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Prevalence and Outcomes of Previously Healthy Adults Among Patients Hospitalized with Community-Onset Sepsis

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Abstract

Background: Devastating cases of sepsis in previously healthy patients have received widespread attention and helped catalyze state and national mandates to improve sepsis detection and care. It is unclear, however, what proportion of patients hospitalized with sepsis were previously healthy and how their outcomes compare to patients with comorbidities.

Research Question: Among adults hospitalized with community-onset sepsis, how many are previously healthy and how do their outcomes compare to those with comorbidities?

Study Design and Methods: We retrospectively identified all adults with community-onset sepsis hospitalized in 373 U.S. hospitals from 2009–2015 using clinical indicators of presumed infection and organ dysfunction (CDC's Adult Sepsis Event criteria). Comorbidities were

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identified using ICD-9-CM codes. We applied generalized linear mixed models to measure the associations between the presence or absence of comorbidities and short-term mortality (in-hospital death or discharge to hospice), adjusting for severity-of-illness on admission.

Results: Of 6,715,286 hospitalized patients, 337,983 (5.0%) had community-onset sepsis. Most sepsis patients (329,052; 97.4%) had at least one comorbidity; only 2.6% were previously healthy. Patients with sepsis who were previously healthy were younger than those with comorbidities (mean 58.0 ± 19.8 vs 67.0 ± 16.5 years), less likely to require ICU care on admission (37.9% vs 50.5%), and more likely to be discharged home (57.9% vs 45.6%) rather than to subacute facilities (16.3% vs 30.8%) but had higher short-term mortality rates (22.8% vs 20.8%, p<.001 for all). The association between previously healthy status and higher short-term mortality persisted after risk-adjustment (adjusted OR 1.99 [95% CI 1.87–2.13])).

Interpretation: The vast majority of patients hospitalized with community-onset sepsis have pre-existing comorbidities. However, previously healthy patients may be more likely to die when they present to the hospital with sepsis compared to patients with comorbidities. These findings underscore the importance of early sepsis recognition and treatment for all patients.

Keywords

sepsis; comorbidity; mortality; epidemiology

Sepsis is a leading cause of death, disability, and cost.[1,2] Despite its high burden, awareness of sepsis among the general public, lay media, and policymakers has traditionally been low.[3,4] Over the last decade, however, devastating cases of sepsis in previously healthy people, including children, young adults, and celebrities, have received widespread attention and, along with efforts of federal agencies and professional societies, helped catalyze state and national mandates to improve sepsis detection and care.[5–7]

Notwithstanding these high-profile cases of sepsis in previously healthy people, it is unclear what fraction of adults hospitalized with sepsis fit this profile. A better understanding of the prevalence of previously healthy status among patients hospitalized with sepsis and how their outcomes compare to those of patients with comorbidities may help improve sepsis recognition, quality of care, and prognostication in an important population and provide context for high-profile reports of sepsis-associated deaths in previously healthy patients. We sought to address these questions using objective clinical criteria to identify patients with community-onset sepsis and a comprehensive administrative definition to identify comorbid conditions.

METHODS

Design, Data Sources, and Population

This was a retrospective cohort study of adults ≥20 years old admitted to 373 U.S. hospitals between January 2009-September 2015 (corresponding to the end of ICD9-CM code use era). Data were drawn from three non-overlapping datasets: Cerner HealthFacts, HCA Healthcare, and Institute for Health Metrics. These datasets are collectively representative of U.S. hospitals in size, teaching status, and geographical distribution.[8] The study was

approved with a waiver of informed consent by the institutional review board at Harvard Pilgrim Health Care Institute.

