

ORIGINAL RESEARCH

Cardiovascular Events Among Survivors of Sepsis Hospitalization: A Retrospective Cohort Analysis

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BACKGROUND: Sepsis is associated with an elevated risk of late cardiovascular events among hospital survivors.

METHODS AND RESULTS: We included OptumLabs Data Warehouse patients from 2009 to 2019 who survived a medical/nonsurgical hospitalization lasting at least 2 nights. The association between sepsis during hospitalization, based on explicit and implicit discharge *International Classification of Diseases, Ninth Revision (ICD-9)/Tenth Revision (ICD-10)* diagnosis codes, with subsequent death and rehospitalization was analyzed using Kaplan–Meier survival analysis and multivariable Cox proportional-hazards models. The study population included 2 258 464 survivors of nonsurgical hospitalization (5 396 051 total patient-years of follow-up). A total of 808 673 (35.8%) patients had a sepsis hospitalization, including implicit sepsis only in 448 644, explicit sepsis only in 124 841, and both in 235 188. Patients with sepsis during hospitalization had an elevated risk of all-cause mortality (adjusted hazard ratio [HR], 1.27 [95% CI, 1.25–1.28]; $P < 0.001$), all-cause rehospitalization (adjusted HR, 1.38 [95% CI, 1.37–1.39]; $P < 0.001$), and cardiovascular hospitalization (adjusted HR, 1.43 [95% CI, 1.41–1.44]; $P < 0.001$), especially heart failure hospitalization (adjusted HR, 1.51 [95% CI, 1.49–1.53]). Patients with implicit sepsis had higher risk than those with explicit sepsis. A sensitivity analysis using the first hospitalization yielded concordant results for cardiovascular hospitalization (adjusted HR, 1.78 [95% CI, 1.76–1.78]; $P < 0.001$), as did a propensity-weighted analysis (adjusted HR, 1.52 [95% CI, 1.50–1.54]; $P < 0.001$).

CONCLUSIONS: Survivors of sepsis hospitalization are at elevated risk of early and late post-discharge death as well as cardiovascular and non-cardiovascular rehospitalization. This hazard spans the spectrum of cardiovascular events and may suggest that sepsis is an important cardiovascular risk factor.

Key Words: heart failure ■ mortality ■ myocardial infarction ■ sepsis

See Editorial by Wardi et al.

Sepsis is a leading cause of hospitalization, disability, and death worldwide.^{1,2} Despite improvements in the recognition and management of patients with sepsis, short-term mortality in this group remains high.^{3,4} Survivors of hospitalization for sepsis remain at elevated risk of death and other adverse clinical events.^{4–7} The multitude of pathophysiologic mechanisms linking sepsis with adverse outcomes

include persistent inflammation with immune dysregulation, oxidative stress, and the consequences of acute organ dysfunction, including acute kidney injury (AKI).^{8,9} These residual risk pathways remain active after clinical recovery from sepsis, posing the potential for late adverse events to be triggered by a remote episode of sepsis.⁸ Sepsis survivors may suffer from neurocognitive impairment, physical weakness, and

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CLINICAL PERSPECTIVE

What Is New?

- In this retrospective cohort analysis of 2.25 million adult hospital survivors, those with sepsis during hospitalization were at higher risk of death, rehospitalization for any cause, and hospitalization for cardiovascular events during follow-up, even after adjustment for relevant clinical variables or the propensity to have sepsis during hospitalization.
- Hospital survivors with sepsis were at higher risk of all major cardiovascular events throughout the duration of follow-up, including both atherosclerotic and non-atherosclerotic cardiovascular events, with heart failure hospitalization being both the most common cardiovascular event and the cardiovascular event associated with the greatest attributable hazard from sepsis during hospitalization.

What Are the Clinical Implications?

- The excess risk of cardiovascular events in sepsis survivors is substantial enough in magnitude that sepsis should be considered a non-traditional risk factor for cardiovascular events, and further research is needed to determine how best to mitigate this risk in this vulnerable population.

Nonstandard Abbreviation and Acronym

AKI acute kidney injury

other functional limitations; additionally, complications directly related to hospitalization and logistical challenges during follow-up can contribute to health care burden in patients following sepsis.⁷

Cardiovascular disease (CVD) is increasingly recognized as both a risk factor for and a potential consequence of sepsis.¹⁰ The role of inflammation and infection as simultaneous drivers of CVD progression and triggers for CVD events has been recognized for many years across a multitude of contexts, including both early events during hospitalization and late post-discharge events.¹¹ Survivors of sepsis demonstrate an excess risk of mortality and CVD events that may persist for years after hospitalization.^{6,12,13} Complications of sepsis such as AKI have likewise been associated with a higher risk of subsequent CVD events.¹⁴⁻¹⁶ If the elevated risk of CVD events after recovery from sepsis was amenable to preventative therapy, then cardiovascular prevention strategies might be an important component of the care of survivors of sepsis.

Prior studies have observed an association between sepsis and an excess hazard of late postdischarge CVD events; however, a recent meta-analysis of observational studies found that the quality of evidence supporting this association was low because of methodologic limitations of the published studies.¹² Prior studies used variable definitions for sepsis, often inadequately stratified patients by baseline CVD risk and prevalent CVD, and frequently provided limited detail regarding the type of CVD events that occurred or did not include all major CVD events.¹² Furthermore, the comparison group without sepsis in some prior studies may have included lower-risk patients, potentially inflating the apparent risk associated with sepsis attributable to higher baseline risk in the sepsis group. Subsequent higher-quality studies using more robust methods have shown similar associations, but important questions remain.¹³ Therefore, we sought to describe the association between sepsis during hospitalization and subsequent death and rehospitalization (including hospitalization for CVD events) among hospital survivors in a large contemporary cohort while accounting for preexisting CVD and acute organ failure during hospitalization. We hypothesized that hospital survivors with sepsis would have a higher risk of subsequent mortality, rehospitalization, and postdischarge CVD events than hospital survivors without sepsis.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. This manuscript conforms to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for observational studies. The Mayo Clinic Institutional Review Board determined that this study was exempt from review as it used preexisting, deidentified data.

Study Population

In this retrospective cohort analysis, we used de-identified administrative claims data from the OptumLabs Data Warehouse, which contains medical and pharmacy claims and enrollment records for commercial and Medicare Advantage insurance enrollees. The database contains longitudinal health information on enrollees, representing a diverse mixture of ages, ethnicities, and geographic regions across the United States.^{17,18}

Our goal was to identify a study population with an increased risk of CVD events to ensure that we did not compare patients with sepsis with high CVD risk with patients without sepsis with low CVD risk. Therefore, we included adult patients (≥ 18 years) hospitalized for at least 2 nights for nonsurgical encounters (medical

disease-related group) between January 1, 2009, and December 31, 2019. To minimize loss to follow-up, patients were required to have continuous medical insurance coverage for at least 6 months before the index hospital admission and 30 days after the index hospital discharge. To enrich the study population in patients with or at risk of CVD events, additional inclusion criteria included ≥ 1 of the following: preexisting CVD diagnosis before hospital admission (Table S1), CVD diagnosis during the index hospitalization, age ≥ 50 years, age ≥ 40 years plus ≥ 1 CVD risk factors (Table S2), or age ≥ 30 years plus ≥ 2 CVD risk factors.

Sepsis Definitions

To ensure that our results were not confounded by subsequent sepsis hospitalizations in the nonsepsis group, patients were assigned to mutually exclusive groups on the basis of whether they had a hospitalization with sepsis during the study period. Hospitalizations were categorized as sepsis or nonsepsis on the basis of primary and secondary discharge *International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9/10-CM)* codes for sepsis or established criteria based on combinations of ICD-9/10 codes.¹ All patients meeting the criteria for sepsis during any hospitalization within the study period were classified as having sepsis, and all patients who did not meet criteria for sepsis during any hospitalization within the study period were classified as not having sepsis. For patients with multiple hospitalizations during the study period, the first hospitalization for sepsis was used as the index hospitalization (even if there were prior nonsepsis hospitalizations). If there was not a diagnosis of sepsis during a hospitalization, then the first hospitalization was used as the index hospitalization. Sepsis was further classified as explicit, implicit, or both on the basis of ICD-9/10 diagnosis codes from the index hospitalization.¹ Explicit sepsis was defined as the presence of diagnosis codes for sepsis or septic shock (Table S3).¹ Implicit sepsis was defined using established criteria based on the presence of ≥ 1 diagnoses for infection combined with ≥ 1 diagnoses for acute organ dysfunction during the index hospitalization (Table S4).^{1,19} We performed a sensitivity analysis by reassigning the sepsis and nonsepsis groups on the basis of the discharge diagnoses from the first eligible hospitalization during the study period.

Covariates

Patient demographic characteristics included age (18–54, 55–64, 65–74, 75+ years), sex (female or male), race or ethnicity (Black, White, Asian, Hispanic), region (Midwest, Northeast, South, West), type of health plan (commercial, Medicare Advantage), and year of the index hospitalization. Comorbidities of interest included

prior CVD (coronary artery disease, myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass grafting or other cardiac surgery, heart failure, cardiomyopathy, atrial fibrillation, supraventricular tachycardia, stroke, ventricular tachycardia, implantable cardioverter-defibrillator or pacemaker), the number of CVD risk factors (hypertension, hyperlipidemia, diabetes, chronic kidney disease/dialysis, obesity, smoking), and the number of all-cause hospitalizations in the prior 6 months. Additional covariates included indicators for diagnoses or procedures during the index hospitalization (infection, organ failure, admission to intensive care unit [ICU], use of invasive ventilation, hemodialysis, CVD diagnosis), and index hospitalization length of stay (Table S5).

Outcomes

Patients were followed from index hospital discharge until the end of the study period (December 31, 2020), the end of insurance enrollment, or death, whichever happened first. Mortality was obtained from the Social Security Administration's Death Master File and discharge status information. Outcomes included all-cause mortality after hospital discharge, all-cause rehospitalization, and CVD events. A CVD event was defined as the first rehospitalization in which the primary diagnosis was for heart failure, myocardial infarction, angina, atrial fibrillation/flutter, cardiac arrest, coronary disease, valve disease, cardiomyopathy, supraventricular tachycardia, ventricular tachycardia, stroke, or intracranial hemorrhage. Two composite outcomes were also analyzed: (1) all-cause mortality or all-cause hospitalization and (2) all-cause mortality or CVD hospitalization.

Statistical Analysis

Baseline patient characteristics were reported as frequencies (percentages) for categorical data and means (SD) for continuous variables. Unadjusted event rates were reported for each outcome using the number of patients with the given event as numerator and person-years (time to the first event, death, or end of enrollment) as the denominator. Kaplan–Meier survival analysis was used to estimate postdischarge events rates, with groups compared by log-rank test. Cox proportional hazards regressions with multivariable adjustment were used to compare nonsepsis to sepsis index hospitalizations for each outcome. Results were presented as hazard ratios (HRs) and 95% CIs. The Fine and Gray method was used to consider death as a competing risk when assessing nonfatal outcomes in the Cox models. The proportional hazard assumptions were tested using Schoenfeld residual plots, and no violations of the assumptions were found. All models included the covariates age, sex, race, region, health plan, index year, history of CVD, number of cardiovascular risk factors,

index hospitalization characteristics (infection, organ failure, ICU, ventilator, hemodialysis, CVD diagnosis), and number of prior hospitalizations. Subgroup analyses included stratification by sepsis type, age, sex, race, health plan, pharmacy coverage, prior CVD, number of CVD risk factors, prior hospitalization status, and index hospitalization characteristics (ICU, CVD, organ failure, renal failure, and shock) for each outcome. A propensity score for sepsis was generated using multivariable logistic regression, and the main analysis was repeated using propensity score overlap weighting, with variables included in the propensity score shown in [Table S6](#); all standardized mean differences were <0.001 after propensity weighting. All analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) and Stata 15.1 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics

We identified 2 258 464 survivors of nonsurgical hospitalizations between 2009 and 2019 ([Figure S1](#)), encompassing 5 396 051 total patient-years of postdischarge follow-up. The overall mean (SD) age of the cohort was 64.4 (14.6) years. The majority were women (54.4%), White (62.5%), from the South (45.8%), and enrolled in a Medicare Advantage health plan (53.6%).

A total of 808 673 (35.8%) patients had sepsis during at least 1 hospitalization in the study period, including implicit sepsis only in 448 644, explicit sepsis only in 124 841, and both in 235 188 ([Figure S1](#)). An *ICD-9/10* code for septic shock was present in 43 188 (12.0%) of patients with explicit sepsis. Patients with sepsis hospitalizations differed substantially from patients hospitalized without sepsis ([Table 1](#)), including older age, more Medicare Advantage enrollees, more infection and organ failure, more comorbidities and CVD risk factors, more preexisting and inpatient CVD diagnoses (including all examined CVD diagnoses), greater use of critical care therapies (including the need for ICU care), and a longer hospital length of stay. The most common hospital discharge disease-related groups in patients without sepsis included cardiovascular/circulatory (19.0%), digestive (15.7%), respiratory (12.8%), nervous system (12.0%), and mental health (5.3%). Additional differences in hospitalization characteristics were observed among patients with sepsis when groups with implicit sepsis, explicit sepsis, and both were compared ([Table 2](#)). In general, the group with explicit sepsis had the lowest risk profile, and the group with both implicit and explicit sepsis had the highest risk profile.

Outcomes

Compared with patients hospitalized without a sepsis diagnosis, patients hospitalized with sepsis had an

elevated risk of all examined postdischarge adverse events ([Table 3](#)), including all-cause mortality (adjusted HR, 1.27 [95% CI, 1.25–1.28]; $P<0.001$; [Figure 1](#)), all-cause rehospitalization (adjusted HR, 1.38 [95% CI, 1.37–1.39]; $P<0.001$), cardiovascular hospitalization (adjusted HR, 1.43 [95% CI, 1.41–1.44]; $P<0.001$; [Figure 2](#)), and the composite of all-cause mortality and either all-cause hospitalization or cardiovascular hospitalization. Event rates were higher in the sepsis group at both early and late time points ([Tables S7](#) through [S9](#)). The risk of all postdischarge adverse events was elevated for implicit sepsis, explicit sepsis, and both compared with patients without sepsis, with variability in the magnitude of excess risk based on the sepsis definition ([Table 3](#)). The highest crude risk of posthospitalization adverse events was observed in the implicit sepsis group, followed by the group with both implicit and explicit sepsis, followed by the group with explicit sepsis, with the lowest event rate in the group without sepsis ([Figures 2](#) and [3](#)). Survivors of hospitalizations with sepsis were at elevated risk of subsequent hospitalization for each major type of CVD event (coronary, heart failure, stroke, arrhythmia, and shock), hospitalization for infection, and hospitalization for other noncardiovascular/noninfection indications ([Table 4](#)). The excess risk associated with sepsis appeared to be highest for hospitalization for heart failure (adjusted HR, 1.51 [95% CI, 1.49–1.53]). Patients with sepsis during hospitalization had an excess risk of rehospitalization for infection (adjusted HR, 1.99 [95% CI, 1.94–2.04]); by definition, subsequent infection hospitalizations in the no-sepsis group did not meet the criteria for sepsis.

