within each taxonomy, the relative distribution of patient and hospitalization characteristics between sepsis subtypes (CAS, HCAS, HAS) were similar. Thus, the distribution of patient features may be consistent across sepsis subtypes. The observed distributions of CAS, HCAS, and HAS followed those seen in prior efforts, suggesting that these identification strategies are robust to the newer ICD-10 coding strategies as well as newer sepsis identification taxonomies.¹⁰

Although easily accessed, hospital discharge data have a key limitation—the absence of clinical data. Discharge data cannot capture key measures important to identifying and characterizing sepsis including vital signs, use of antibiotics, and the timing of infection and organ dysfunction. Many advocate the use of clinical data to define the epidemiology of sepsis.^{18,22–24} In a study of data from 7 health systems, Rhee et al²⁴ identified sepsis hospitalizations using clinical data such as blood cultures, antibiotic and vasopressor administration, mechanical ventilation, and laboratory test measures. The incidence of sepsis in the Rhee et al²⁴ study was 60 per 1000 hospitalizations; although lower than the Angus estimate and higher than the explicit sepsis estimate, this figure is very similar to the Martin et al⁶ and SEP-1 estimates observed in our study. However, although similar to the CAS mortality seen with explicit sepsis codes, the 15% mortality observed in the Rhee study is far higher than the CAS and HCAS mortality that we

TABLE 2 Incidence rates and hospital course of sepsis hospitalizations in the Vizient clinical data base/resource manager, 2016–2019

Measure	Martin sepsis (N = 1,718,257; incidence: 75.8 per 1000 hospitalizations)			Angus sepsis (N = 2,749,163; incidence: 121.3 SEP-1 sepsis (N = 1,624,909; incidence: 71.7 per 1000 hospitalizations)			“Explicit” sepsis (N = 655,853; incidence: 28.9 per 1000 hospitalizations)					
	CAS (n = 1,179,941)	HCAS (n = 364,217)	HAS (n = 177,099)	CAS (n = 1,845,027)	HCAS (n = 585,820)	HAS (n = 318,316)	CAS (n = 1,125,674)	HCAS (n = 330,807)	HAS (n = 168,428)	CAS (n = 419,649)	HCAS (n = 144,125)	HAS (n = 92,079)
ICU admissions, No. (%) ^a	12,918 (1.1)	4124 (1.1)	2698 (1.5)	20,343 (1.1)	6148 (1.0)	4720 (1.5)	12,901 (1.1)	4082 (1.2)	2658 (1.6)	7718 (1.8)	2547 (1.8)	1756 (1.9)
Length of stay, median days (IQR)	5 (3–9)	6 (4–11)	14 (7–26)	6 (3–10)	6 (4–11)	13 (7–23)	5 (3–9)	7 (4–11)	14 (7–25)	7 (4–12)	7 (4–13)	15 (8–28)
Length of ICU stay, median days (IQR)	3 (1–6)	3 (2–6)	6 (3–14)	3 (2–6)	3 (2–6)	6 (3–13)	3 (1–6)	3 (2–6)	6 (3–14)	3 (2–7)	3 (2–7)	7 (3–15)
Hospital mortality, % (95% CI)	7.4% (7.4–7.5)	12.1% (11.9–12.2)	21.1% (21.0–21.3)	6.5% (6.4–6.5)	9.6% (9.5–9.7)	16.0% (15.8–16.1)	7.9% (7.9–8.0)	13.3% (13.2–13.4)	22.6% (22.4–22.8)	16.5% (16.4–16.6)	23.2% (23.0–23.4)	32.9% (32.6–33.2)
Odds of mortality ^b , OR (95% CI)	Ref.	1.4 (1.4–1.4)	3.3 (3.2–3.3)	Ref.	1.4 (1.4–1.4)	2.8 (2.8–2.9)	Ref.	1.4 (1.4–1.4)	3.3 (3.2–3.3)	Ref.	1.3 (1.3–1.3)	2.7 (2.6–2.7)

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; CAS, community-acquired sepsis; HCAS, healthcare associated sepsis; HAS, hospital-acquired sepsis; Ref., Reference.

^a Includes patients admitted to ICU on hospital day 1.

^b Multivariate mixed model comparing healthcare associated and hospital-acquired sepsis mortality with community acquired sepsis. Adjusted for age, sex, race, and Vizient expected mortality, accounting for clustering by hospital.

observed with the Martin, Angus, and SEP-1 taxonomies. Although electronic health record systems are rapidly evolving, enhancing our ability to conduct analyses similar to that of Rhee et al, the decision algorithms for identifying clinical data are still relatively complex. For example, it is difficult to identify infections in electronic health records or the elements of the sequential organ failure assessment (SOFA).²² There is even disagreement about the clinical parameters that comprise sepsis.²⁵

Could discharge data sets remain an important pillar for characterizing the overall burden and course of sepsis? The stability of our estimates across varying coding strategies assures that they may be useful even as sepsis identification constructs evolve. However, coding may be vulnerable to documentation bias. In an analysis of data from 2 academic hospitals, the incidence of hospitalizations with sepsis codes rose dramatically whereas hospitalizations with corresponding objective clinical markers remained stable or decreased.¹⁸ However, if one's goal is to understand the characteristics of the population (vs its total burden), this bias may be acceptable.

In conclusion, we demonstrated the use of varying strategies to characterize the incidence and outcomes of sepsis at academic medical centers in the United States. Our results highlight important considerations when hospital discharge data are used to characterize the epidemiology of sepsis nationally.

AUTHOR CONTRIBUTIONS

Henry E. Wang conceived the study and acquired the data set. Hei Kit Chan analyzed the data. All authors provided interpretation of the data. Hei Kit Chan drafted the manuscript, and all authors contributed substantially to its revision. Henry E. Wang takes responsibility for the paper as a whole.

CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

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SUPPORTING INFORMATION

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

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