Sepsis Definition

Prior epidemiologic studies have primarily used administrative data to define sepsis, but these are limited by low sensitivity, inconsistent definitions, and variable diagnosis and coding practices that are changing over time.[9–13] We therefore identified sepsis hospitalizations using CDC Adult Sepsis Event surveillance criteria,[8] which require concurrent clinical indicators of *presumed serious infection* (blood culture order and ≥4 consecutive antibiotic days, or fewer if the patient died, was discharged to hospice, or transferred to another acute hospital before 4 days) and *acute organ dysfunction* (initiation of vasopressors or mechanical ventilation; elevated lactate; or changes in baseline creatinine or glomerular filtration rate, bilirubin, or platelet count). This validated definition has previously been shown to have comparable sensitivity and higher specificity than "implicit" administrative definitions (i.e, concurrent infection and organ dysfunction codes) and comparable specificity with higher sensitivity than "explicit" sepsis diagnosis codes relative to Sepsis-3 criteria as determined by medical record reviews.[8] We focused on patients with community-onset sepsis, defined by blood cultures drawn and first antibiotic administered on hospital day 1 or 2.[14]

Definitions of Comorbidities

Although the Charlson[15] and Elixhauser[16] scores are commonly used to define comorbidities, both methods are optimized for mortality prediction rather than accurate descriptive epidemiology. Indeed, many important chronic comorbidities are not included in either scale, including cystic fibrosis, congenital immunodeficiencies, and leukemia. In addition, some diagnoses, such as fluid and electrolyte disorders, may better reflect acute rather than chronic conditions. To develop a comprehensive set of diagnoses indicative of chronic medical comorbidities, two clinicians (M.A. and C.R.) independently reviewed all ICD9-CM codes in the Agency for Healthcare Research and Quality (AHRQ) Clinical Classifications Software.[17] Comorbidities were classified as major (e.g., heart failure, malignancy) or minor (e.g., hypertension, benign neoplasm) based on their likely impact on patients' short-term mortality (eTable 1, Supplement). Pregnancy with no other comorbidities was considered a separate category, given its temporary nature and the relatively higher risk of sepsis during this period.[18] Cohen's Kappa for agreement between evaluators on defining chronic comorbidities was 97.5% indicating a high level of agreement. Disagreements were resolved by a third clinician (M.K). Previously healthy patients were defined as those without any chronic comorbidity codes.

Statistical Analysis

Descriptive statistics were used to summarize continuous variables using means and standard deviations and categorical variables using frequencies and percentages. Between-group comparisons were performed using t-test and chi-square for continuous and categorical variables, respectively. A generalized linear mixed model analysis was used to fit a logistic regression model to determine the association between comorbid status (as a binary variable) and short-term mortality (defined as in-hospital death or discharge

to hospice), adjusting for age, gender, race, infection site (as determined by ICD-9-CM codes)[19], and severity of illness on admission (need for ICU admission, vasopressors, mechanical ventilation, creatinine, bilirubin, platelet count, white blood cell count, hematocrit, anion gap, aspartate transaminase, and albumin). Missing data for laboratory values were assumed to be normal, as is commonly done for severity of illness scores. Individual hospitals were treated as random effects. Model results from the three data sources were compiled using study-level meta-analysis (SLMA).[20]

We conducted sensitivity analyses using two alternate definitions of "previously healthy": 1) a broader definition that included patients without major comorbidities but did include those with minor comorbidities, pregnancy, or no comorbidities, and 2) a narrower definition that included only relatively young patients (<60 years old) without any major comorbidities. All statistical analyses were conducted in R version 3.6.1, and $p<.05$ (two-sided) was considered statistically significant.

RESULTS

The cohort included 6,715,286 adult hospitalizations, most of which occurred in the Southern US (52.8%), medium-sized hospitals (58.2%), and non-teaching facilities (51.5%). Among these 6.7 million hospitalizations, 337,983 (5.0%) had community-onset sepsis. Most sepsis patients had at least one comorbidity (96.1% major, 1.2% minor alone, 0.1% pregnancy alone); only 8,931 (2.6%) were previously healthy. By comparison, 6.2% of hospitalized patients without sepsis were previously healthy ($p<.001$, Figure 1). Hospitalized patients without sepsis also had fewer major comorbidities compared to patients with sepsis (Figure 1). Among patients with sepsis, the most common comorbidities were hypertension without complications, anemia, and diabetes (Figure 2). Previously healthy sepsis patients were younger (mean 58 vs 67 years) than sepsis patients with comorbidities. Notably, half (50.6%) of previously healthy sepsis patients were less than 60 years old compared to less than a third (31.0%) for the same age group among the comorbid sepsis patients.