Subgroup Analyses

The presence of sepsis during hospitalization was associated with an elevated risk of postdischarge all-cause mortality, all-cause rehospitalization, and cardiovascular hospitalization in each of the predefined subgroups ([Tables S10](#) through [S14](#)). The strength of association between sepsis and outcomes varied across these subgroups, with significant interaction terms observed in most subgroups. For all-cause postdischarge mortality, the adjusted HR values were higher for patients aged <65 years (particularly those aged <50 years), non-White race, commercial insurance enrollees, those without CVD (preexisting or diagnosed during hospitalization), those without organ failure (including AKI or shock), those with recent prior hospitalization, and those who did not receive ICU care. The excess risk of all-cause hospitalization (using death as a competing risk) was consistent in all subgroups, with only modest differences in risk. For cardiovascular hospitalization (using death as a competing risk), the adjusted HR values were higher for patients aged <65 years and commercial insurance enrollees, those without CVD

Table 1. Patient Characteristics of Hospitalizations With and Without Sepsis (Any Type)

	No sepsis (N=1 449 821)	Sepsis (N=808 673)	Total (N=2 258 464)	P value
Age, y				<0.0001
Mean (SD)	62.0 (14.8)	68.7 (13.2)	64.4 (14.6)	
Age group, n (%)				<0.0001
18–54 y	450 919 (31.1)	124 249 (15.4)	575 168 (25.5)	
55–64 y	347 422 (24.0)	158 929 (19.7)	506 351 (22.4)	
65–74 y	285 200 (19.7)	194 439 (24.0)	479 639 (21.2)	
75+ years	366 280 (25.3)	331 056 (40.9)	697 336 (30.9)	
Sex, n (%)				<0.0001
Female	789 512 (54.5)	438 058 (54.2)	1 227 570 (54.4)	
Male	660 309 (45.5)	370 615 (45.8)	1 030 924 (45.6)	
Race or ethnicity, n (%)				<0.0001
Asian	29 040 (2.0)	15 111 (1.9)	44 151 (2.0)	
Black	175 979 (12.1)	111 710 (13.8)	287 689 (12.7)	
Hispanic	104 385 (7.2)	56 236 (7.0)	160 621 (7.1)	
White	888 816 (61.3)	522 351 (64.6)	1 411 167 (62.5)	
Unknown	251 601 (17.4)	103 265 (12.8)	354 866 (15.7)	
Region, n (%)				<0.0001
Midwest	404 171 (27.9)	226 434 (28.0)	630 605 (27.9)	
Northeast	227 047 (15.7)	132 902 (16.4)	359 949 (15.9)	
South	666 092 (45.9)	368 145 (45.5)	1 034 237 (45.8)	
West	149 456 (10.3)	80 006 (9.9)	229 462 (10.2)	
Unknown	3055 (0.2)	1186 (0.1)	4241 (0.2)	
Health plan, n (%)				<0.0001
Commercial	789 400 (54.4)	257 979 (31.9)	1 047 379 (46.4)	
Medicare advantage	660 421 (45.6)	550 694 (68.1)	1 211 115 (53.6)	
Index year, n (%)				<0.0001
2009	130 672 (9.0)	42 340 (5.2)	173 012 (7.7)	
2010	118 177 (8.2)	44 137 (5.5)	162 314 (7.2)	
2011	125 063 (8.6)	51 960 (6.4)	177 023 (7.8)	
2012	132 417 (9.1)	58 639 (7.3)	191 056 (8.5)	
2013	131 258 (9.1)	64 373 (8.0)	195 631 (8.7)	
2014	118 103 (8.1)	63 891 (7.9)	181 994 (8.1)	
2015	107 710 (7.4)	61 976 (7.7)	169 686 (7.5)	
2016	119 401 (8.2)	78 149 (9.7)	197 550 (8.7)	
2017	142 898 (9.9)	101 541 (12.6)	244 439 (10.8)	
2018	157 028 (10.8)	116 084 (14.4)	273 112 (12.1)	
2019	167 094 (11.5)	125 583 (15.5)	292 677 (13.0)	
Prior CVD, n (%)	642 309 (44.3)	496 616 (61.4)	1 138 925 (50.4)	<0.0001
Coronary artery disease	446 032 (30.8)	356 481 (44.1)	802 513 (35.5)	<0.0001
Myocardial infarction	133 617 (9.2)	126 051 (15.6)	259 668 (11.5)	<0.0001
Percutaneous coronary intervention	103 615 (7.1)	80 653 (10.0)	184 268 (8.2)	<0.0001
Coronary artery bypass grafting	85 075 (5.9)	73 615 (9.1)	158 690 (7.0)	<0.0001
Valve procedure	11 597 (0.8)	10 459 (1.3)	22 056 (1.0)	<0.0001
Heart failure	222 407 (15.3)	256 655 (31.7)	479 062 (21.2)	<0.0001
Cardiomyopathy	100 189 (6.9)	96 784 (12.0)	196 973 (8.7)	<0.0001
Atrial fibrillation	203 769 (14.1)	189 976 (23.5)	393 745 (17.4)	<0.0001
Supraventricular tachycardia	47 782 (3.3)	37 337 (4.6)	85 119 (3.8)	<0.0001
Stroke	133 088 (9.2)	138 394 (17.1)	271 482 (12.0)	<0.0001
Ventricular tachycardia	48 135 (3.3)	47 666 (5.9)	95 801 (4.2)	<0.0001
Implanted cardiac device	69 439 (4.8)	65 183 (8.1)	134 622 (6.0)	<0.0001

(Continued)

Table 1. Continued

	No sepsis (N=1 449 821)	Sepsis (N=808 673)	Total (N=2 258 464)	P value
Number of CVD risk factors				<0.0001
0	132 031 (9.1)	38 526 (4.8)	170 557 (7.6)	
1	236 741 (16.3)	82 449 (10.2)	319 190 (14.1)	
2	397 542 (27.4)	170 337 (21.1)	567 879 (25.1)	
3	372 798 (25.7)	225 234 (27.9)	598 032 (26.5)	
4	222 209 (15.3)	181 266 (22.4)	403 475 (17.9)	
5	77 777 (5.4)	91 303 (11.3)	169 080 (7.5)	
6	10 723 (0.7)	19 558 (2.4)	30 281 (1.3)	
CVD during index hospitalization, n (%)	651 451 (44.9)	453 454 (56.1)	1 104 905 (48.9)	<0.0001
Heart failure	204 613 (14.1)	225 294 (27.9)	429 907 (19.0)	<0.0001
Myocardial infarction	55 056 (3.8)	41 637 (5.1)	96 693 (4.3)	<0.0001
Angina	37 072 (2.6)	8 435 (1.0)	45 507 (2.0)	<0.0001
Atrial fibrillation	207 768 (14.3)	168 809 (20.9)	376 577 (16.7)	<0.0001
Arrest	5626 (0.4)	6974 (0.9)	12 600 (0.6)	<0.0001
Coronary artery disease	267 646 (18.5)	167 828 (20.8)	435 474 (19.3)	<0.0001
Valve disease	176 252 (12.2)	124 402 (15.4)	300 654 (13.3)	<0.0001
Cardiomyopathy	76 338 (5.3)	54 715 (6.8)	131 053 (5.8)	<0.0001
Supraventricular tachycardia	19 657 (1.4)	15 716 (1.9)	35 373 (1.6)	<0.0001
Ventricular tachycardia	27 752 (1.9)	23 518 (2.9)	51 270 (2.3)	<0.0001
Stroke	133 127 (9.2)	60 554 (7.5)	193 681 (8.6)	<0.0001
Intracranial bleed	36 876 (2.5)	12 669 (1.6)	49 545 (2.2)	<0.0001
Shock during index hospitalization, n (%)	7141 (0.5)	56 228 (7.0)	63 369 (2.8)	<0.0001
Cardiogenic	1728 (0.1)	4616 (0.6)	6344 (0.3)	<0.0001
Septic	0 (0.0)	44 099 (5.5)	44 099 (1.9)	<0.0001
Infection during index hospitalization				
Central nervous system	2621 (0.2)	3769 (0.5)	6390 (0.3)	<0.0001
Cardiac/vascular	9231 (0.6)	11 786 (1.5)	21 017 (0.9)	<0.0001
Ear/nose/throat/upper respiratory	14 039 (1.0)	15 748 (1.9)	29 787 (1.3)	<0.0001
Pulmonary	68 570 (4.7)	277 549 (34.3)	346 119 (15.3)	<0.0001
Gastrointestinal	52 010 (3.6)	31 670 (3.9)	83 680 (3.7)	<0.0001
Genitourinary	81 736 (5.6)	247 626 (30.6)	329 362 (14.6)	<0.0001
Skin/soft tissue/bone/joint	73 925 (5.1)	82 120 (10.2)	156 045 (6.9)	<0.0001
Bacterial/fungal	83 972 (5.8)	381 206 (47.1)	465 178 (20.6)	<0.0001
Iatrogenic	14 444 (1.0)	21 269 (2.6)	35 713 (1.6)	<0.0001
Sepsis/bacteremia	3242 (0.2)	168 363 (20.8)	171 605 (7.6)	<0.0001
Index hospitalization, n (%)				
Organ failure	337 252 (23.3)	686 402 (84.9)	1 023 654 (45.3)	<0.0001
ICU admission	449 257 (31.0)	357 378 (44.2)	806 635 (35.7)	<0.0001
Ventilator	11 580 (0.8)	41 662 (5.2)	53 242 (2.4)	<0.0001
Hemodialysis	4625 (0.3)	17 447 (2.2)	22 072 (1.0)	<0.0001
Length of stay, d				<0.0001
Mean (SD)	4.2 (4.2)	6.7 (7.5)	5.1 (5.8)	
No. of hospitalizations in prior 6mo				<0.0001
Mean (SD)	0.1 (0.4)	0.4 (0.8)	0.2 (0.6)	

CVD indicates cardiovascular disease; and ICU, intensive care unit.

(preexisting or diagnosed during hospitalization), those with recent prior hospitalization, and those with shock or organ failure during hospitalization. Similar patterns were observed across subgroups for the

composite outcomes of death and all-cause or cardiovascular rehospitalization. The risk of postdischarge adverse outcomes varied according to the presence and type of infection diagnosis codes (Table S15).

Table 2. Patient Characteristics of Hospitalizations With Sepsis According to the Type of Sepsis

	Both implicit and explicit (N=235188)	Explicit only (N=124841)	Implicit only (N=448644)	Total (N=808673)	P value
Age, y					<0.0001
Mean (SD)	68.8 (13.2)	64.0 (14.4)	69.9 (12.6)	68.7 (13.2)	
Age group, n (%)					<0.0001
18–54y	34 786 (14.8)	32 687 (26.2)	56 776 (12.7)	124 249 (15.4)	
55–64y	46 585 (19.8)	29 249 (23.4)	83 095 (18.5)	158 929 (19.7)	
65–74y	58 620 (24.9)	26 736 (21.4)	109 083 (24.3)	194 439 (24.0)	
75+ y	95 197 (40.5)	36 169 (29.0)	199 690 (44.5)	331 056 (40.9)	
Sex, n (%)					<0.0001
Female	117 700 (50.0)	66 682 (53.4)	253 676 (56.5)	438 058 (54.2)	
Male	117 488 (50.0)	58 159 (46.6)	194 968 (43.5)	370 615 (45.8)	
Race or ethnicity, n (%)					<0.0001
Asian	5102 (2.2)	2806 (2.2)	7203 (1.6)	15 111 (1.9)	
Black	31 520 (13.4)	14 069 (11.3)	66 121 (14.7)	111 710 (13.8)	
Hispanic	16 773 (7.1)	10 560 (8.5)	28 903 (6.4)	56 236 (7.0)	
White	151 089 (64.2)	77 294 (61.9)	293 968 (65.5)	522 351 (64.6)	
Unknown	30 704 (13.1)	20 112 (16.1)	52 449 (11.7)	103 265 (12.8)	
Region					<0.0001
Midwest	65 166 (27.7)	33 670 (27.0)	127 598 (28.4)	226 434 (28.0)	
Northeast	39 230 (16.7)	21 857 (17.5)	71 815 (16.0)	132 902 (16.4)	
South	103 667 (44.1)	54 627 (43.8)	209 851 (46.8)	368 145 (45.5)	
West	26 702 (11.4)	14 451 (11.6)	38 853 (8.7)	80 006 (9.9)	
Unknown	423 (0.2)	236 (0.2)	527 (0.1)	1186 (0.1)	
Health plan, n (%)					<0.0001
Commercial	73 111 (31.1)	59 432 (47.6)	125 436 (28.0)	257 979 (31.9)	
Medicare advantage	162 077 (68.9)	65 409 (52.4)	323 208 (72.0)	550 694 (68.1)	
Index year, n (%)					<0.0001
2009	8659 (3.7)	6055 (4.9)	27 626 (6.2)	42 340 (5.2)	
2010	9074 (3.9)	6409 (5.1)	28 654 (6.4)	44 137 (5.5)	
2011	11 630 (4.9)	7560 (6.1)	32 770 (7.3)	51 960 (6.4)	
2012	13 601 (5.8)	8529 (6.8)	36 509 (8.1)	58 639 (7.3)	
2013	16 087 (6.8)	9375 (7.5)	38 911 (8.7)	64 373 (8.0)	
2014	17 523 (7.5)	10 140 (8.1)	36 228 (8.1)	63 891 (7.9)	
2015	18 762 (8.0)	10 420 (8.3)	32 794 (7.3)	61 976 (7.7)	
2016	24 895 (10.6)	13 151 (10.5)	40 103 (8.9)	78 149 (9.7)	
2017	33 288 (14.2)	15 816 (12.7)	52 437 (11.7)	101 541 (12.6)	
2018	38 603 (16.4)	18 195 (14.6)	59 286 (13.2)	116 084 (14.4)	
2019	43 066 (18.3)	19 191 (15.4)	63 326 (14.1)	125 583 (15.5)	
Prior CVD, n (%)	141 890 (60.3)	60 720 (48.6)	294 006 (65.5)	496 616 (61.4)	<0.0001
Coronary artery disease	100 358 (42.7)	42 409 (34.0)	213 714 (47.6)	356 481 (44.1)	<0.0001
Myocardial infarction	35 489 (15.1)	13 170 (10.5)	77 392 (17.3)	126 051 (15.6)	<0.0001
Percutaneous coronary intervention	22 277 (9.5)	8911 (7.1)	49 465 (11.0)	80 653 (10.0)	<0.0001
Coronary artery bypass grafting	20 558 (8.7)	7654 (6.1)	45 403 (10.1)	73 615 (9.1)	<0.0001
Valve procedure	3251 (1.4)	1338 (1.1)	5870 (1.3)	10 459 (1.3)	<0.0001
Heart failure	70 934 (30.2)	23 998 (19.2)	161 723 (36.0)	256 655 (31.7)	<0.0001
Cardiomyopathy	26 866 (11.4)	9081 (7.3)	60 837 (13.6)	96 784 (12.0)	<0.0001
Atrial fibrillation	54 241 (23.1)	20 462 (16.4)	115 273 (25.7)	189 976 (23.5)	<0.0001
Supraventricular tachycardia	10 647 (4.5)	4894 (3.9)	21 796 (4.9)	37 337 (4.6)	<0.0001
Stroke	40 243 (17.1)	15 073 (12.1)	83 078 (18.5)	138 394 (17.1)	<0.0001
Ventricular tachycardia	13 590 (5.8)	4590 (3.7)	29 486 (6.6)	47 666 (5.9)	<0.0001
Implanted device	17 934 (7.6)	5946 (4.8)	41 303 (9.2)	65 183 (8.1)	<0.0001

(Continued)

