

Longitudinal Study of the Effects of Bacteremia and Sepsis on 5-year Risk of Cardiovascular Events

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Background. The long-term and cumulative effect of multiple episodes of bacteremia and sepsis across multiple hospitalizations on the development of cardiovascular (CV) events is uncertain.

Methods. We conducted a longitudinal study of 156 380 hospitalizations in 47 009 patients (≥ 18 years old) who had at least 2 inpatient admissions at an academic tertiary care center in St Louis, Missouri, from 1 January 2008 through 31 December 2012. We used marginal structural models, estimated by inverse probability weighting (IPW) of bacteremia or sepsis and IPW of censoring, to estimate the marginal causal effects of bacteremia and sepsis on developing the first observed incident CV event, including stroke, transient ischemic attack, and myocardial infarction (MI), during the study period.

Results. Bacteremia and sepsis occurred during 4923 (3.1%) and 5544 (3.5%) hospitalizations among 3932 (8.4%) and 4474 (9.5%) patients, respectively. CV events occurred in 414 (10.5%) and 538 (12.0%) patients with prior episodes of bacteremia or sepsis, respectively, vs 3087 (7.2%) and 2963 (7.0%) patients without prior episodes of bacteremia or sepsis. The causal odds of experiencing a CV event was 1.52-fold (95% confidence interval [CI], 1.21- to 1.90-fold) and 2.39-fold (95% CI, 1.88- to 3.03-fold) higher in patients with prior instances of bacteremia or sepsis, respectively, compared to those without. Prior instances of septic shock resulted in a 6.91-fold (95% CI, 5.34- to 8.93-fold) increase in the odds of MI.

Conclusions. Prior instances of bacteremia and sepsis substantially increase the 5-year risk of CV events.

Keywords. bloodstream infection; causal inference; inverse probability weighting; marginal structural model; time-varying confounding.

Cardiovascular (CV) disease affects one-quarter of the US population, costs the healthcare system more than \$315.4 billion annually, and is a leading cause of death [1]. Although traditional risk factors for CV disease are well documented, identifying unrecognized factors that may trigger CV events and are amenable to interventions is vitally important [2]. A targeted intervention on potential preventable causes of CV events could have a significant impact on public health and clinical practice.

Several studies suggest an association between infection and subsequent CV events [3–14]. These investigations found a substantial (2-fold to >20-fold) increase in the risk of CV events shortly after acute infection [8, 10–13], and additionally, found that the increased risk may persist for many years [3, 4, 14]. Short- and long-lived alterations in systemic inflammation as well as demand ischemia, endothelial dysfunction, and procoagulant changes in the blood provide a biological basis for the associations between infections and increased CV disease risk [15, 16].

There are some limitations to these previous observational studies, however. Studies that reported the long-term effects of infection on the risk of CV events only considered a single episode of infection rather than the cumulative effects of repeated infections [3–5, 9–11, 14]. Some studies relied on case-crossover designs [17] that are not suited to study the effects of exposures, such as infections, that may not be transient [5–9]. Finally, few studies validated infection status with positive microbiology cultures [7, 8, 12].

The study objective is to estimate the effects of bacteremia and sepsis on 5-year risk of CV events. There are >1.7 million hospitalizations per year in the United States involving sepsis [18]. Despite reports on the short-term effects of bacteremia [12] and sepsis [10, 13] on the risk of CV events, no study has characterized the effects of multiple episodes of bacteremia and sepsis across multiple hospitalizations over a long-term period.

METHODS

Study Design

We conducted a longitudinal study of all patients ≥ 18 years of age admitted to Barnes-Jewish Hospital (BJH), between 1 January 2008 and 31 December 2012. BJH is an academic tertiary care referral center affiliated with the Washington University School of Medicine in St Louis, Missouri. Clinical, laboratory, pharmacy, and hospital administrative data were extracted from the medical informatics repository of the BJC HealthCare's Center for

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Clinical Excellence. The study was approved by the Human Research Protection Office of the Washington University School of Medicine with a waiver of written informed consent.

Definition of Outcomes and Exposures

The primary outcome of interest was the first observed CV event, defined as stroke, transient ischemic attack (TIA), or myocardial infarction (MI) during the study period. Identification of CV events was based on the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* discharge diagnosis codes for stroke (430, 431, 433.x1, and 434.x1), TIA (435.x), and MI (410.x).

Bacteremia was defined as having at least 1 positive blood culture during a hospitalization for a known bacterial or fungal pathogen, excluding common skin contaminants such as *Bacillus* species, coagulase-negative staphylococci, *Corynebacterium* species, *Micrococcus* species, and *Propionibacterium* species. Sepsis, severe sepsis, and septic shock were identified by the *ICD-9-CM* codes 995.91, 995.92, and 785.52, respectively. Additionally, a composite exposure of “any sepsis”, which included all 3 *ICD-9-CM* codes, was created for the purpose of sensitivity analysis.