Compared to sepsis patients with comorbidities, previously healthy sepsis patients required vasopressors on admission more often (28.9% vs 26.8%) but less mechanical ventilation (12.6% vs 24.1%) and ICU care (37.9% vs. 50.5%) ($p<0.001$ for al comparisons) (Table 1). Previously healthy sepsis patients were less likely to have coding for a specific site of infection, such as pneumonia or a urinary tract infection, but had similar distributions of pathogens identified on blood cultures compared to patients with comorbidities (Table 2). Previously healthy patients had higher short-term mortality rates (22.8% vs 20.8%) but were more likely to be discharged home (57.9% vs 45.6) versus subacute facilities (16.3% vs 30.8%) ($p<0.001$ for all comparisons).

After controlling for baseline characteristics and severity-of-illness on admission, the association between previously healthy status and short-term death persisted (adjusted odds ratio 1.99 [95% CI 1.87–2.13]) (Table 3). Among sepsis patients with comorbidities, failure to thrive, solid cancer, stem cell transplant, chronic liver disease, hematologic malignancy, and dementia were most strongly associated with increased mortality (Figure 2). The

association between previously healthy status and mortality in sepsis patients was consistent across all three datasets (eTable 2, Supplement).

When defining “previously healthy” as no major comorbidities (i.e., only pregnancy, minor comorbidities, or no comorbidities), the prevalence amongst sepsis patients was 3.9% and short-term mortality was 18.3% vs 21.0% for those with major comorbidities. When defining previously healthy as age <60 and no comorbidities and non-pregnant, the prevalence amongst sepsis patients was 1.3% and short-term mortality was 14.6%% vs 20.9% for those ≥60 or with comorbidities. However, after adjusting for age, gender, race, infection site, and severity of illness, the “previously healthy” group using both these definitions still had a higher risk for short-term mortality (adjusted odds ratio 1.32 [95% CI 1.25–1.40] and 2.01 [95% CI 1.82–2.22], respectively).

DISCUSSION

High-profile reports of sepsis in previously healthy patients have increased sepsis awareness and helped catalyze sepsis reporting and management mandates. Despite these high-profile reports, our study suggests that previously healthy patients account for less than 3% of patients hospitalized with sepsis. However, these patients may be more likely to die when they present to the hospital with sepsis compared to those with comorbid conditions. The risk-adjusted association between previously healthy status and higher mortality when hospitalized with sepsis was similar when expanding the definition of “previously healthy” to include comorbidities expected to have a relatively low debilitating effect on functional status, and when narrowing the definition to focus on relatively younger adults without any comorbidities.

The prevalence of comorbid conditions among hospitalized patients with sepsis was substantially higher compared to hospitalized patients without sepsis. The high prevalence of comorbid conditions among patients with sepsis is consistent with prior work demonstrating that many comorbidities are risk factors for developing and dying from sepsis.[21–23] Several serious comorbidities, particularly oncologic diagnoses, dementia, and chronic liver disease were associated with a very high risk of sepsis-associated mortality, consistent with prior studies.[24–26] This underscores the importance of preventative care and health maintenance to reduce the risk of acquiring and dying from sepsis.[27] Notably, several comorbidities, such as diabetes, benign neoplasms, immunodeficiency disorders, and anemia, were actually associated with a lower risk of mortality. This likely reflects the fact that these analyses were relative comparisons amongst patients hospitalized with sepsis rather than a general outpatient healthy cohort. As such, if the average patient with sepsis has multiple severe comorbidities, some conditions may be associated with lower mortality even if they are not inherently protective. Similarly, our findings should not be interpreted to imply that healthy individuals are more likely overall to develop or die from sepsis, as we did not assess sepsis incidence rates in the general population but rather focused on patients hospitalized with sepsis alone.