Table 2. Continued

	Both implicit and explicit (N=235188)	Explicit only (N=124841)	Implicit only (N=448644)	Total (N=808673)	P value
Number of cardiovascular risk factors, n (%)					<0.0001
0	11 796 (5.0)	8455 (6.8)	18 275 (4.1)	38 526 (4.8)	
1	23 805 (10.1)	17 328 (13.9)	41 316 (9.2)	82 449 (10.2)	
2	48 115 (20.5)	30 498 (24.4)	91 724 (20.4)	170 337 (21.1)	
3	65 368 (27.8)	33 735 (27.0)	126 131 (28.1)	225 234 (27.9)	
4	53 208 (22.6)	23 873 (19.1)	104 185 (23.2)	181 266 (22.4)	
5	26 889 (11.4)	9 609 (7.7)	54 805 (12.2)	91 303 (11.3)	
6	6 007 (2.6)	1 343 (1.1)	12 208 (2.7)	19 558 (2.4)	
CVD during index hospitalization, n (%)	137 651 (58.5)	49 267 (39.5)	266 536 (59.4)	453 454 (56.1)	<0.0001
Heart failure	66 993 (28.5)	15 851 (12.7)	142 450 (31.8)	225 294 (27.9)	<0.0001
Myocardial infarction	17 420 (7.4)	2 812 (2.3)	21 405 (4.8)	41 637 (5.1)	<0.0001
Angina	2 020 (0.9)	997 (0.8)	5 418 (1.2)	8 435 (1.0)	<0.0001
Atrial fibrillation	52 976 (22.5)	17 170 (13.8)	98 663 (22.0)	168 809 (20.9)	<0.0001
Arrest	3 146 (1.3)	175 (0.1)	3 653 (0.8)	6 974 (0.9)	<0.0001
Coronary artery disease	44 354 (18.9)	18 733 (15.0)	104 741 (23.3)	167 828 (20.8)	<0.0001
Valve disease	40 929 (17.4)	14 317 (11.5)	69 156 (15.4)	124 402 (15.4)	<0.0001
Cardiomyopathy	16 513 (7.0)	4 037 (3.2)	34 165 (7.6)	54 715 (6.8)	<0.0001
Supraventricular tachycardia	6 027 (2.6)	1 862 (1.5)	7 827 (1.7)	15 716 (1.9)	<0.0001
Ventricular tachycardia	8 741 (3.7)	1 610 (1.3)	13 167 (2.9)	23 518 (2.9)	<0.0001
Stroke	17 790 (7.6)	5 018 (4.0)	37 746 (8.4)	60 554 (7.5)	<0.0001
Intracranial bleed	3 246 (1.4)	819 (0.7)	8 604 (1.9)	12 669 (1.6)	<0.0001
Shock during index hospitalization, n (%)	48 182 (20.5)	509 (0.4)	7 537 (1.7)	56 228 (7.0)	<0.0001
Cardiogenic	2 762 (1.2)	31 (0.0)	1 823 (0.4)	4 616 (0.6)	<0.0001
Septic	42 858 (18.2)	330 (0.3)	911 (0.2)	44 099 (5.5)	<0.0001
Infection during index hospitalization, n (%)	235 188 (100.0)	117 667 (94.3)	448 644 (100.0)	801 499 (99.1)	<0.0001
Central nervous system	1 199 (0.5)	551 (0.4)	2 019 (0.5)	3 769 (0.5)	<0.0001
Cardiac/vascular	2 487 (1.1)	1 582 (1.3)	7 717 (1.7)	11 786 (1.5)	<0.0001
Ear/nose/throat/upper respiratory	1 610 (0.7)	1 879 (1.5)	12 259 (2.7)	15 748 (1.9)	<0.0001
Pulmonary	69 577 (29.6)	20 889 (16.7)	187 083 (41.7)	277 549 (34.3)	<0.0001
Gastrointestinal	7 247 (3.1)	6 853 (5.5)	17 570 (3.9)	31 670 (3.9)	<0.0001
Genitourinary	65 487 (27.8)	33 508 (26.8)	148 631 (33.1)	247 626 (30.6)	<0.0001
Skin/soft tissue/bone/joint	19 046 (8.1)	17 619 (14.1)	45 455 (10.1)	82 120 (10.2)	<0.0001
Bacterial/fungal	195 940 (83.3)	92 910 (74.4)	92 356 (20.6)	381 206 (47.1)	<0.0001
Iatrogenic	8 060 (3.4)	6 427 (5.1)	6 782 (1.5)	21 269 (2.6)	<0.0001
Sepsis/bacteremia	114 320 (48.6)	48 276 (38.7)	5 767 (1.3)	168 363 (20.8)	<0.0001
Index hospitalization, n (%)					
Organ failure	235 188 (100.0)	2 570 (2.1)	448 644 (100.0)	686 402 (84.9)	<0.0001
ICU admission	136 785 (58.2)	34 516 (27.6)	186 077 (41.5)	357 378 (44.2)	<0.0001
Ventilator	22 470 (9.6)	77 (0.1)	19 115 (4.3)	41 662 (5.2)	<0.0001
Hemodialysis	6 548 (2.8)	78 (0.1)	10 821 (2.4)	17 447 (2.2)	<0.0001
Length of stay, d					<0.0001
Mean (SD)	8.1 (8.3)	4.9 (4.6)	6.5 (7.6)	6.7 (7.5)	
No. of hospitalizations in prior 6mo					<0.0001
Mean (SD)	0.4 (0.8)	0.4 (0.8)	0.4 (0.8)	0.4 (0.8)	

CVD indicates cardiovascular disease; and ICU, intensive care unit.

Table 3. Event Rates (per 100 Person-Years) and Adjusted Hazard Ratio Values for Mortality and Hospitalization Outcomes Each Sepsis Group to Patients Without Sepsis

Outcomes	No sepsis (ref)			All sepsis			Hazard ratio (95% CI)	P value
	No. with events	Person-years	Event rate per 100	No. with events	Person years	Event rate per 100		
Outcomes	N=1 449 821			N=808 673				
Mortality	167 493	3 701 524	4.52	220 428	1 694 527	13.01	1.27 (1.25–1.28)	<0.001
All-cause hospitalization*	604 851	2 488 921	24.30	481 263	901 985	53.36	1.38 (1.37–1.39)	<0.001
CVD hospitalization*	261 245	3 250 160	8.04	267 829	1 314 742	20.37	1.43 (1.41–1.44)	<0.001
Composite 1†	661 469	2 488 921	26.58	538 228	901 985	59.67	1.35 (1.34–1.36)	<0.001
Composite 2‡	360 403	3 250 160	11.09	377 514	1 314 742	28.71	1.37 (1.35–1.38)	<0.001
	No sepsis (ref)			Implicit sepsis only				
Outcomes	N=1 449 821			N=448 644				
Mortality	167 493	3 701 524	4.52	135 616	935 100	14.50	1.23 (1.21–1.25)	<0.001
All-cause hospitalization*	604 851	2 488 921	24.30	346 926	472 068	73.49	1.46 (1.44–1.47)	<0.001
CVD hospitalization*	261 245	3 250 160	8.04	294 021	697 599	42.15	1.54 (1.52–1.56)	<0.001
Composite 1†	661 469	2 488 921	26.58	314 406	427 068	73.62	1.40 (1.39–1.42)	<0.001
Composite 2‡	360 403	3 250 160	11.09	230 492	697 599	33.04	1.43 (1.41–1.44)	<0.001
	No sepsis (ref)			Explicit sepsis only				
Outcomes	N=1 449 821			N=124 841				
Mortality	167 493	3 701 524	4.52	20 448	294 409	6.95	1.31 (1.28–1.33)	<0.001
All-cause hospitalization*	604 851	2 488 921	24.30	74 236	174 319	42.59	1.33 (1.31–1.34)	<0.001
CVD hospitalization*	261 245	3 250 160	8.04	50 370	248 370	20.28	1.37 (1.35–1.38)	<0.001
Composite 1†	661 469	2 488 921	26.58	69 652	174 319	39.96	1.30 (1.29–1.31)	<0.001
Composite 2‡	360 403	3 250 160	11.09	39 636	248 370	15.96	1.33 (1.31–1.34)	<0.001
	No sepsis (ref)			Both sepsis types				
Outcomes	N=1 449 821			N=235 188				
Mortality	167 493	3 701 524	4.52	64 364	465 018	13.84	1.22 (1.20–1.24)	<0.001
All-cause hospitalization*	604 851	2 488 921	24.30	174 031	255 598	68.09	1.32 (1.30–1.33)	<0.001
CVD hospitalization*	261 245	3 250 160	8.04	142 808	368 772	38.73	1.26 (1.24–1.28)	<0.001
Composite 1†	661 469	2 488 921	26.58	154 170	255 598	60.32	1.33 (1.31–1.34)	<0.001
Composite 2‡	360 403	3 250 160	11.09	107 386	368 772	29.12	1.28 (1.27–1.30)	<0.001

CVD indicates cardiovascular disease; and ref, reference group.
 *Death was considered as a competing risk when examining the risk of all-cause or CVD rehospitalization.
 †Composite 1 includes death or all-cause rehospitalization.
 ‡Composite 2 includes death or CVD rehospitalization.

Sensitivity Analyses

When the main analyses were repeated using propensity score overlap weighting, HR values associated with sepsis were slightly higher for all-cause mortality (adjusted HR, 1.33 [95% CI, 1.32–1.35]; $P<0.001$), all-cause rehospitalization (adjusted HR, 1.47 [95% CI, 1.46–1.48]; $P<0.001$), and CVD hospitalization (adjusted HR 1.52, 95% CI, 1.50–1.54; $P<0.001$). Using data from the first hospitalization during the study period, 547 063 patients were classified as sepsis and the remaining 1 659 352 were classified as no

sepsis; within the sepsis group, 91 272 were classified as explicit sepsis, 292 748 were classified as implicit sepsis, and 163 043 were classified as both. Patients with sepsis were at elevated risk of postdischarge adverse events (Table 5), with smaller HR values for all-cause mortality (adjusted HR, 1.10 [95% CI, 1.08–1.11]; $P<0.001$) and all-cause rehospitalization (adjusted HR, 1.07 [95% CI, 1.06–1.07]; $P<0.001$) and a larger HR value for cardiovascular hospitalization (adjusted HR, 1.78 [95% CI, 1.76–1.78]; $P<0.001$) when compared with the main analysis.

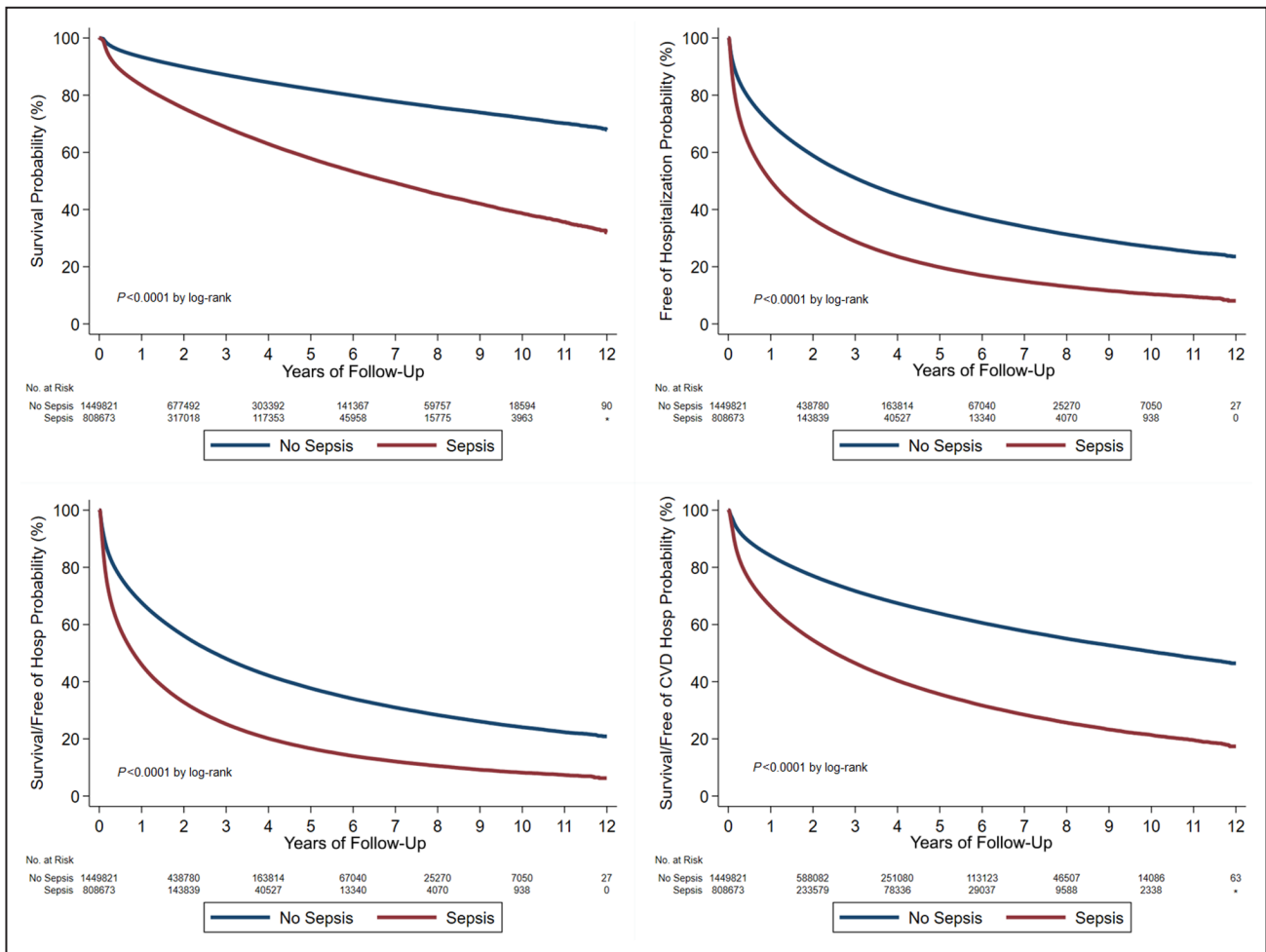


Figure 1. Kaplan–Meier curves demonstrating postdischarge event rates in patients with sepsis (all definitions combined) vs those without sepsis, including all-cause mortality (top left), all-cause rehospitalization (top right), the composite of death or all-cause rehospitalization (bottom left), and the composite of death or cardiovascular hospitalization (bottom right).

DISCUSSION

Summary of Findings

In this study of >2 million hospitalized nonsurgical patients with or at risk for CVD who survived to discharge, we observed that a high proportion of patients were hospitalized with sepsis on the basis of diagnosis codes. Survivors of sepsis hospitalization were at elevated risk of subsequent death and rehospitalization, with a heightened risk of hospitalizations for CVD events. Patients hospitalized with sepsis were at increased risk of all types of CVD events, including atherosclerotic and nonatherosclerotic events. This excess risk was greatest in magnitude for heart failure hospitalization. The excess risk developed early after hospitalization (within the first 6–12 months) and accumulated over time out to 12 years of follow-up. An excess risk of adverse events was observed regardless of the sepsis definition (ie, implicit versus explicit)

and type of infection. However, the crude event rates were higher among patients with implicit sepsis than those with explicit sepsis, potentially attributable to the uniform presence of organ dysfunction in patients with implicit sepsis. The excess risk of posthospitalization adverse events was consistent across all predefined subgroups, including those with and without CVD or organ failure. The relative hazard posed by sepsis was generally greater among lower-risk subgroups, such as younger patients, those with commercial insurance, those without CVD, and those without organ failure. When we restricted the analysis to the first hospitalization during the study period, the excess relative hazard of CVD hospitalization associated with sepsis increased, strengthening our main findings. These data highlight the importance of sepsis during hospitalization as a powerful risk factor for subsequent adverse events, including death, reinfection, and major cardiovascular events.

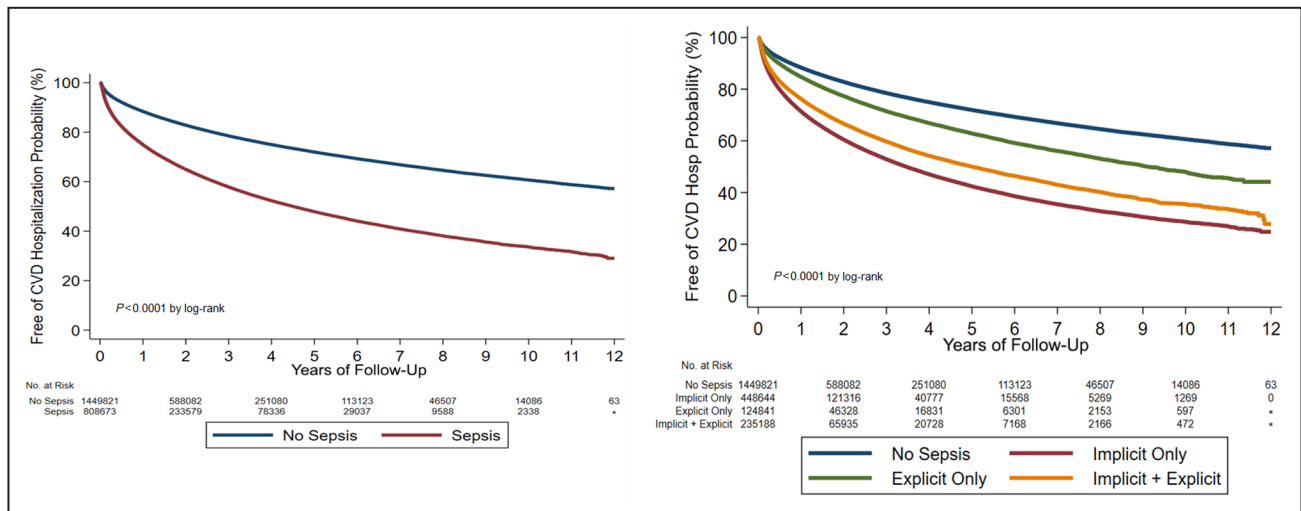


Figure 2. Kaplan–Meier curves demonstrating postdischarge cardiovascular rehospitalization rates in patients with sepsis vs those without sepsis, including all sepsis definitions combined (left) and patients with sepsis separated by the sepsis definition (right).

Comparison With Prior Studies

Our results are broadly consistent with prior studies using heterogeneous methodologies that have observed an elevated risk of short- and long-term cardiovascular events and death among survivors of sepsis.¹² A meta-analysis of 27 observational studies demonstrated an excess risk of myocardial infarction, stroke, and heart failure after hospitalization for sepsis, with pooled adjusted HR values of 1.65 to 1.77 and wide variability across studies.¹² Our study population represents the largest published study of postdischarge CVD outcomes associated with sepsis in medical patients. The only larger study we identified examining postsepsis CVD events specifically examined the short-term risk of arterial and venous thrombosis associated with postoperative sepsis.²⁰ Our point estimates for the excess risk of CVD events based on our adjusted HR values are more modest than observed in this meta-analysis, which may reflect differences in our study population, period of enrollment, sepsis definitions, or CVD end point definitions. Notably, the prior meta-analysis concluded that many of the included studies were of low quality, and many lacked appropriate nonsepsis controls for comparison, leaving uncertainty about the extent to which differences in baseline characteristics could have biased the findings.¹² A subsequent study published after the meta-analysis included 250 000 hospital survivors with sepsis from Ontario who were propensity matched to nonsepsis hospital survivors, demonstrating a higher risk of all-cause mortality and CVD events after sepsis hospitalization.¹³ Their reported HR estimates were similar to those we observed using a different cohort and different methodology (HR, 1.26 for all-cause mortality and 1.30

for major CVD events), and notably these authors observed a higher HR for younger patients as we found.¹³ Together with our analysis, this study provides higher-quality evidence supporting the association between sepsis hospitalization and subsequent CVD events, supporting and expanding on the findings of the recent meta-analysis.^{12,13}

Unlike prior studies, we specifically enriched our population with higher-risk medical patients (including older patients with or at risk for CVD) with a minimum 2-night hospital length of stay to ensure that we did not use low-risk patients as a comparator group. The high observed event rates in the no-sepsis group confirm that we achieved this goal and demonstrate that sepsis confers an added hazard even when superimposed on an elevated baseline risk. We included patients with sepsis based on either explicit or implicit criteria, the latter representing a higher-risk cohort with a greater event rate. As such, we believe that our robust methodology in a broader study population has led to more accurate point estimates as we have adjusted for a more comprehensive number of covariates (particularly those reflecting in-hospital diagnoses and treatments) and examined several clinically relevant subgroups. As observed in the study from Ontario, the HR estimates for death and CVD hospitalization were higher for several lower-risk subgroups, including those without prior or current CVD, suggesting that our results might apply equally to populations not enriched in CVD.¹³ In addition to a higher risk of subsequent risk of death and hospitalization for CVD events, sepsis survivors were at high risk of reinfection and hospitalization for other causes.⁷ This highlights the broad spectrum of elevated risk in this population, warranting close monitoring after hospital discharge.

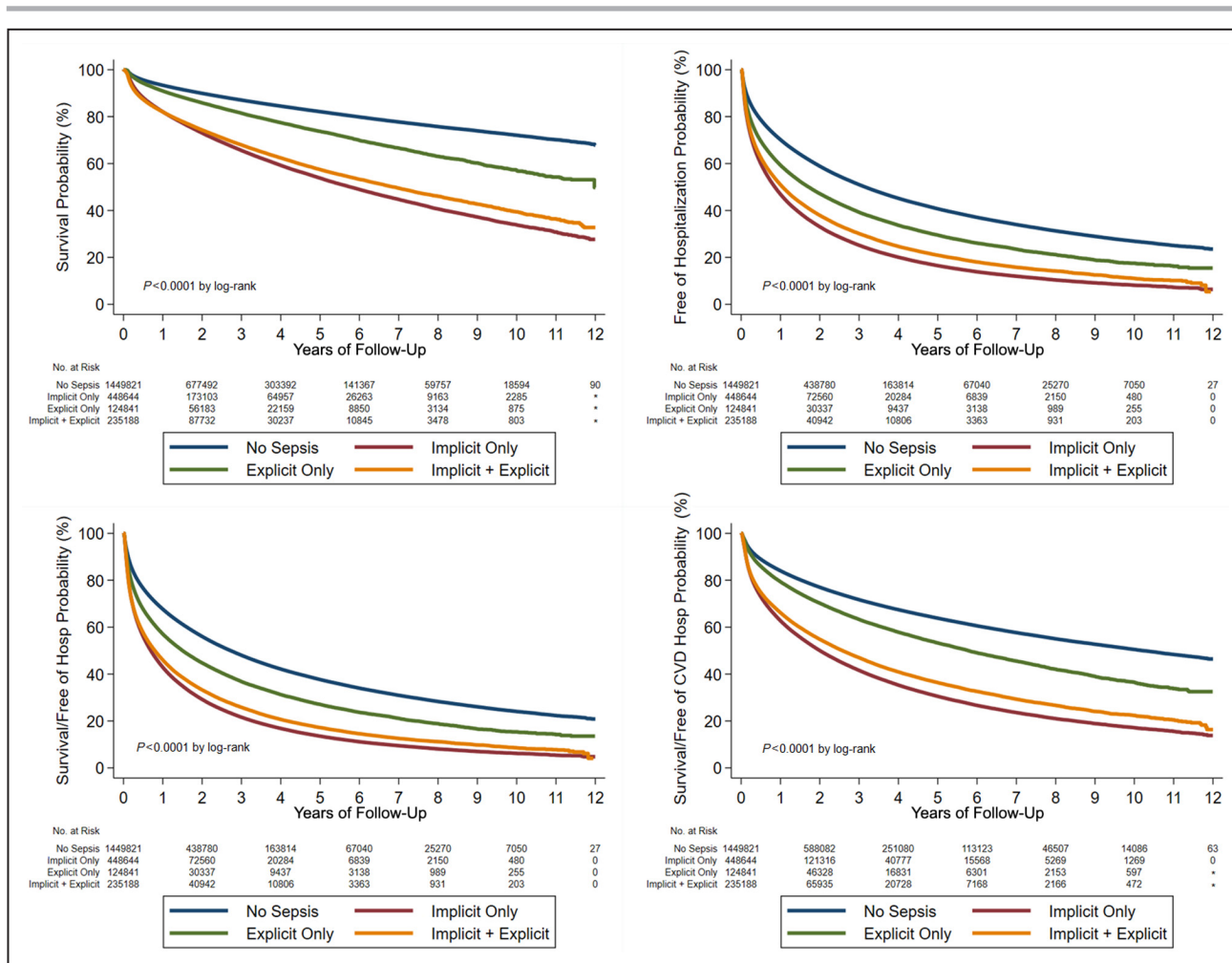


Figure 3. Kaplan–Meier curves demonstrating postdischarge event rates in patients with sepsis (separated by definition) vs those without sepsis, including all-cause mortality (top left), all-cause rehospitalization (top right), the composite of death or all-cause rehospitalization (bottom left) and the composite of death or cardiovascular hospitalization (bottom right).

Sepsis Definition and Subsequent Outcomes

We observed that the association between sepsis and clinical outcomes varied according to the definition of sepsis, which can guide the interpretation of prior studies. Implicit sepsis, defined as the presence of infection and acute organ dysfunction, accounted for most cases of sepsis in our cohort and was associated with a higher risk of adverse postdischarge events, including death and rehospitalization for cardiovascular and noncardiovascular causes.^{1,19} Explicit sepsis, defined as the presence of specific diagnosis codes for sepsis, was present less often and usually in combination with implicit sepsis.^{1,21} Contrary to some prior studies, patients with explicit sepsis alone had a lower overall risk profile, with younger age and a lower prevalence of acute organ failure, comorbidities, and the need for critical care therapies.²¹ These patients had the lowest risk of subsequent adverse events of all sepsis groups after adjustment, although their risk exceeded that of

patients without sepsis. Interestingly, the group with implicit sepsis alone had the highest risk of postdischarge events despite their intermediate severity of illness. This may imply that recognition of sepsis (ie, based on documentation using diagnosis codes) may portend better late outcomes in hospitalized patients by ensuring timely treatment, emphasizing the importance of diagnosing sepsis to ensure optimal patient care. Alternatively, the accuracy of these different sepsis definitions for underlying sepsis could have impacted the association with outcomes simply because of differences in the true prevalence of sepsis in the groups.^{1,21–24} The use of ICD codes to identify sepsis cases is challenging because of limited sensitivity and specificity using either explicit or implicit definitions, potentially with underestimation of sepsis prevalence using explicit criteria and overestimation of sepsis prevalence when both criteria are combined.^{21–24} Use of administrative codes to define sepsis will therefore result in some misclassification of the exposure, which

Table 4. Event Rates (per 100 Person-Years) and Adjusted Hazard Ratio Values for Individual Hospitalization End Points Comparing the Overall Sepsis Group to Patients Without Sepsis

	No sepsis (ref)			Sepsis			Hazard ratio (95% CI)	P value
	No. with events	Person-years	Event rate per 100	No. with events	Person years	Event rate per 100		
Outcomes	N=1 449 821			N=808 673				
CVD hospitalization								
Coronary	88 942	139 260	63.87	84 589	109 833	77.02	1.26 (1.24–1.29)	<0.001
Heart failure	138 138	205 377	67.26	179 931	201 849	89.14	1.51 (1.49–1.53)	<0.001
Stroke	71 189	114 893	61.96	64 223	88 657	72.44	1.35 (1.32–1.38)	<0.001
Arrhythmia	104 505	157 507	66.35	115 046	141 100	81.54	1.45 (1.42–1.47)	<0.001
Shock	12 125	20 674	58.65	16 968	25 335	66.97	1.38 (1.31–1.45)	<0.001
Infection hospitalization	32 341	51 274	63.07	66 482	78 848	84.32	1.99 (1.94–2.04)	<0.001
Other non-CVD/non-infection hospitalizations	442 726	534 480	82.83	352 197	316 577	111.25	1.42 (1.40–1.43)	<0.001

CVD indicates cardiovascular disease; and ref, reference group.

is expected to weaken the observed associations. Despite this limitation, the strong associations that we observed using a variety of adjustment methods supports the likelihood that a true association exists.

The requirement for acute organ dysfunction to define implicit sepsis may explain the excess risk of subsequent events among hospital survivors, and subgroup analyses generally demonstrated a weaker association between sepsis and outcomes in patients with organ failure (including AKI or shock). AKI itself is a known predictor of death and CVD events, and our data demonstrate an additive risk of sepsis and AKI for postdischarge events.^{14–16} The consistent association between sepsis and adverse outcomes across subgroups with and without various manifestations of critical illness helps to demonstrate the potential hazard from sepsis beyond the known harmful effects of its downstream complications and argues against the presence of critical illness itself as the sole mediator of this association.

Clinical Implications

Patients with sepsis during hospitalization differed substantially from patients without sepsis, with a higher overall risk profile including a greater degree of critical illness and more acute and chronic CVD including prior hospitalizations. However, patients with sepsis remained at higher risk of subsequent adverse outcomes even after adjusting or stratifying for these relevant factors. Prior studies have demonstrated that postdischarge CVD events are associated with higher mortality during follow-up in survivors of sepsis, suggesting that CVD events likely contribute to the increased late mortality.²⁵ Our subgroup analyses demonstrated that although the absolute risk of events associated with sepsis was highest in patients with a

higher risk profile (including older patients, those with CVD, and those with organ failure), the relative excess hazard was greatest in lower-risk patients who likely have fewer competing risks. A similar finding was observed in a recent population-based study, which observed that the hazard associated with sepsis was greater for younger patients who had a lower baseline risk.¹³ Therefore, providers need to be cognizant that sepsis during hospitalization can reclassify otherwise low-risk patients into a group needing diligent follow-up because of their elevated risk of adverse events. Our analysis adds to the growing evidence base highlighting the multitude of potential complications that survivors of sepsis face after hospital discharge, including death, reinfection, cardiovascular events, and rehospitalization.¹² Survivors of sepsis were at elevated risk of a broad array of CVD events, including atherosclerotic and nonatherosclerotic events, highlighting the multitude of adverse outcomes associated with sepsis and necessitating a comprehensive approach to CVD prevention in this high-risk group. Among the different CVD events we examined, heart failure was most common, and the adjusted HR value was highest for heart failure, whereas it was highest for myocardial infarction in the prior meta-analysis.¹² Heart failure, either preexisting or during the index hospitalization, was approximately 2-fold more common among patients with sepsis, and heart failure is a known risk factor for sepsis.²⁶ Acute myocardial dysfunction is a well-known complication of sepsis, and a substantial incidence of new-onset heart failure has been described in survivors of sepsis.^{27,28} There are numerous potential explanations for this strong association between sepsis hospitalization and subsequent heart failure, including a variety of pathophysiologic mechanisms by which sepsis-induced inflammation and neurohormonal

Table 5. Event Rates (per 100 Patient-Years) and Adjusted Hazard Ratios for Each of the End Points of Interest in Patients With and Without Sepsis, as a Function of Sepsis Group Using Data From the First Hospitalization During the Study Period (Sensitivity Analysis)

	No sepsis (ref)			Sepsis			Hazard ratio (95% CI)	P Value
	No. with events	Person-years	Event rate per 100	No. with events	Person-years	Event rate per 100		
Outcomes	N=1 659 352			N=547 063				
Mortality	238 248	4 390 012	5.43	131 365	1 222 026	10.75	1.10 (1.08–1.11)	<0.001
All-cause hospitalization*	808 926	2 676 486	30.22	302 109	699 730	43.18	1.07 (1.06–1.07)	<0.001
CVD hospitalization*	261 245	3 938 648	6.63	160 297	984 526	16.28	1.78 (1.76–1.80)	<0.001
Composite 1†	865 744	2 676 486	32.35	336 890	699 730	48.15	1.07 (1.07–1.08)	<0.001
Composite 2‡	431 158	3 938 648	10.95	227 740	984 526	23.13	1.39 (1.38–1.40)	<0.001
	No sepsis (ref)			Implicit sepsis only				
Outcomes	N=1 659 352			N=292 748				
Mortality	238 248	4 390 012	5.43	79 501	651 202	12.21	1.13 (1.11–1.14)	<0.001
All-cause hospitalization*	808 926	2 676 486	30.22	172 040	355 334	48.42	1.13 (1.12–1.14)	<0.001
CVD hospitalization*	261 245	3 938 648	6.63	97 308	507 145	19.19	1.96 (1.93–1.99)	<0.001
Composite 1†	865 744	2 676 486	32.35	191 629	355 334	53.93	1.13 (1.12–1.14)	<0.001
Composite 2‡	431 158	3 938 648	10.95	136 038	507 145	26.82	1.48 (1.47–1.50)	<0.001
	No sepsis (ref)			Explicit sepsis only				
Outcomes	N=1 659 352			N=91 272				
Mortality	238 248	4 390 012	5.43	12 463	225 988	5.51	1.06 (1.04–1.08)	<0.001
All-cause hospitalization*	808 926	2 676 486	30.22	42 919	142 887	30.04	1.00 (0.99–1.01)	0.469
CVD hospitalization*	261 245	3 938 648	6.63	18 326	195 493	9.37	1.66 (1.63–1.69)	<0.001
Composite 1†	865 744	2 676 486	32.35	45 878	142 887	32.11	1.01 (1.00–1.02)	0.139
Composite 2‡	431 158	3 938 648	10.95	24 979	195 493	12.78	1.31 (1.29–1.32)	<0.001
	No sepsis (ref)			Both sepsis types				
Outcomes	N=1 659 352			N=163 043				
Mortality	238 248	4 390 012	5.43	39 401	344 836	11.43	1.09 (1.08–1.11)	<0.001
All-cause hospitalization*	808 926	2 676 486	30.22	87 105	201 509	43.23	1.03 (1.01–1.04)	<0.001
CVD hospitalization*	261 245	3 938 648	6.63	44 663	281 889	15.84	1.60 (1.57–1.62)	<0.001
Composite #1†	865 744	2 676 486	32.35	99 383	201 509	49.32	1.06 (1.05–1.07)	<0.001
Composite #2‡	431 158	3 938 648	10.95	66 723	281 889	23.67	1.31 (1.29–1.33)	<0.001

CVD indicates cardiovascular disease; and ref, reference group.
 *Death was considered as a competing risk when examining the risk of all-cause or CVD rehospitalization.
 †Composite 1 includes death or all-cause rehospitalization.
 ‡Composite 2 includes death or CVD rehospitalization.

activation may aggravate myocardial dysfunction as well as more pragmatic reasons including discontinuation of beneficial heart failure therapies (deprescription) during or after hospitalization.^{27–29}

Clinicians caring for survivors of sepsis need to be aware of their high risk of both atherosclerotic and non-atherosclerotic (ie, heart failure) CVD events, ensuring close follow-up and diligent medication optimization. Such an approach may be needed even for patients without preexisting CVD, insofar as sepsis may accelerate underlying CVD progression in at-risk patients. While the relative excess risk associated with sepsis

was generally higher in groups with a lower baseline risk, the absolute excess risk was greater in higher-risk cohorts, including older patients and those with CVD. This makes it essential to optimize guideline-directed medical therapies for survivors of sepsis with CVD at hospital discharge and to ensure that medication reconciliation occurs to avoid deprescription. Future studies must determine which, if any, standard CVD prevention medications such as aspirin, statins, renin-angiotensin-aldosterone system antagonists, or beta blockers might reduce the risk of subsequent CVD events in sepsis survivors. While prior use of CVD

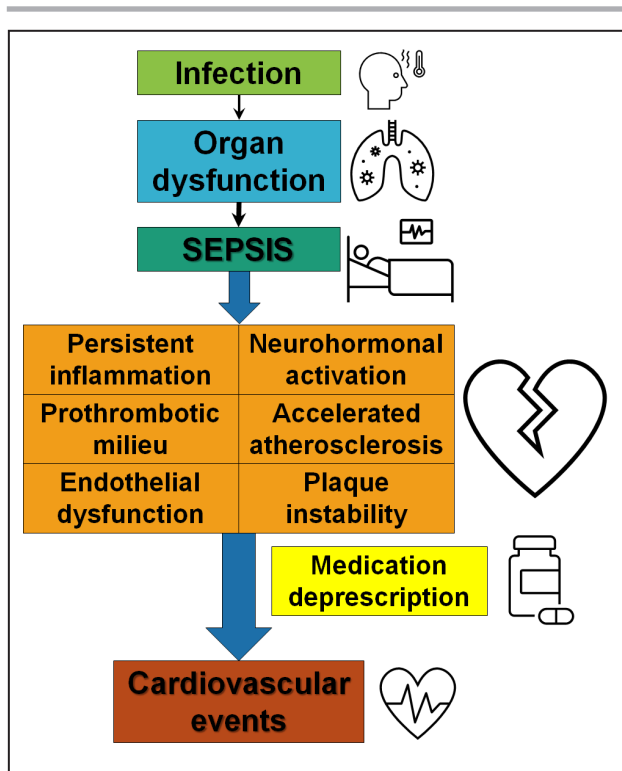


Figure 4. Conceptual model describing potential pathways by which sepsis during hospitalization may be associated with postdischarge cardiovascular events.