Our observation that short-term mortality rates were higher in previously healthy patients vs comorbid patients who do develop and present to the hospital with sepsis is novel and

counterintuitive. One potential explanation is that previously healthy patients may wait longer to present to the hospital and therefore are more severely ill on presentation. In contrast, patients with comorbidities may be followed more closely by their healthcare providers and may be quicker to go to the hospital for symptoms of sepsis. This is supported by the slightly higher rates of vasopressor use on admission in the previously healthy group, as shock is the most severe manifestation of sepsis. The relative resilience of these patients may also mean a higher burden of infection is present by the time they develop symptoms severe enough to necessitate hospitalization. Some healthy patients who are unfortunate enough to acquire a life-threatening infection may also produce an overzealous immune response leading to greater organ dysfunction and risk of death. Interestingly, though, aside from the higher rate of vasopressor use, the previously healthy group had overall lower rates of organ dysfunction on admission. The observation that the previously healthy group had less organ dysfunction at presentation, along with our analysis demonstrating persistently higher mortality rates even after adjusting for severity of illness on admission, raises the possibility that worse outcomes might be mediated by differences in how these patients are treated. In particular, sepsis diagnosis and treatment might be delayed in previously healthy patients if clinicians presume younger and healthier patients are less likely to have or develop sepsis or if clinicians presume these patients have a better prognosis. The lower rates of ICU admission indirectly support this possibility. Delays and worse outcomes may also occur if healthy patients more often have unusual infections or infections without a clear source, a possibility supported by the lower rate of specific infectious diagnoses observed in this group. Notably, though, healthy patients with sepsis had similar types and distributions of bloodstream pathogens compared to comorbid patients. Another possibility is that less severe illnesses may be inappropriately treated as sepsis more often when comorbid conditions are present due to the difficulty differentiating whether acute organ dysfunctions are due to infection versus non-infectious exacerbations of pre-existing comorbidities. Furthermore, there is known genetic variability in the predisposition to infection and sepsis;[28] it is possible that genetically predisposed patients may present earlier in life and also be more likely to succumb to these infections.

Our finding that less than 3% of sepsis hospitalizations occurred in previously healthy adults must be taken in the context of the high overall national incidence of sepsis. The CDC, for example, estimates that sepsis afflicts 1.7 million adults annually in the United States.[29] This then translates into sepsis potentially affecting over 40,000 previously healthy adults and contributing to 10,000 deaths each year. These figures underscore the total burden of sepsis among healthy adults, particularly given prior work showing that even previously healthy patients who survive a sepsis hospitalization go on to have worse long-term outcomes compared to patients with nonseptic critical illness and the general population.[30]

Our study has several limitations. First, our data source did not allow us to examine sepsis incidence and impact among the full non-hospitalized population of healthy and chronically ill patients. However, our goal was to better understand, among patients hospitalized for sepsis, how many have no comorbid conditions and how their outcomes compare to patients hospitalized with sepsis who do have comorbid conditions. Second, there is no gold standard definition for comorbidity in the context of descriptive epidemiology. We assessed all potential ICD-9 codes, however, to develop a comprehensive definition explicitly for

this purpose. Third, the distinction between previously healthy and comorbid patients is somewhat arbitrary, as many patients with chronic comorbidities can nonetheless be highly functional and have life expectancies that mirror healthy patients. Fourth, we did not have pre-hospitalization diagnosis codes from outpatient encounters or prior hospitalizations to augment our comorbidity identification strategy hence some patients with comorbidities may have been miscoded as previously healthy. Similarly, without medical record reviews we cannot rule out the possibility that physicians and hospitals may have preferentially coded for acute rather than chronic conditions in some severely ill patients with sepsis.[31,32] Conversely, coding errors could have led to overestimation of the prevalence of some comorbidities, particularly if some hospitals miscoded some acute organ dysfunctions as chronic conditions. Fifth, the Adult Sepsis Event definition relies on blood culture orders and antibiotics to identify patients with sepsis, and it is possible that clinicians' thresholds to perform these actions as well as to admit patients to the hospital may be different in patients who are healthy vs comorbid at baseline. This could introduce selection bias into our analysis. However, these limitations would likely apply to other sepsis surveillance methods as well. Sixth, as described above we have only limited insight into the mechanisms underlying the higher mortality rates in previously healthy sepsis patients. This is an important topic for future research. Seventh, our data were limited to adult patients and so we have no insight into the extent to which our findings apply to children. This is a particularly important area for additional research given the high burden of sepsis among children and their generally greater health and resilience compared to adults.[33] Lastly, our study was conducted using data that preceded the COVID-19 pandemic. It will be important in the future to update our analyses with pandemic data given that many young and healthy patients have been hospitalized and died from severe COVID-19, and the growing consensus that SARS-CoV-2 is a valid and important cause of sepsis.[34]