The sepsis syndrome and resultant organ dysfunction can aggravate cardiovascular disease through multiple mechanisms, and this can be exacerbated by purposeful or inadvertent medication deprescription during or after hospitalization.^{7,9–12,24,29}

prevention medications such as statins does not appear to influence the short-term outcomes of patients with sepsis, this does not rule out a potential benefit of these drugs for preventing late atherosclerotic CVD events after discharge.³⁰ Given the complex residual risk pathways that may drive adverse events among survivors of sepsis (Figure 4), novel mechanistic approaches to CVD prevention in this group may be needed.⁹

Limitations

As with all observational studies using administrative data, this analysis is limited by the documentation of diagnosis codes to identify diseases of interest. None of these diagnosis codes is completely sensitive or specific, and variability in how these codes were documented across sites over time could have influenced our results.²¹ In addition, we used a combination of implicit and explicit sepsis definitions, recognizing that these differ in accuracy and vary in their strength of association with outcomes.^{1,22} We did not have a gold-standard sepsis definition for comparison and could not use contemporary clinical sepsis definitions.³¹ Because of the timing of our study period, patients with

COVID-19 were not represented in this sample, and the association between sepsis and subsequent CVD outcomes might differ in this group.

This analysis can only demonstrate associations and cannot prove causation, so we could not determine whether sepsis occurs in patients at higher risk of CVD or whether sepsis increases the risk of CVD directly. We were only able to adjust for known confounders available in OptumLabs Data Warehouse, and we cannot exclude residual confounding as a mediator of the observed results. Specifically, we did not have available data on all relevant CVD risk factors, including diet, lifestyle, or family history. We lack sufficient data to provide mechanistic insights about the direction and pathophysiology of the associations between sepsis and cardiovascular disease. We hypothesize that the persistent inflammatory milieu associated with sepsis survivorship may promote the progression of CVD or trigger CVD events, although a multitude of other biological pathways might contribute to the observed associations.^{8,10,11}

We specifically focused on medical hospitalizations lasting at least 2 nights to ensure a fair comparator group, precluding us from commenting on patients with surgical hospitalizations or shorter hospitalizations. We included any patient with a sepsis hospitalization in the sepsis group, so our population was enriched in patients with sepsis; therefore, our data cannot be used to determine the prevalence of sepsis hospitalizations directly and our estimates for the excess hazard of subsequent infection hospitalizations are likely exaggerated. OptumLabs Data Warehouse includes only commercial insurance and Medicare Advantage enrollees (who account for approximately one-third of Medicare enrollees), which could affect the generalizability of our findings. Although this study includes a nationally representative sample of the US population, it does not include Medicaid, Medicare fee-for-service, or uninsured populations, who typically have lower income and lower socioeconomic status and may be medically underserved with a worse risk factor profile. While we can identify no specific reason why the direction of the association between sepsis and subsequent outcomes would be divergent in these nonincluded groups (even though nonincluded patients may potentially be at higher risk of CVD and other adverse events), it is likely that the magnitude of this association and overall event rates would differ.

CONCLUSIONS

Sepsis during hospitalization is common in hospital survivors and is associated with a higher risk of subsequent death, rehospitalization, and CVD events. The high global burden of sepsis results in many survivors of sepsis worldwide who will be at elevated risk of CVD

complications after hospital discharge. The increased risk for CVD after sepsis hospitalization necessitates diligent follow-up and optimization of guideline-directed medical therapies in patients with preexisting CVD. It is imperative to determine the mechanisms underlying this association and whether standard medical therapies for cardiovascular prevention are efficacious for reducing the risk of CVD events associated with sepsis survivorship in the absence of preexisting CVD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S15
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Cardiovascular Disease (CVD) based on hospital discharge International Classification of Disease 9th and 10th Revisions Clinical Modification (ICD-9/10) codes.

A. Pre-existing CVD

CVD diagnosis	ICD-9 diagnosis codes	ICD-10 diagnosis codes	ICD-9 procedure codes	ICD-10 procedure codes
Prior MI	410.xx, 412.xx	I21.xx, I22.xx, I23.xx, I25.2x	--	--
CAD	410.xx-414.xx, 429.2	I20.xx-I25.xx	--	--
Heart failure	428.x, 402.x1, 404.x1, 404.x3, 398.91	I50.x, I97.13x, I11.0, I13.0, I13.2, I09.81	--	--
Cardiomyopathy	425.1x, 425.4, 425.5, 425.7, 425.8, 425.9, 674.5x	B33.24, E88.89, F10.988, I25.5, I42.1, I42.2, I42.6, I42.7, I42.8, I42.9, I43, O90.3	--	--
HTN	401.xx-405.xx	I10.xx-I15.xx	--	--
CKD	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.3, 585.4, 585.5, 585.6, 792.5, 996.81, V56.xx	T81.502x, T81.512x, T81.522x, T81.532x, T81.592x, T85.611x, T85.621x, T85.631x, T85.691x, T85.71x, I12.0, I13.11, I13.2, I95.3	--	--

		N18.3, N18.4, N18.5, N18.6, R88.0, T86.1x, Y84.1, Z48.22, Z49.xx, Z91.15, Z94.0, Z99.2		
SVT	427.0	I47.1	--	--
Atrial fibrillation/flutter	427.3x	I48.x	--	--
VT	427.1, 427.4x, 427.5	I46.2, I46.8, I46.9, I47.0, I47.2, I49.0x	--	--
Hyperlipidemia	272.0, 272.1, 272.2, 272.4	E78.0x, E78.1, E78.2, E78.4, E78.5	--	--
Obesity	278.00, 278.01, 278.03, V85.3x, V85.4x	E66.1, E66.2, E66.8, E66.9, E66.0x, Z68.3x, Z68.4x	--	--
Diabetes mellitus (Defined as either 2 outpatient visits with diagnoses codes or 1 inpatient stay with diagnoses codes)	250.xx, 362.0x, 357.2, 366.41	E08.xx, E09.xx, E10.xx, E11.xx, E13.xx	--	--
Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 444	I63.x, I74.x	--	--

Prior PCI	V45.82	Z98.61, Z95.5	00.66, 36.0x CPT codes: 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996, 92975, 92977	0270x, 0271x, 0272x, 0273x, 02C0, 02C1, 02C2, 02C3
Prior CABG	V45.81, 414.02, 414.03, 414.04, 414.05	I25.810, I25.812, Z95.1, T82.21, I25.7x except I25.75x	36.1x CPT codes: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536 HCPC: 4110F	02100x, 02110x, 02120x, 02130x
Prior valve replacement	--	--	35.24, 35.22, 35.26, 35.28, 35.23, 35.21, 35.25, 35.27,	02RG0JZ, 02RF0JZ, 02RH0JZ,

		<p>35.12, 35.11, 35.13, 35.14, 35.33, 35.05, 35.06, 35.07, 35.08, 35.09, 35.96, 35.97, 35.00, 35.01, 35.02, 35.03, 35.04</p> <p>CPT codes: 33405, 33430, 33406, 33410, 33411, 33412, 33413, 33465, 33475, 33422, 33425, 33426, 33427, 33400, 33401, 33403, 33864, 33460, 33464, 33474, 33417, 33468, 33496, 33600, 33602, 33418, 33419, 33361, 33362, 33363, 33364, 33365, 33366, 33367, 33368, 33369, 33420, 33470, 33471, 33477, 92987</p>	<p>02RJ0JZ, 02RG07Z, 02RG08Z, 02RG0KZ, 02RF07Z, 02RF08Z, 02RF0KZ, 02RH07Z, 02RH08Z, 02RH0KZ, 02RJ07Z, 02RJ08Z, 02RJ0KZ, 027G04Z, 027G0DZ, 027G0ZZ, 02NG0ZZ, 02QG0ZZ, 02CG0ZZ, 02UG0JZ, 027F0ZZ, 02NF0ZZ, 02QF0ZZ, 02UF0JZ, 027H0ZZ, 02NH0ZZ, 02QH0ZZ, 027J0ZZ, 02NJ0ZZ, 02QJ0ZZ, 02UH0JZ, 02UJ0JZ,</p>
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			HCPC codes: 0257T, 0258T, 0259T, 0262T, 0318T	02RF37H, 02RF37Z, 02RF38H, 02RF38Z, 02RF3JH, 02RF3JZ, 02RF3KH, 02RF3KZ, 02RF47Z, 02RF48Z, 02RF4KZ, 02RG37H, 02RG37Z, 02RG38H, 02RG38Z, 02RG3JH, 02RG3KH, 02RG3KZ, 02RG47Z, 02RG48Z, 02RG4KZ, 02RH37H, 02RH37Z, 02RH38H, 02RH38Z, 02RH3JH, 02RH3JZ, 02RH3KH, 02RH3KZ, 02RH47Z, 02RH48Z, 02RH4KZ,
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				02RJ47Z, 02RJ48Z, 02RJ4KZ, X2RF332, 027F3ZZ, 027G3ZZ, 027H3ZZ, 027J3ZZ, 02CF3ZZ, 02CF4ZZ, 02CG3ZZ, 02CG4ZZ, 02CH3ZZ, 02CH4ZZ, 02CJ3ZZ, 02CJ4ZZ, 02NF3ZZ, 02NF4ZZ, 02NG3ZZ, 02NG4ZZ, 02NH3ZZ, 02NH4ZZ, 02NJ3ZZ, 02NJ4ZZ, 02UG3JZ
Prior ICD/PPM	V53.31, V45.00, V45.01, 996.01, 996.61, V45.02	Z95.0, Z45.0x, Z95.810	37.71, 37.75, 37.76, 37.79, 37.80, 37.81, 37.82, 37.85, 37.86, 37.89, 39.64, 89.45, 89.46, 89.47,	02HK0JZ, 02HK3JZ, 02HK4JZ, 02HK0MZ, 02HK3MZ, 02HK4MZ, 02HK0NZ,

		<p>89.48, 37.70, 37.72, 37.73, 37.83, 37.87, 37.20, 37.94, 37.95, 37.96, 37.97, 37.98, 89.49, 00.50, 00.51, 00.52, 00.53, 00.54</p> <p>CPT codes: 33216, 33207, 33212, 33218, 33222, 33224, 33225, 33227, 33233, 93279, 93286, 93288, 93293, 93294, 93296, 93724, 33217, 33206, 33208, 33213, 33221, 93280, 93281, 33228, 33229, 33220, 33214, 33215, 33223, 33230, 33231, 33240, 33241, 33249, 33262, 33263, 33264, 93260, 93261, 93282, 93283, 93284,</p>	<p>02HK3NZ, 02HK4NZ, 0JH804Z, 0JH834Z, 0JH604Z, 0JH634Z, 0JH805Z, 0JH835Z, 0JH605Z, 0JH635Z, 4B02XSZ, 02WA0NZ, 02WA3NZ, 02WA4NZ, 02WA0MZ, 02WA3MZ, 02WA4MZ, 02H60JZ, 02H63JZ, 02H64JZ, 02H60MZ, 02H63MZ, 02H64MZ, 02H60NZ, 02H63NZ, 02H64NZ, 0JH806Z, 0JH836Z, 0JH606Z, 0JH636Z, 0JH808Z, 0JH838Z, 0JH608Z,</p>
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			93287, 93289, 93295, 33226 HCPC codes: 0389T, 0390T, 0391T	0JH638Z, 02H40KZ, 02H43KZ, 02H44KZ, 02H70KZ, 02H73KZ, 02H74KZ, 02HL0K, 02HL3KZ, 02HL4KZ, 02HN0KZ, 02HN3KZ, 02HN4KZ, 02H60K, 02H63KZ, 02H64K, 02HK0KZ, 02HK3KZ, 02HK4KZ, 4B02XTZ, 0JH807Z, 0JH837Z, 0JH607Z, 0JH637Z, 02H40NZ, 02H43NZ, 02H44NZ, 02H40JZ, 02H43JZ, 02H44JZ, 02HN0JZ, 02HN3JZ, 02HN4JZ
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Prior dialysis	--	--	39.95, 54.98 CPT codes: 90935, 90937, 90940, 90965, 90966, S9335, 99512, 90945, 90947, 90969, 90970, 90999, G0257	5A1D00Z, 5A1D60Z, 3E1M39Z Revenue codes: 0820-0829, 0800, 0802-0809, 0830- 0859, 0880-0889
History of smoking	V15.82, 649.0x, 305.1, 989.84	F17.xxx, O99.33x, T65.2x, Z53.01, Z71.6, Z72.0, Z87.891	CPT codes: 1034F, 4000F, 4001F, 4004F, 99406, 99407, C9801, C9802, D1320, G0375, G0376, G0436, G0437, G8402, G8453, G8455, G9276, G9458, G9792	--
Active smoking (i.e. documented within 30 days prior to index hospitalization)	649.0x, 305.1, 989.84	F17.xxx, O99.33x, Z53.01, Z72.0	--	--

B. CVD during index hospitalization

Diagnosis	ICD-9 codes	ICD-10 codes
Heart failure	428.x, 402.x1, 404.x1, 404.x3, 398.91	I50.x, I97.13x, I11.0, I13.0, I13.2, I09.81

Acute MI	410.x1	I21.x
Unstable angina	411.1	I20.0, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790
Atrial fibrillation or flutter	427.3x	I48.x
Cardiac arrest / VF	427.4x, 427.5	I46.x, I49.0x
Cardiogenic shock	785.51	R57.0
Coronary disease	414.x (except 414.1x)	I25.1x, I25.7x, I25.8x, I25.9
Valve disease of any type	424.0-3, 394.x, 396.x, 746.6	I05-I08.x, I34-I37.x, Q23.3
Cardiomyopathy	425.1x, 425.4, 425.5, 425.7, 425.8, 425.9, 674.5x	B33.24, E88.89, F10.988, I25.5, I42.1, I42.2, I42.6, I42.7, I42.8, I42.9, I43, O90.3
SVT other than AF	427.0	I47.1
VT other than VF	427.1, 427.4x, 427.5	I46.2, I46.8, I46.9, I47.0, I47.2, I49.0x
Ischemic Stroke/systemic embolism	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 444	I63.x, I74.x
Intracranial hemorrhage	430, 431, 432.x, 852.x, 853.x, 800.2x, 800.3x, 800.7x, 800.8x, 801.2x, 801.3x, 801.7x, 801.8x, 803.2x, 803.3x, 803.7x, 803.8x, 804.2x, 804.3x, 804.7x, 804.8x	I60.x, I61.x, S06.34x, S06.35x, S06.36x, S06.37x, S06.38x, S06.4x, S06.5x, S06.6x

Table S2. Cardiovascular Risk Factors based on hospital discharge International Classification of Disease 9th and 10th Revisions Clinical Modification (ICD-9/10) codes.

Risk Factor	ICD-9 diagnosis codes	ICD-10 diagnosis codes
Hypertension	401.xx-405.xx	I10.xx-I15.xx
Hyperlipidemia	272.0, 272.1, 272.2, 272.4	E78.0x, E78.1, E78.2, E78.4, E78.5
Diabetes mellitus	250.xx, 362.0x, 357.2, 366.41	E08.xx, E09.xx, E10.xx, E11.xx, E13.xx
Chronic kidney disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.3, 585.4, 585.5, 585.6, 792.5, 996.81, V56.xx	T81.502x, T81.512x, T81.522x, T81.532x, T81.592x, T85.611x, T85.621x, T85.631x, T85.691x, T85.71x, I12.0, I13.11, I13.2, I95.3, N18.3, N18.4, N18.5, N18.6, R88.0, T86.1x, Y84.1, Z48.22, Z49.xx, Z91.15, Z94.0, Z99.2
Obesity	278.00, 278.01, 278.03, V85.3x, V85.4x	E66.1, E66.2, E66.8, E66.9, E66.0x, Z68.3x, Z68.4x
Tobacco dependence	649.0x, 305.1, 989.84	F17.xxx, O99.33x, Z53.01, Z72.0

Table S3. Explicit Sepsis Definition based on hospital discharge International Classification of Disease 9th and 10th Revisions Clinical Modification (ICD-9/10) codes.

Diagnosis	ICD-9 diagnosis codes	ICD-10 diagnosis codes
Sepsis	995.9x, 038.x, 790.7, 020.0, 112.5, 112.81 117.9	A40.x, A41.x, R65.1x, R65.20, R78.81, A02.1, A20.7, A22.7, A26.7, A32.7, A42.7, B37.7
Septic shock	785.52	R65.21

Table S4. Implicit Sepsis Definition based on hospital discharge International Classification of Disease 9th and 10th Revisions Clinical Modification (ICD-9/10) codes. Implicit sepsis required at least one ICD-9/10 code for infection (A) and at least one ICD-9/10 code for organ dysfunction.

A. Infection

Diagnosis	ICD-9 diagnosis codes	ICD-10 diagnosis codes
Bacterial/fungal infections	001-005, 008-018, 020-027, 031-041, 090-098, 100-104, 110-112, 114-118	A00-05, A09, A15, A17-19, A20-28, A30-32, A35-49, A50-54, A65-69, B35-49, B95-96
CNS	320, 322, 324, 325	G00, G01, G06, G08
Cardiac/vascular	420, 421, 451	I30, I33, I80
ENT/URI	461-465	J01-04, J06
Pulmonary	481, 482, 485, 586, 491.21, 494, 510, 513	J13, J14, J15, J18, J95.81x, J69.0, J47, J44.0, J86, J85
GI	540-542, 562.01/03, 562.11/13, 566, 567, 569.5, 569.83, 572.0, 572.1, 575.0	K35-37, K57.0x, K57.2x, K57.4x, K57.8x, K57.92, K57.93, K61, K65, K63.1, K63.0, K75.0, K75.1, K81.0, K81.2
GU	590, 597, 599.0, 601, 614-616	N10, N39.0, N34, N41, N70-73
Skin/soft tissue/bone/joint	681-683, 686, 711.0, 730, 785.4, 728.86	I96, M72.6, L03-04, L08, M00, M86,
Iatrogenic	998.5, 999.3	T81.4x, T82.6x, T82.7x, T83.5x, T83.6x, T84.5x, T84.6x, T84.7x, T85.7x, T87.5x, T88.0x, T80.2x
Sepsis/bacteremia	995.9x, 790.7, 785.52	R65.1x, R65.2x R78.81, T81.12x

B. Organ dysfunction

Diagnosis	ICD-9 diagnosis codes	ICD-10 diagnosis codes	ICD-9 procedure codes	ICD-10 procedure codes
Respiratory failure	518.81, 518.82, 518.85, 786.09, 799.1	J96.0x, J96.2x, J96.9x, R06.03, R09.2	96.7x	5A1935Z 5A1945Z 5A1955Z
Circulatory failure	458.x, 785.5x, 796.3	R57.9, I95.x, R65.21	---	---
Renal failure	584.x, 580.x	N00.x, N17.x	39.95	5A1D70Z 5A1D80Z 5A1D90Z
Hepatic failure	570, 572.2, 573.3	K72.0x, K72.9x, K75.9	---	---
Hematologic failure	286.2, 286.6, 286.9, 287.3x, 287.4x, 287.5	D65, D69.5x, D69.6, D68.9	---	---
Metabolic failure	276.2	E87.2	---	---
Neurologic failure	293.xx, 348.1, 348.3x, 780.01, 780.09	G92, G93.4x, G93.1, F05, R41.0, F06.0, F06.2, R40.20, R40.4, R40.1, R41.82	89.14	4A00x4Z where x=3,7,8,X 4A01x4Z where x=3,7,8,X 4A10x4Z where x=3,7,8,X 4A11x4Z where x=3,7,8,X

Table S5. Index Hospitalization Characteristics based on hospital discharge International Classification of Disease 9th and 10th Revisions Clinical Modification (ICD-9/10) codes.

Characteristic	ICD-9 diagnosis codes	ICD-10 diagnosis codes	ICD-9 procedure codes	ICD-10 procedure codes
Infection	See Supplementary Table 2A		--	--
Organ failure	See Supplementary Table 2B		--	--
Intensive care unit	Revenue codes: 020x, 021x		--	--
Invasive ventilation	--	--	96.70, 96.71, 96.72	5A1935Z, 5A1945Z, 5A1955Z
Hemodialysis	--	--	39.95	5A1D70Z, 5A1D80Z, 5A1D90Z
CVD diagnosis	See Supplementary Table 3B		--	--

Table S6: Variables included in the propensity score for sepsis and standard mean differences between the sepsis and no sepsis groups before and after propensity score overlap weighting.

	Before Propensity Score Weighting			After Propensity Score Weighting		
	No sepsis (N=1,449,821)	Sepsis (N=808,673)	Standardized Difference	No sepsis (N=1,449,821)	Sepsis (N=808,673)	Standardized Difference
Age group						
18-54 years	450919 (31.1%)	124249 (15.4%)	0.379	21.2%	21.2%	0.000
55-64 years	347422 (24.0%)	158929 (19.7%)	0.105	22.1%	22.1%	0.000
65-74 years	285200 (19.7%)	194439 (24.0%)	0.106	22.3%	22.3%	0.000
75+ years	366280 (25.3%)	331056 (40.9%)	0.338	34.3%	34.3%	0.000
Sex						
Female	789512 (54.5%)	438058 (54.2%)	0.006	55.5%	55.5%	0.000
Male	660309 (45.5%)	370615 (45.8%)	0.006	44.5%	44.5%	0.000
Race						
Unknown	251601 (17.4%)	103265 (12.8%)	0.128	14.8%	14.8%	0.000
Asian	29042 (2.0%)	15110 (1.9%)	0.010	1.8%	1.8%	0.000
Black	175974 (12.1%)	111714 (13.8%)	0.050	13.0%	13.0%	0.000
Hispanic	104386 (7.2%)	56237 (7.0%)	0.010	7.3%	7.3%	0.000
White	888818 (61.3%)	522347 (64.6%)	0.068	63.1%	63.1%	0.000
Region						
Unknown	3055 (0.2%)	1186 (0.1%)	0.015	0.2%	0.2%	0.000
Midwest	404171 (27.9%)	226434 (28.0%)	0.003	27.5%	27.5%	0.000
Northeast	227047 (15.7%)	132902 (16.4%)	0.021	16.1%	16.1%	0.000
South	666092 (45.9%)	368145 (45.5%)	0.008	46.4%	46.4%	0.000
West	149456 (10.3%)	80006 (9.9%)	0.014	9.8%	9.8%	0.000
Health plan						

Commercial	789400 (54.4%)	257979 (31.9%)	0.467	41.4%	41.4%	0.000
Medicare Advantage	660421 (45.6%)	550694 (68.1%)	0.467	58.6%	58.6%	0.000
Pharmacy coverage	992543 (68.5%)	604885 (74.8%)	0.141	72.0%	72.0%	0.000
Infection type						
Bacteria/fungal	83972 (5.8%)	381206 (47.1%)	1.061	31.2%	31.2%	0.000
CNS	2621 (0.2%)	3769 (0.5%)	0.050	0.4%	0.4%	0.000
Cardiovascular	9231 (0.6%)	11786 (1.5%)	0.081	1.6%	1.6%	0.000
ENT/URI	14039 (1.0%)	15748 (1.9%)	0.082	2.6%	2.6%	0.000
Pulmonary	68570 (4.7%)	277549 (34.3%)	0.805	17.0%	17.0%	0.000
GI	52010 (3.6%)	31670 (3.9%)	0.017	5.9%	5.9%	0.000
GU	81736 (5.6%)	247626 (30.6%)	0.686	23.2%	23.2%	0.000
Skin/soft tissue/bone/joint	73925 (5.1%)	82120 (10.2%)	0.191	14.3%	14.3%	0.000
Iatrogenic	14444 (1.0%)	21269 (2.6%)	0.123	3.2%	3.2%	0.000
Sepsis/bacteremia	3242 (0.2%)	168363 (20.8%)	0.713	2.3%	2.3%	0.000
Organ failure type						
Respiratory	85496 (5.9%)	258185 (31.9%)	0.705	14.9%	14.9%	0.000
Circulatory	61094 (4.2%)	138130 (17.1%)	0.427	9.9%	9.9%	0.000
Renal	136693 (9.4%)	338870 (41.9%)	0.801	24.1%	24.1%	0.000
Hepatic	8512 (0.6%)	17715 (2.2%)	0.137	1.6%	1.6%	0.000
Hematologic	42621 (2.9%)	81473 (10.1%)	0.292	7.2%	7.2%	0.000
Metabolic	26155 (1.8%)	53766 (6.6%)	0.243	4.3%	4.3%	0.000
Neurologic	76993 (5.3%)	179734 (22.2%)	0.506	12.7%	12.7%	0.000
Comorbidities						
MI	133617 (9.2%)	126051 (15.6%)	0.194	11.9%	11.9%	0.000
CAD	446032 (30.8%)	356481 (44.1%)	0.278	37.1%	37.1%	0.000

Heart failure	222407 (15.3%)	256655 (31.7%)	0.394	23.0%	23.0%	0.000
Cardiomyopathy	100189 (6.9%)	96784 (12.0%)	0.174	9.0%	9.0%	0.000
Hypertension	1069012 (73.7%)	691060 (85.5%)	0.294	80.8%	80.8%	0.000
Chronic kidney disease	121454 (8.4%)	162920 (20.1%)	0.341	14.1%	14.1%	0.000
SVT	47782 (3.3%)	37337 (4.6%)	0.068	3.7%	3.7%	0.000
Atrial fibrillation/flutter	203769 (14.1%)	189976 (23.5%)	0.243	18.0%	18.0%	0.000
VT	48135 (3.3%)	47666 (5.9%)	0.123	4.3%	4.3%	0.000
Hyperlipidemia	1010638 (69.7%)	621013 (76.8%)	0.161	73.7%	73.7%	0.000
Obesity	394056 (27.2%)	248730 (30.8%)	0.079	29.5%	29.5%	0.000
Diabetes	440949 (30.4%)	352441 (43.6%)	0.275	38.1%	38.1%	0.000
Stroke	133088 (9.2%)	138394 (17.1%)	0.236	12.6%	12.6%	0.000
PCI	103615 (7.1%)	80653 (10.0%)	0.101	8.1%	8.1%	0.000
CABG	85075 (5.9%)	73615 (9.1%)	0.123	7.3%	7.3%	0.000
Valve procedure	11597 (0.8%)	10459 (1.3%)	0.049	1.0%	1.0%	0.000
ICD/PPM	69439 (4.8%)	65183 (8.1%)	0.134	6.3%	6.3%	0.000
Renal failure requiring dialysis	17198 (1.2%)	26182 (3.2%)	0.140	2.1%	2.1%	0.000
History of smoking	456169 (31.5%)	321588 (39.8%)	0.174	35.0%	35.0%	0.000
Active smoker	296008 (20.4%)	189433 (23.4%)	0.073	21.3%	21.3%	0.000
Index hospitalization						
ICU	449257 (31.0%)	357378 (44.2%)	0.275	32.9%	32.9%	0.000
Invasive ventilation	11580 (0.8%)	41662 (5.2%)	0.258	2.2%	2.2%	0.000
Hemodialysis	4625 (0.3%)	17447 (2.2%)	0.167	1.0%	1.0%	0.000
CV diagnosis						
Heart failure	204613 (14.1%)	225294 (27.9%)	0.342	19.7%	19.7%	0.000
MI	55056 (3.8%)	41637 (5.1%)	0.065	3.6%	3.6%	0.000
Angina	37072 (2.6%)	8435 (1.0%)	0.114	1.2%	1.2%	0.000
Atrial fibrillation	207768 (14.3%)	168809 (20.9%)	0.172	16.2%	16.2%	0.000
Cardiac arrest	5626 (0.4%)	6974 (0.9%)	0.060	0.5%	0.5%	0.000
Cardiogenic shock	1732 (0.1%)	4615 (0.6%)	0.077	0.3%	0.3%	0.000

CAD	267646 (18.5%)	167828 (20.8%)	0.058	19.0%	19.0%	0.000
Valve disease	176252 (12.2%)	124402 (15.4%)	0.094	12.9%	12.9%	0.000
Cardiomyopathy	76338 (5.3%)	54715 (6.8%)	0.063	5.5%	5.5%	0.000
SVT	19657 (1.4%)	15716 (1.9%)	0.046	1.5%	1.5%	0.000
VT	27752 (1.9%)	23518 (2.9%)	0.065	2.1%	2.1%	0.000
Stroke	133127 (9.2%)	60554 (7.5%)	0.061	7.0%	7.0%	0.000
Intracranial bleeding	36876 (2.5%)	12669 (1.6%)	0.069	1.7%	1.7%	0.000

Table S7: 30-day event rates (per 100 patients) in patients with and without sepsis, as a function of sepsis group.

	No Sepsis (ref)			Sepsis		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes	N=1,449,821			N=808,673		
Mortality	3,329	1,449,821	0.23	6,355	808,673	0.79
All-cause hospitalization	103,387	1,446,672	7.15	95,608	802,667	11.91
CVD hospitalization	34,934	1,446,672	2.41	38,569	802,667	4.81
Composite #1	106,382	1,446,672	7.35	101,565	802,667	12.65
Composite #2	38,122	1,446,672	2.64	44,741	802,667	5.57
	No Sepsis (ref)			Implicit Sepsis Only		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes	N=1,449,821			N=448,644		
Mortality	3,329	1,449,821	0.23	2,750	448,644	0.61
All-cause hospitalization	103,387	1,446,672	7.15	56,465	446,062	12.66
CVD hospitalization	34,934	1,446,672	2.41	24,813	446,062	5.56
Composite #1	106,382	1,446,672	7.35	58,973	446,062	13.22
Composite #2	38,122	1,446,672	2.64	27,446	446,062	6.15
	No Sepsis (ref)			Explicit Sepsis Only		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes	N=1,449,821			N=124,841		
Mortality	3,329	1,449,821	0.23	247	124,841	0.20
All-cause hospitalization	103,387	1,446,672	7.15	12,399	124,612	9.95
CVD hospitalization	34,934	1,446,672	2.41	3,393	124,612	2.72
Composite #1	106,382	1,446,672	7.35	12,599	124,612	10.11
Composite #2	38,122	1,446,672	2.64	3,625	124,612	2.91

	No Sepsis (ref)			Both Sepsis Types		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes		N=1,449,821			N=235,188	
Mortality	3,329	1,449,821	0.23	3,358	235,188	1.43
All-cause hospitalization	103,387	1,446,672	7.15	26,744	231,993	11.53
CVD hospitalization	34,934	1,446,672	2.41	10,363	231,993	4.47
Composite #1	106,382	1,446,672	7.35	29,993	231,993	12.93
Composite #2	38,122	1,446,672	2.64	13,670	231,993	5.89

Table S8: 90-day event rates (per 100 patients) in patients with and without sepsis, as a function of sepsis group.