INTERPRETATION

This large cohort study using detailed clinical data from 373 U.S. hospitals demonstrates that the vast majority of patients hospitalized with community-onset sepsis have pre-existing comorbidities. However, previously healthy patients may be at higher risk for death when they do develop sepsis. These findings underscore the importance of preventative care and health maintenance to prevent sepsis hospitalizations, provide context for high-profile reports about sepsis deaths in previously healthy people, and underscore the importance of early sepsis recognition and treatment for all patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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These funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

ABBREVIATION LIST:

(AHRQ)	Agency for Healthcare Research and Quality
(SLMA)	Study-level meta-analysis
(CDC)	Centers for Disease Control and Prevention

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TAKE-HOME POINTS

Study Question:

What proportion of patients hospitalized for sepsis are previously healthy and how do their outcomes compare to patients with comorbidities?

Results:

In this cohort study of 6.7 million patients admitted to 373 US hospitals, only 2.6% of patients with sepsis were previously healthy, compared to 6.2% of those hospitalized without sepsis. Short-term mortality rates were higher in previously healthy patients versus those with comorbidities (22.8% vs 20.8%), a finding that persisted after risk adjustment.

Interpretation:

The vast majority of patients who develop sepsis have comorbidities, but previously healthy patients may be at higher risk for death when they do develop sepsis.

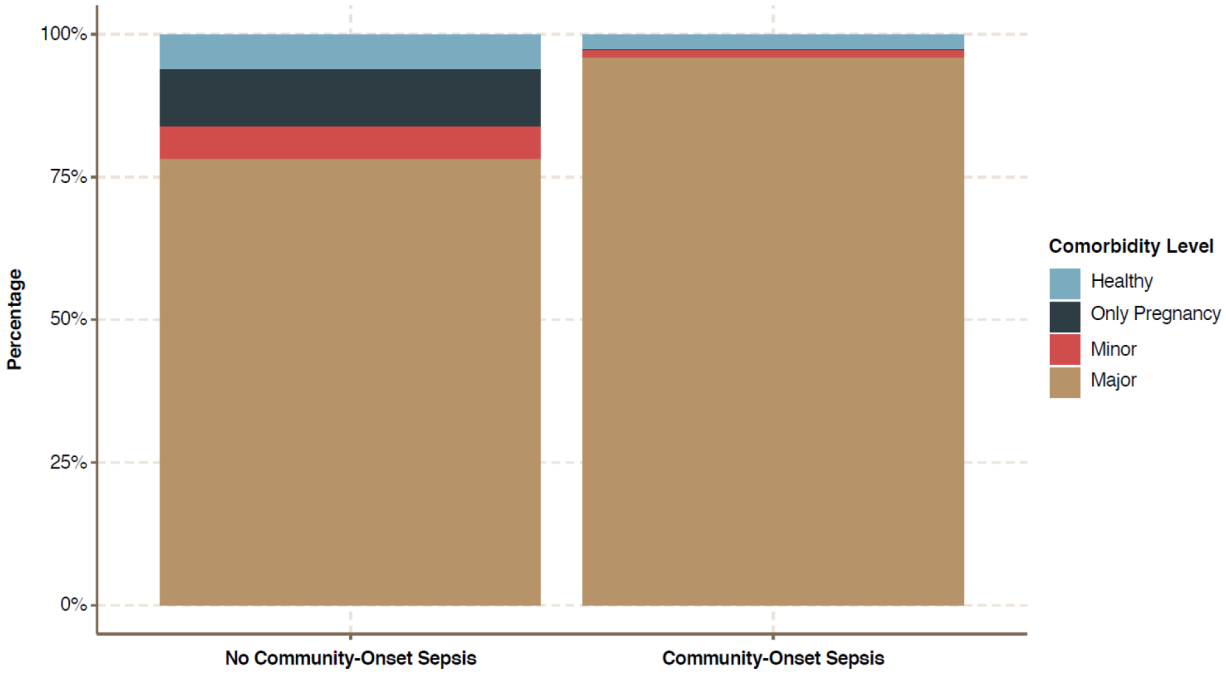

Figure 1.
Prevalence of comorbidities in hospitalized patients with and without community-onset sepsis.

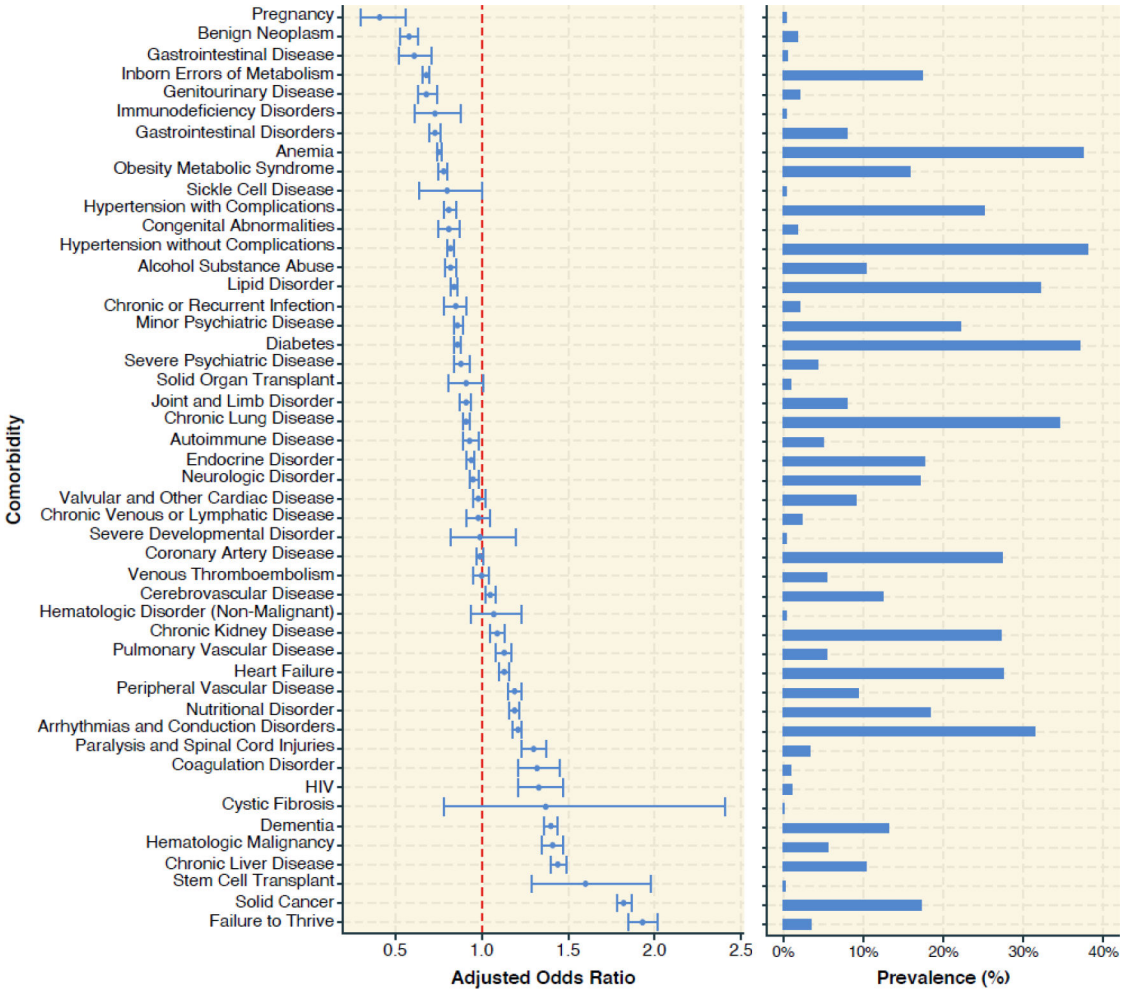

Figure 2.