	No Sepsis (ref)			Sepsis		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes	N=1,449,821			N=808,673		
Mortality	38,419	1,449,821	2.65	54,776	808,673	6.77
All-cause hospitalization	211,510	1,341,267	15.77	212,135	718,898	29.51
CVD hospitalization	74,867	1,341,267	5.58	92,702	718,898	12.90
Composite #1	235,200	1,341,267	17.54	242,744	718,898	33.77
Composite #2	106,018	1,341,267	7.90	134,079	718,898	18.65
	No Sepsis (ref)			Implicit Sepsis Only		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes	N=1,449,821			N=448,644		
Mortality	38,419	1,449,821	2.65	31,314	448,644	6.98
All-cause hospitalization	211,510	1,341,267	15.77	124,503	397,909	31.29
CVD hospitalization	74,867	1,341,267	5.58	58,801	397,909	14.78
Composite #1	235,200	1,341,267	17.54	140,995	397,909	35.43
Composite #2	106,018	1,341,267	7.90	81,522	397,909	20.49
	No Sepsis (ref)			Explicit Sepsis Only		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes	N=1,449,821			N=124,841		
Mortality	38,419	1,449,821	2.65	4,067	124,841	3.26
All-cause hospitalization	211,510	1,341,267	15.77	26,588	115,517	23.02
CVD hospitalization	74,867	1,341,267	5.58	8,115	115,517	7.02
Composite #1	235,200	1,341,267	17.54	28,583	115,517	24.74
Composite #2	106,018	1,341,267	7.90	11,270	115,517	9.76
	No Sepsis (ref)			Both Sepsis Types		

	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes		N=1,449,821			N=235,188	
Mortality	38,419	1,449,821	2.65	19,395	235,188	8.25
All-cause hospitalization	211,510	1,341,267	15.77	61,044	205,472	29.71
CVD hospitalization	74,867	1,341,267	5.58	25,786	205,472	12.55
Composite #1	235,200	1,341,267	17.54	73,166	205,472	35.61
Composite #2	106,018	1,341,267	7.90	41,287	205,472	20.09

Table S9: One-year event rates (per 100 patients) in patients with and without sepsis, as a function of sepsis group.

	No Sepsis (ref)			Sepsis		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes		N=1,449,821			N=808,673	
Mortality	98,865	1,449,821	6.82	133,624	808,673	16.52
All-cause hospitalization	395,079	1,027,742	38.44	367,434	524,886	70.00
CVD hospitalization	151,195	1,027,742	14.71	178,674	524,886	34.04
Composite #1	440,830	1,027,742	42.89	416,748	524,886	79.40
Composite #2	221,919	1,027,742	21.59	261,390	524,886	49.80
	No Sepsis (ref)			Implicit Sepsis Only		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes		N=1,449,821			N=448,644	
Mortality	98,865	1,449,821	6.82	79,888	448,644	17.81
All-cause hospitalization	395,079	1,027,742	38.44	216,632	286,201	75.69
CVD hospitalization	151,195	1,027,742	14.71	112,965	286,201	39.47
Composite #1	440,830	1,027,742	42.89	244,546	286,201	85.45
Composite #2	221,919	1,027,742	21.59	160,111	286,201	55.94
	No Sepsis (ref)			Explicit Sepsis Only		
	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes		N=1,449,821			N=124,841	
Mortality	98,865	1,449,821	6.82	11,621	124,841	9.31
All-cause hospitalization	395,079	1,027,742	38.44	47,176	88,898	53.07
CVD hospitalization	151,195	1,027,742	14.71	17,100	88,898	19.24
Composite #1	440,830	1,027,742	42.89	50,940	88,898	57.30
Composite #2	221,919	1,027,742	21.59	24,836	88,898	27.94
	No Sepsis (ref)			Both Sepsis Types		

	No. with Events	No. of Enrollees	Event Rate per 100	No. with Events	No. of Enrollees	Event Rate per 100
Outcomes		N=1,449,821			N=235,188	
Mortality	98,865	1,449,821	6.82	42,115	235,188	17.91
All-cause hospitalization	395,079	1,027,742	38.44	103,626	149,787	69.18
CVD hospitalization	151,195	1,027,742	14.71	48,599	149,787	32.45
Composite #1	440,830	1,027,742	42.89	121,262	149,787	80.96
Composite #2	221,919	1,027,742	21.59	76,443	149,787	51.03

Table S10: Risk of all-cause post-discharge mortality associated with sepsis (all definitions) across subgroups. P values for interaction are unadjusted.

	No Sepsis (ref)			Sepsis			Hazard Ratio (95% CI)	P Value	P Value for interaction
	No. with Events	Person Years	Event Rate per 100	No. with Events	Person Years	Event Rate per 100			
Age group									
All <65 years	25,610	2,127,816	1.20	31,370	646,525	4.85	1.83 (1.77, 1.90)	<0.0001	<0.0001
65+ years	141,883	1,573,707	9.02	189,058	1,048,002	18.04	1.22 (1.20, 1.23)	<0.0001	
50-64 years	21,442	1,306,173	1.64	26,855	471,293	5.70	1.87 (1.80, 1.94)	<0.0001	
<50 years	4,168	821,643	0.51	4,515	175,232	2.58	2.04 (1.86, 2.23)	<0.0001	
Sex									
Male	81,297	1,641,434	4.95	104,053	755,290	13.78	1.28 (1.25, 1.30)	<0.0001	0.0001
Female	86,196	2,060,089	4.18	116,375	939,237	12.39	1.26 (1.24, 1.28)	<0.0001	
Race/Ethnicity									
Asian	2,910	76,916	3.78	3,910	32,400	12.07	1.28 (1.16, 1.42)	<0.0001	<0.0001
Black	21,512	426,475	5.04	32,457	225,903	14.37	1.31 (1.26, 1.36)	<0.0001	
Hispanic	8,382	261,598	3.20	12,216	115,521	10.57	1.32 (1.25, 1.40)	<0.0001	
White	120,942	2,287,774	5.29	155,325	1,113,655	13.95	1.23 (1.21, 1.25)	<0.0001	
All non-White	46,551	1,413,750	3.29	65,103	580,872	11.21	1.37 (1.34, 1.41)	<0.0001	
Health plan									
Commercial	23,033	2,055,952	1.12	22,546	564,867	3.99	1.82 (1.75, 1.89)	<0.0001	<0.0001
Medicare Advantage	144,460	1,645,572	8.78	197,882	1,129,660	17.52	1.21 (1.19, 1.22)	<0.0001	
Pharmacy coverage									
No	43,648	1,271,498	3.43	47,650	457,007	10.43	1.26 (1.22, 1.29)	<0.0001	<0.0001
Yes	123,845	2,430,026	5.10	172,868	1,237,520	13.97	1.27 (1.25, 1.29)	<0.0001	
Prior CVD									
No	56,704	2,153,457	2.63	53,264	724,153	7.36	1.35 (1.32, 1.38)	<0.0001	<0.0001
Yes	110,789	1,548,067	7.16	167,164	970,374	17.23	1.21 (1.19, 1.23)	<0.0001	
# of CVD risk factors									
<3	74,282	2,066,007	3.60	69,862	653,848	10.68	1.25 (1.22, 1.27)	<0.0001	<0.0001
3+	93,211	1,635,516	5.70	150,566	1,040,680	14.47	1.28 (1.26, 1.30)	<0.0001	
ICU during index hospitalization									
No	112,668	2,589,391	4.35	118,549	976,556	12.14	1.26 (1.24, 1.28)	<0.0001	<0.0001
Yes	54,825	1,112,133	4.93	101,879	717,971	14.19	1.19 (1.16, 1.22)	<0.0001	

CVD diagnosis during index hospitalization										0.0183
No	62,629	2,123,764	2.95	68,723	808,795	8.50	1.42 (1.39, 1.45)	<0.0001		
Yes	104,864	1,577,759	6.65	151,705	885,732	17.13	1.14 (1.12, 1.16)	<0.0001		
Any organ failure during index hospitalization										<0.0001
No	108,553	2,950,183	3.68	19,810	287,247	6.90	1.32 (1.29, 1.34)	<0.0001		
Yes	58,940	751,841	7.84	200,618	1,407,280	14.26	1.07 (0.99, 1.16)	0.0810		
AKI during index hospitalization										<0.0001
No	141,152	3,417,975	4.13	118,658	1,012,190	11.72	1.73 (1.71, 1.75)	<0.0001		
Yes	26,341	283,549	9.29	101,770	682,337	14.91	1.17 (1.04, 1.32)	0.0107		
Shock during index hospitalization										<0.0001
No	166,144	3,686,045	4.51	203,020	1,588,099	12.78	1.75 (1.74, 1.77)	<0.0001		
Yes	1,349	15,478	8.72	17,408	106,428	16.36	1.25 (0.96, 1.62)	0.0951		
Prior hospitalization within 6 months										<0.0001
No	141,241	3,327,474	4.24	142,197	1,292,286	11.00	1.71 (1.69, 1.73)	<0.0001		
Yes	26,252	374,049	7.02	78,231	402,241	19.45	1.96 (1.91, 2.01)	<0.0001		

Table S11: Risk of all-cause hospitalization associated with sepsis (all definitions) across subgroups, using death as a competing risk. P values for interaction are unadjusted.

	No Sepsis (ref)			Sepsis			Hazard Ratio (95% CI)	P Value	P Value for interaction
	No. with Events	Person Years	Event Rate per 100	No. with Events	Person Years	Event Rate per 100			
Age group									<0.0001
All <65 years	283,275	1,498,742	18.90	149,842	366,018	40.94	1.41 (1.39, 1.42)	<0.0001	
65+ years	321,576	990,179	32.48	331,421	535,967	61.84	1.38 (1.37, 1.40)	<0.0001	
50-64 years	186,450	910,128	20.49	114,415	263,050	43.50	1.40 (1.38, 1.42)	<0.0001	
<50 years	96,825	588,614	16.45	35,427	102,968	34.41	1.43 (1.40, 1.46)	<0.0001	
Sex									0.0633
Male	275,890	1,110,995	24.83	220,045	408,805	53.83	1.40 (1.38, 1.41)	<0.0001	
Female	328,961	1,377,925	23.87	261,218	493,180	52.97	1.36 (1.35, 1.37)	<0.0001	
Race/Ethnicity									<0.0001
Asian	10,714	55,156	19.42	8,425	18,533	45.46	1.39 (1.32, 1.47)	<0.0001	
Black	77,968	279,093	27.94	70,695	112,682	62.74	1.39 (1.36, 1.42)	<0.0001	
Hispanic	40,992	180,242	22.74	32,394	63,544	50.98	1.36 (1.32, 1.39)	<0.0001	
White	383,756	1,512,054	25.38	315,346	584,355	53.96	1.37 (1.36, 1.38)	<0.0001	
All non-white	221,095	976,867	22.63	165,917	317,631	52.24	1.39 (1.37, 1.41)	<0.0001	
Health plan									<0.0001
Commercial	266,937	1,476,499	18.08	125,152	343,381	36.45	1.40 (1.38, 1.41)	<0.0001	
Medicare Advantage	337,914	1,012,422	33.38	356,111	558,604	63.75	1.37 (1.36, 1.38)	<0.0001	
Pharmacy coverage									<0.0001
No	181,967	872,619	20.85	115,058	256,588	44.84	1.39 (1.37, 1.41)	<0.0001	
Yes	422,884	1,616,302	26.16	366,205	645,397	56.74	1.37 (1.36, 1.38)	<0.0001	
Prior CVD									0.9397
No	290,899	1,529,893	19.01	157,655	436,839	36.09	1.36 (1.35, 1.37)	<0.0001	
Yes	313,952	959,028	32.74	323,608	465,147	69.57	1.39 (1.37, 1.40)	<0.0001	
# of CVD risk factors									<0.0001
<3	285,977	1,448,908	19.74	152,889	384,889	39.72	1.34 (1.33, 1.36)	<0.0001	
3+	318,874	1,040,012	30.66	328,374	517,096	63.50	1.41 (1.39, 1.42)	<0.0001	
ICU during index hospitalization									<0.0001
No	415,107	1,740,894	23.84	265,585	529,558	50.15	1.36 (1.35, 1.37)	<0.0001	
Yes	189,744	748,027	25.37	215,678	372,427	57.91	1.36 (1.35, 1.38)	<0.0001	

CVD diagnosis during index hospitalization								<0.0001	
No	304,717	1,471,436	20.71	191,886	463,331	41.41	1.38 (1.36, 1.39)	<0.0001	
Yes	300,134	1,017,485	29.50	289,377	438,654	65.97	1.35 (1.34, 1.37)	<0.0001	
Any organ failure during index hospitalization								<0.0001	
No	453,049	1,993,195	22.73	63,461	170,660	37.19	1.32 (1.31, 1.33)	<0.0001	
Yes	151,802	495,726	30.62	417,802	731,326	57.13	1.41 (1.35, 1.48)	<0.0001	
AKI during index hospitalization								<0.0001	
No	540,494	2,304,326	23.46	271,301	554,121	48.96	1.44 (1.43, 1.45)	<0.0001	
Yes	64,357	184,595	34.86	209,962	347,864	60.36	1.43 (1.32, 1.54)	<0.0001	
Shock during index hospitalization								0.2293	
No	601,916	2,478,483	24.29	449,627	845,574	53.17	1.48 (1.47, 1.49)	<0.0001	
Yes	2,935	10,437	28.12	31,636	56,411	56.08	1.46 (1.21, 1.75)	<0.0001	
Prior hospitalization within 6 months								<0.0001	
No	519,636	2,276,338	22.83	323,812	738,119	43.87	1.44 (1.43, 1.45)	<0.0001	
Yes	85,215	212,583	40.09	157,451	163,867	96.08	1.61 (1.59, 1.63)	<0.0001	

Table S12: Risk of cardiovascular hospitalization associated with sepsis (all definitions) across subgroups, using death as a competing risk. P values for interaction are unadjusted.

	No Sepsis (ref)			Sepsis			Hazard Ratio (95% CI)	P Value	P Value for interaction
	No. with Events	Person Years	Event Rate per 100	No. with Events	Person Years	Event Rate per 100			
Age group									<0.0001
All <65 years	81,181	1,968,649	4.12	61,582	547,440	11.25	1.57 (1.54, 1.61)	<0.0001	
65+ years	180,064	1,281,510	14.05	206,247	767,302	26.88	1.42 (1.40, 1.44)	<0.0001	
50-64 years	63,060	1,186,143	5.32	50,842	391,200	13.00	1.60 (1.56, 1.64)	<0.0001	
<50 years	18,121	782,506	2.32	10,740	156,240	6.87	1.61 (1.53, 1.68)	<0.0001	
Sex									<0.0001
Male	133,482	1,411,355	9.46	126,422	581,976	21.72	1.42 (1.40, 1.44)	<0.0001	
Female	127,763	1,838,805	6.95	141,407	732,766	19.30	1.43 (1.41, 1.46)	<0.0001	
Race/Ethnicity									0.0006
Asian	4,567	68,998	6.62	4,618	25,830	17.88	1.34 (1.23, 1.47)	<0.0001	
Black	37,084	365,637	10.14	42,385	166,599	25.44	1.42 (1.38, 1.46)	<0.0001	
Hispanic	16,939	232,796	7.28	17,799	90,771	19.61	1.33 (1.28, 1.39)	<0.0001	
White	171,886	1,986,376	8.65	177,931	856,362	20.78	1.43 (1.41, 1.45)	<0.0001	
All non-white	89,359	1,263,784	7.07	89,898	458,381	19.61	1.43 (1.40, 1.45)	<0.0001	
Health plan									<0.0001
Commercial	76,461	1,908,542	4.01	48,447	492,057	9.85	1.55 (1.52, 1.59)	<0.0001	
Medicare Advantage	184,784	1,341,618	13.77	219,382	822,685	26.67	1.39 (1.37, 1.41)	<0.0001	
Pharmacy coverage									<0.0001
No	70,172	1,139,965	6.16	58,798	370,641	15.86	1.44 (1.41, 1.48)	<0.0001	
Yes	191,073	2,110,194	9.05	209,031	944,101	22.14	1.42 (1.40, 1.44)	<0.0001	
Prior CVD									<0.0001
No	78,951	2,010,555	3.93	57,480	637,568	9.02	1.48 (1.45, 1.51)	<0.0001	
Yes	182,294	1,239,605	14.71	210,349	677,175	31.06	1.41 (1.39, 1.43)	<0.0001	
# of CVD risk factors									<0.0001
<3	101,518	1,875,800	5.41	69,903	549,927	12.71	1.41 (1.39, 1.44)	<0.0001	
3+	159,727	1,374,360	11.62	197,926	764,815	25.88	1.44 (1.42, 1.46)	<0.0001	
ICU during index hospitalization									<0.0001
No	155,273	2,324,377	6.68	137,926	779,891	17.69	1.43 (1.41, 1.45)	<0.0001	
Yes	105,972	925,783	11.45	129,903	534,851	24.29	1.39 (1.36, 1.42)	<0.0001	

CVD diagnosis during index hospitalization								<0.0001	
No	66,913	2,010,432	3.33	67,654	709,162	9.54	1.51 (1.48, 1.54)	<0.0001	
Yes	194,332	1,239,728	15.68	200,175	605,580	33.06	1.38 (1.36, 1.40)	<0.0001	
Any organ failure during index hospitalization								<0.0001	
No	181,765	2,617,466	6.94	27,878	243,137	11.47	1.35 (1.33, 1.37)	<0.0001	
Yes	79,480	632,694	12.56	239,951	1,071,605	22.39	1.52 (1.43, 1.62)	<0.0001	
AKI during index hospitalization								<0.0001	
No	224,763	3,016,407	7.45	140,743	806,814	17.44	1.50 (1.48, 1.51)	<0.0001	
Yes	36,482	233,753	15.61	127,086	507,928	25.02	1.52 (1.38, 1.67)	<0.0001	
Shock during index hospitalization								<0.0001	
No	259,601	3,237,222	8.02	250,427	1,231,974	20.33	1.59 (1.57, 1.60)	<0.0001	
Yes	1,644	12,938	12.71	17,402	82,768	21.03	1.34 (1.02, 1.76)	0.0366	
Prior hospitalization within 6 months								<0.0001	
No	223,079	2,939,026	7.59	175,757	1,035,258	16.98	1.54 (1.52, 1.55)	<0.0001	
Yes	38,166	311,134	12.27	92,072	279,484	32.94	1.73 (1.70, 1.77)	<0.0001	

Table S13: Risk of the composite of all-cause death and all-cause hospitalization associated with sepsis (all definitions) across subgroups. P values for interaction are unadjusted.