Adjusted risk for short-term mortality and prevalence of different comorbidities among patients with sepsis.

Odds ratios are adjusted for demographics, severity-of-illness on admission, and type of infection. Prevalence percentages do not sum to 100% as patients can have multiple comorbidities.

Table 1.

Characteristics of Patients with Community-Sepsis by Comorbid vs Previously Healthy Status (n=337,983).

Characteristic	Comorbid (n=329,052, 97.4%)	Previously Healthy (n=8,931, 2.6%)	p-value
Charlson Score (mean ± sd)	2.3 ± 2.1	0 ± 0.4	<.001
Elixhauser Score (mean ± sd)	10.4 ± 8.9	1.4 ± 2.6	<.001
Age, years (mean ± sd)	67.0 ± 16.5	58.0 ± 19.8	<.001
Age Category			<.001
[20, 40)	22,419 (91.7)	2,031 (8.3)	
[40, 60)	79,733 (97.0)	2,491 (3.0)	
[60, 80)	140,794 (98.1)	2,723 (1.9)	
> 80	86,106 (98.1)	1,686 (1.9)	
Male Sex (%)	159,603 (48.5)	4,419 (49.5)	0.07
Race (%)			<.001
White	232,034 (71.4)	5,961 (68)	
Asian	8,538 (2.6)	210 (2.4)	
Black	45,367 (14)	1,301 (14.8)	
Hispanic	28,903 (8.9)	865 (9.9)	
Other	10,129 (3.1)	431 (4.9)	
ICU Admission (%)	166,307 (50.5)	3,389 (37.9)	<.001
ICU LOS, days (mean ± sd)	6.3 ± 11.7	6.4 ± 27.6	0.83
Hospital LOS, days (mean ± sd)	10.7 ± 10.4	9.5 ± 11.4	<.001
CDC Organ Dysfunction			
Ventilation (%)	79,219 (24.1)	1,123 (12.6)	<.001
Vasopressors (%)	88,338 (26.8)	2,580 (28.9)	<.001
Lactate (%)	152,834 (46.4)	3,843 (43)	<.001
Creatinine (%)	161,199 (49)	3,957 (44.3)	<.001
Bilirubin (%)	27,360 (8.3)	1,187 (13.3)	<.001
Platelet (%)	33,210 (10.1)	978 (11)	0.008
Positive Blood Culture (%)	51,839 (15.8)	1,503 (16.8)	.006
Infection Diagnosis			
Septicemia Bacteremia	152625 (46.4)	2427 (27.2)	<.001
Pulmonary	159573 (48.5)	2088 (23.4)	<.001
Genitourinary	108,275 (32.9)	1,468 (16.4)	<.001
Intra-Abdominal	44,012 (13.4)	1,124 (12.6)	0.03
Skin and Soft Tissue	34,134 (10.4)	753 (8.4)	<.001
Bone/Joint	9,429 (2.9)	122 (1.4)	<.001
Obstetrics/Gynecology	1,812 (0.6)	73 (0.8)	<.001
Central Nervous System	3,159 (1)	102 (1.1)	0.082
Other	59,613 (18.1)	879 (9.8)	<.001
Disposition (%)			
Death	159573 (48.5) 47,565 (14.5)	1,773 (19.9)	
Hospice	20,878 (6.3)	256 (2.9)	

Characteristic	Comorbid (n=329,052, 97.4%)	Previously Healthy (n=8,931, 2.6%)	p-value
Hospital Transfer	9,184 (2.8)	278 (3.1)	
Subacute Facility	10,1347 (30.8)	1,454 (16.3)	
Home	150,078 (45.6)	5,170 (57.9)	

Table 2.

Positive Blood Culture Pathogens for Patients with Community-Onset Sepsis by Comorbid vs Previously Healthy Status.

	Community-Onset Sepsis and Positive Blood Cultures (n=53,342)		
	Comorbid (n= 51,839)	**Previously Healthy (n= 1,503)**	**P-value**
PATHOGEN [a]			
Escherichia	12,804 (24.7)	396 (26.3)	0.144
Streptococcus	10,367 (20)	354 (23.6)	<.001
Staph aureus	10,617 (20.5)	276 (18.4)	0.045
Klebsiella	4,843 (9.3)	166 (11)	0.026
Enterococcus	4,035 (7.8)	110 (7.3)	0.507
Yeast	2,602 (5)	69 (4.6)	0.453
Proteus	2,008 (3.9)	60 (4)	0.815
Pseudomonas	2,259 (4.4)	53 (3.5)	0.119
Enterobacter	1,360 (2.6)	36 (2.4)	0.585
Bacteroides	1,039 (2)	32 (2.1)	0.734
PATHOGEN TYPE			
Gram-negative (%)	25,647 (49.5)	765 (50.9)	0.276
Gram-positive (%)	24,499 (47.3)	706 (47)	0.826
Anaerobe (%)	2,874 (5.5)	86 (5.7)	0.767
Fungus(%)	2,799 (5.4)	70 (4.7)	0.209
Polymicrobial (%)	3,688 (7.1)	110 (7.3)	0.276

[a]Patient can have multiple pathogens; pathogens are sorted by decreasing prevalence in the previously healthy group.

Table 3.

Risk-Adjusted Multivariable Model Results for Short-Term Mortality in Sepsis Patients (n=337,983).

Variable	OR (95% CI)	P-value
Previously Healthy	1.99 (1.87–2.13)	<.001
Demographics		
Age	1.04 (1.04–1.04)	<.001
Male Gender	1.01 (0.99–1.02)	0.599
Race		
White	Reference	-
Asian	0.9 (0.84–0.96)	0.002
Black	0.95 (0.92–0.98)	0.001
Hispanic	1.03 (0.99–1.08)	0.153
Other	0.92 (0.87–0.97)	0.003
Severity-of-Illness on Admission [a]		
ICU Admission	1.35 (1.32–1.39)	<.001
CDC Organ Dysfunction – Ventilation	2.33 (2.27–2.38)	<.001
CDC Organ Dysfunction – Vasopressors	2.27 (2.22–2.32)	<.001
Peak Creatinine (mg/dL)	1.01 (1.01–1.01)	<.001
Peak Bilirubin (mg/dL)	1.09 (1.09–1.09)	<.001
Minimum Platelet (× 10^9/L)	1.000 (1.000–1.000)	<.001
Peak WBC (x 10^9/L)	1.01 (1.01–1.01)	<.001
Peak AST (units/L)	1.000 (1.000–1.000)	<.001
Minimum Hematocrit (%)	1.002 (1.001–1.003)	0.002
Peak Anion Gap (mEq/L)	1.03 (1.03–1.03)	<.001
Minimum Albumin (mg/dL)	0.54 (0.53–0.54)	<.001
Port/Type of Infection		
Septicemia Bacteremia	1.34 (1.32–1.37)	<.001
Pulmonary	1.11 (1.09–1.14)	<.001
Genitourinary	0.7 (0.68–0.72)	<.001
Intra-Abdominal	0.67 (0.65–0.69)	<.001
Skin and Soft Tissue	0.66 (0.63–0.68)	<.001
Bone/Joint	0.61 (0.57–0.66)	<.001
Obstetrics/Gynecology	0.56 (0.46–0.67)	<.001
Central Nervous System	1.19 (1.07–1.31)	0.001
Other	0.68 (0.66–0.7)	<.001

The numbers in the Table reflect model results compiled from all three data sources.

[a] Missing lab values were imputed with normal values.