	No Sepsis (ref)			Sepsis			Hazard Ratio (95% CI)	P Value	P Value for interaction
	No. with Events	Person Years	Event Rate per 100	No. with Events	Person Years	Event Rate per 100			
Age group									<0.0001
All <65 years	291,368	1,498,742	19.44	157,129	366,018	42.93	1.41 (1.39, 1.43)	<0.0001	
65+ years	370,101	990,179	37.38	381,099	535,967	71.10	1.31 (1.30, 1.32)	<0.0001	
50-64 years	193,140	910,128	21.22	120,553	263,050	45.83	1.41 (1.39, 1.43)	<0.0001	
<50 years	98,228	588,614	16.69	36,576	102,968	35.52	1.43 (1.40, 1.46)	<0.0001	
Sex									<0.0001
Male	302,445	1,110,995	27.22	245,964	408,805	60.17	1.36 (1.35, 1.38)	<0.0001	
Female	359,024	1,377,925	26.06	292,264	493,180	59.26	1.33 (1.32, 1.34)	<0.0001	
Race/Ethnicity									<0.0001
Asian	11,681	55,156	21.18	9,447	18,533	50.97	1.37 (1.30, 1.44)	<0.0001	
Black	84,494	279,093	30.27	78,071	112,682	69.28	1.36 (1.34, 1.39)	<0.0001	
Hispanic	43,504	180,242	24.14	35,161	63,544	55.33	1.34 (1.31, 1.38)	<0.0001	
White	425,411	1,512,053	28.13	356,315	584,355	60.98	1.33 (1.32, 1.34)	<0.0001	
All non-white	236,058	976,867	24.16	181,913	317,631	57.27	1.38 (1.36, 1.39)	<0.0001	
Health plan									<0.0001
Commercial	274,975	1,476,499	18.62	131,862	343,381	38.40	1.40 (1.39, 1.42)	<0.0001	
Medicare Advantage	386,464	1,012,422	38.17	406,366	558,604	72.75	1.31 (1.30, 1.33)	<0.0001	
Pharmacy coverage									0.0021
No	197,504	872,619	22.63	128,428	256,588	50.05	1.36 (1.34, 1.37)	<0.0001	
Yes	463,965	1,616,302	28.71	409,800	645,397	63.50	1.34 (1.33, 1.35)	<0.0001	
Prior CVD									0.0684
No	311,293	1,529,893	20.35	172,568	436,839	39.50	1.34 (1.33, 1.35)	<0.0001	
Yes	350,176	959,028	36.51	365,660	465,147	78.61	1.34 (1.33, 1.36)	<0.0001	
# of CVD risk factors									<0.0001
<3	313,403	1,448,908	21.63	174,566	384,889	45.35	1.32 (1.30, 1.33)	<0.0001	
3+	348,066	1,040,012	33.47	363,662	517,096	70.33	1.38 (1.36, 1.39)	<0.0001	
ICU during index hospitalization									<0.0001
No	453,740	1,740,894	26.06	295,253	529,558	55.75	1.33 (1.31, 1.34)	<0.0001	
Yes	207,729	748,027	27.77	242,975	372,427	65.24	1.33 (1.32, 1.35)	<0.0001	

CVD diagnosis during index hospitalization								<0.0001	
No	327,156	1,471,436	22.23	210,233	463,330	45.37	1.36 (1.35, 1.37)	<0.0001	
Yes	334,313	1,017,485	32.86	327,995	438,654	74.77	1.30 (1.29, 1.31)	<0.0001	
Any organ failure during index hospitalization								<0.0001	
No	488,007	1,993,195	24.48	67,929	170,660	39.80	1.30 (1.29, 1.31)	<0.0001	
Yes	173,462	495,726	34.99	470,299	731,326	64.31	1.29 (1.23, 1.35)	<0.0001	
AKI during index hospitalization								<0.0001	
No	587,731	2,304,326	25.51	302,186	554,121	54.53	1.49 (1.48, 1.50)	<0.0001	
Yes	73,738	184,595	39.95	236,042	347,864	67.85	1.33 (1.23, 1.43)	<0.0001	
Shock during index hospitalization								<0.0001	
No	657,871	2,478,483	26.54	500,061	845,574	59.14	1.52 (1.51, 1.53)	<0.0001	
Yes	3,598	10,437	34.47	38,167	56,411	67.66	1.35 (1.14, 1.59)	0.0004	
Prior hospitalization within 6 months								<0.0001	
No	567,958	2,276,337	24.95	361,651	738,119	49.00	1.48 (1.47, 1.49)	<0.0001	
Yes	93,511	212,583	43.99	176,577	163,867	107.76	1.71 (1.69, 1.74)	<0.0001	

Table S14: Risk of the composite of all-cause death and cardiovascular hospitalization associated with sepsis (all definitions) across subgroups. P values for interaction are unadjusted.

	No Sepsis (ref)			Sepsis			Hazard Ratio (95% CI)	P Value	P Value for interaction
	No. with Events	Person Years	Event Rate per 100	No. with Events	Person Years	Event Rate per 100			
Age group									<0.0001
All <65 years	98,844	1,968,649	5.02	78,840	547,440	14.40	1.61 (1.58, 1.65)	<0.0001	
65+ years	261,559	1,281,510	20.41	298,674	767,302	38.93	1.30 (1.29, 1.32)	<0.0001	
50-64 years	77,651	1,186,143	6.55	65,311	391,200	16.70	1.65 (1.62, 1.69)	<0.0001	
<50 years	21,193	782,506	2.71	13,529	156,240	8.66	1.65 (1.58, 1.72)	<0.0001	
Sex									<0.0001
Male	179,941	1,411,355	12.75	177,166	581,976	30.44	1.38 (1.36, 1.40)	<0.0001	
Female	180,462	1,838,805	9.81	200,348	732,766	27.34	1.36 (1.34, 1.37)	<0.0001	
Race/Ethnicity									<0.0001
Asian	6,266	68,998	9.08	6,615	25,831	25.61	1.34 (1.24, 1.44)	<0.0001	
Black	48,976	365,637	13.39	57,135	166,599	34.29	1.37 (1.34, 1.41)	<0.0001	
Hispanic	21,603	232,796	9.28	23,398	90,771	25.78	1.33 (1.28, 1.38)	<0.0001	
White	243,636	1,986,376	12.27	255,958	856,362	29.89	1.35 (1.33, 1.36)	<0.0001	
All non-white	116,767	1,263,784	9.24	121,556	458,381	26.52	1.41 (1.39, 1.43)	<0.0001	
Health plan									<0.0001
Commercial	92,971	1,908,542	4.87	62,512	492,057	12.70	1.60 (1.57, 1.63)	<0.0001	
Medicare Advantage	267,432	1,341,618	19.93	315,002	822,685	38.29	1.30 (1.29, 1.32)	<0.0001	
Pharmacy coverage									0.2842
No	97,088	1,139,965	8.52	84,099	370,641	22.69	1.38 (1.35, 1.40)	<0.0001	
Yes	263,315	2,110,194	12.48	293,415	944,101	31.08	1.36 (1.35, 1.38)	<0.0001	
Prior CVD									<0.0001
No	119,463	2,010,555	5.94	91,352	637,568	14.33	1.42 (1.40, 1.45)	<0.0001	
Yes	240,940	1,239,605	19.44	286,162	677,175	42.26	1.33 (1.32, 1.35)	<0.0001	
# of CVD risk factors									<0.0001
<3	149,962	1,875,800	7.99	111,142	549,927	20.21	1.34 (1.32, 1.36)	<0.0001	
3+	210,441	1,374,360	15.31	266,372	764,815	34.83	1.39 (1.37, 1.41)	<0.0001	
ICU during index hospitalization									<0.0001
No	225,733	2,324,377	9.71	199,256	779,891	25.55	1.35 (1.34, 1.37)	<0.0001	
Yes	134,670	925,783	14.55	178,258	534,851	33.33	1.33 (1.31, 1.35)	<0.0001	

CVD diagnosis during index hospitalization								<0.0001	
No	113,795	2,010,432	5.66	112,143	709,162	15.81	1.46 (1.43, 1.48)	<0.0001	
Yes	246,608	1,239,728	19.89	265,371	605,580	43.82	1.29 (1.28, 1.31)	<0.0001	
Any organ failure during index hospitalization								0.0003	
No	246,419	2,617,466	9.41	38,381	243,137	15.79	1.32 (1.31, 1.34)	<0.0001	
Yes	113,984	632,694	18.02	339,133	1,071,605	31.65	1.28 (1.21, 1.35)	<0.0001	
AKI during index hospitalization								<0.0001	
No	309,359	3,016,407	10.26	203,143	806,814	25.18	1.61 (1.60, 1.62)	<0.0001	
Yes	51,044	233,753	21.84	174,371	507,928	34.33	1.35 (1.23, 1.47)	<0.0001	
Shock during index hospitalization								0.0107	
No	357,892	3,237,222	11.06	349,974	1,231,974	28.41	1.67 (1.66, 1.69)	<0.0001	
Yes	2,511	12,938	19.41	27,540	82,768	33.27	1.27 (1.04, 1.56)	0.0220	
Prior hospitalization within 6 months								<0.0001	
No	357,916	3,237,374	11.06	359,351	1,258,655	28.55	1.67 (1.66, 1.69)	<0.0001	
Yes	2,487	12,786	19.45	18,163	56,087	32.38	1.32 (1.06, 1.64)	0.0129	

Table S15. Risk of each of the outcomes of interest associated with sepsis (all definitions) across subgroups defined by the presence of any infection and by the most common infection subtypes. P values for interaction are unadjusted.

	No Sepsis (ref)			Sepsis			Hazard Ratio (95% CI)	P Value	P Value for interaction
	No. with Events	Person Years	Event Rate per 100	No. with Events	Person Years	Event Rate per 100			
Infection during index hospitalization									
No infection	N=1,114,981			N=7,174					
Mortality	130,463	2,818,188	4.63	1,457	21,570	6.75	1.12 (1.06, 1.17)	<0.0001	<0.0001
All-cause hospitalization	466,191	1,894,523	24.61	4,194	11,541	36.34	1.39 (1.34, 1.43)	<0.0001	<0.0001
CVD hospitalization	210,481	2,451,875	8.58	2,559	16,111	15.88	1.68 (1.61, 1.75)	<0.0001	<0.0001
Death or all-cause hospitalization	510,098	1,894,523	26.92	4,467	11,541	38.71	1.30 (1.26, 1.34)	<0.0001	<0.0001
Death or CVD hospitalization	286,597	2,451,875	11.69	3,121	16,111	19.37	1.42 (1.37, 1.47)	<0.0001	<0.0001
Any infection	N=334,840			N=801,499					
Mortality	37,030	883,335	4.19	218,971	1,672,957	13.09	1.35 (1.33, 1.37)	<0.0001	<0.0001
All-cause hospitalization	138,660	594,397	23.33	477,069	890,445	53.58	1.34 (1.33, 1.35)	<0.0001	0.0251
CVD hospitalization	50,764	798,285	6.36	265,270	1,298,631	20.43	1.38 (1.36, 1.40)	<0.0001	0.0488
Death or all-cause hospitalization	151,371	594,397	25.47	533,761	890,445	59.94	1.31 (1.30, 1.33)	<0.0001	0.0018
Death or CVD hospitalization	73,806	798,285	9.25	374,393	1,298,631	28.83	1.35 (1.34, 1.37)	<0.0001	0.3253
Pulmonary	N=61,653			N=177,274					
Mortality	9,919	138,737	7.15	55,118	352,335	15.64	1.17 (1.07, 1.27)	0.0004	
All-cause hospitalization	26,671	94,698	28.16	111,620	178,787	62.43	1.39 (1.33, 1.46)	<0.0001	
CVD hospitalization	12,752	120,380	10.59	70,233	255,750	27.46	1.38 (1.29, 1.48)	<0.0001	
Death or all-cause hospitalization	29,933	94,698	31.61	124,444	178,787	69.60	1.31 (1.25, 1.38)	<0.0001	
Death or CVD hospitalization	18,651	120,380	15.49	94,685	255,750	37.02	1.26 (1.19, 1.34)	<0.0001	
Bacterial/fungal/iatrogenic/sepsis/bacteremia	N=44,498			N=175,142					
Mortality	4,109	120,625	3.41	42,583	370,595	11.49	1.68 (1.62, 1.75)	<0.0001	
All-cause hospitalization	17,606	82,880	21.24	100,380	202,990	49.45	1.46 (1.43, 1.49)	<0.0001	
CVD hospitalization	5,745	110,198	5.21	50,083	298,827	16.76	1.54 (1.49, 1.59)	<0.0001	
Death or all-cause hospitalization	19,002	82,880	22.93	112,058	202,990	55.20	1.46 (1.43, 1.49)	<0.0001	
Death or CVD hospitalization	8,450	110,198	7.67	73,041	298,827	24.44	1.58 (1.54, 1.63)	<0.0001	
Genitourinary	N=53,178			N=109,157					
Mortality	8,981	133,353	6.73	35,788	223,271	16.03	1.11 (1.03, 1.20)	0.0088	
All-cause hospitalization	23,478	86,849	27.03	68,371	112,441	60.81	1.34 (1.28, 1.41)	<0.0001	
CVD hospitalization	9,410	117,945	7.98	40,115	166,706	24.06	1.44 (1.34, 1.54)	<0.0001	

Sepsis and cardiovascular events

Death or all-cause hospitalization	27,046	86,849	31.14	78,044	112,441	69.41	1.25 (1.20, 1.31)	<0.0001
Death or CVD hospitalization	15,333	117,945	13.00	58,145	166,706	34.88	1.23 (1.17, 1.31)	<0.0001
Multiple		N=59,250			N=267,444			
Mortality	6,789	159,187	4.26	69,181	559,739	12.36	1.26 (1.22, 1.30)	<0.0001
All-cause hospitalization	24,138	108,199	22.31	152,437	309,456	49.26	1.36 (1.34, 1.39)	<0.0001
CVD hospitalization	8,374	145,144	5.77	79,814	448,743	17.79	1.49 (1.45, 1.53)	<0.0001
Death or all-cause hospitalization	26,628	108,199	24.61	171,785	309,456	55.51	1.32 (1.30, 1.34)	<0.0001
Death or CVD hospitalization	12,816	145,144	8.83	116,752	448,743	26.02	1.37 (1.34, 1.41)	<0.0001
Other		N=116,261			N=72,482			
Mortality	7,232	331,433	2.18	16,301	167,017	9.76	1.40 (1.27, 1.54)	<0.0001
All-cause hospitalization	46,767	221,772	21.09	44,261	86,771	51.01	1.30 (1.24, 1.35)	<0.0001
CVD hospitalization	14,483	304,618	4.75	25,025	128,604	19.46	1.48 (1.39, 1.58)	<0.0001
Death or all-cause hospitalization	48,762	221,772	21.99	47,430	86,771	54.66	1.29 (1.24, 1.35)	<0.0001
Death or CVD hospitalization	18,556	304,618	6.09	31,770	128,604	24.70	1.45 (1.37, 1.54)	<0.0001

Figure S1. Flow chart demonstrating study inclusion/exclusion criteria and sepsis groups. *Abbreviations: CVD, cardiovascular disease; DRG, Disease-Related Group; LOS, length of stay; OLDW, OptumLabs® Data Warehouse*