Covariates

Covariates included demographics and risk factors for CV disease and sepsis, based on *ICD-9-CM* discharge diagnosis codes developed by Elixhauser et al [19] and enhanced by Quan et al [20], including hypertension, diabetes, chronic pulmonary disease, renal failure, liver disease, congestive heart failure, cardiac arrhythmias, valvular heart disease, pulmonary circulation disorders, peripheral vascular disorders, coagulopathy, AIDS or human immunodeficiency virus infection, metastatic cancer, lymphoma, obesity, and alcohol abuse. Comorbidities are defined as preexisting nonacute conditions that are unrelated to the primary reason for hospitalization.

Other covariates included statin usage; administration of any vasopressors during the hospitalization; use of nonsteroidal anti-inflammatory drugs; use of antihypertensive medications including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, calcium channel blockers, diuretics, hydralazine, and nitrates; length of hospital stay; admission or transfer to an intensive care unit (ICU); any surgical procedure classified by *ICD-9-CM* procedure codes of the National Healthcare Safety Network [21] that was performed during the course of a hospitalization; prior 30-day hospital admission; and patient residency with St Louis City/County based upon home zip codes, as it was assumed to be less likely to return to BJH if a patient’s residence moved farther away during the study.

The systemic inflammatory response syndrome (SIRS) was defined as having at least 2 of the 4 following criteria on a calendar day: heart rate >90 beats per minute; respiratory rate >20 breaths per minute; body temperature $<36^{\circ}\text{C}$ or $>38.3^{\circ}\text{C}$; and white blood cell count <4000 cells/ μL or $>12\,000$ cells/ μL

[22]. To mitigate for frequent transient changes in heart rate, respiratory rate, and temperature, at least 2 out-of-range measurements of these vital signs had to occur on a given calendar day to be considered counting toward SIRS criteria [23].

Description of Study Cohort

Participants were required to have at least 2 hospitalizations at BJH, which allowed us to record patients’ covariates and comorbidities before a CV event (if any). Thus, patients with a CV event at their first BJH hospitalization were excluded. Patients were censored due to dropout (loss to follow-up) or death, or at the end of follow-up if they did not experience a CV event.

Analytic Approach

Distribution of the study covariates grouped by bacteremia or sepsis hospitalizations was compared using *t* test and a χ^2 test, or their nonparametric alternatives, as appropriate. We used marginal structural models (MSMs) [24] to estimate the marginal causal effects of bacteremia and sepsis on a subsequent CV event. MSMs are a class of causal models that are fitted to expected counterfactual outcomes, that is, the potential outcomes that are expected if all patients were exposed to the condition of interest, compared to if they were unexposed. We estimated parameters of MSMs through a weighted regression model following the inverse probability weighting (IPW) of exposure of interest [25]. Weighting by IPW method creates a pseudo-population, where each hospitalization is assigned a weight, proportional to the probability that bacteremia or sepsis occurs given the measured confounders and comorbidities. Consequently, in the pseudo-population, bacteremia and sepsis become independent of the measured confounders, which are factors that influence the development of bacteremia and sepsis and could also influence the occurrence of CV events. This redistribution of the population by weighting results in removing the confounding bias from the MSMs that are used to estimate average causal effects of exposures on the outcome in the original study population [24, 25].

The IPW approach allows consistent estimation of causal effects in the presence of time-varying confounders [24, 26] that are affected by previous occurrences of exposure. This allows for studying long-term effects and potentially multiple episodes of an exposure by inclusion of its entire observed history, that is, including all longitudinal history of a patient’s evolving characteristics and exposures prior to an occurrence of CV event or censoring. Figure 1 presents a directed acyclic graph [27] characterizing the concept of a time-varying confounder. We also estimated the IPW of censoring, which accounted for the effect of time-varying confounders and covariates on dropout from the study before the end of the follow-up period at the final hospitalization or administrative censoring at the end of study follow-up. For critical exposures such as bacteremia or sepsis and life-threatening conditions such as CV events, it is assumed that patients will be hospitalized. The IPW for censoring assigns a

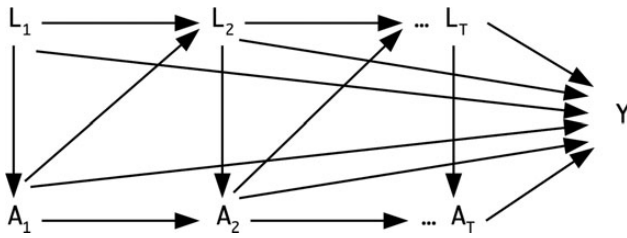


Figure 1. A directed acyclic graph for the time-varying confounding effects of risk factors, comorbidities, medications, and covariates that are also intermediate variables for the effects of bacteremia and sepsis on cardiovascular events. Time-varying exposures, time-varying confounders, and outcome are indicated by A, L, and Y, respectively. Subscripts indicate the time points.

weight to each hospitalization, which is proportional to the probability of remaining uncensored and having the observed covariates recorded [28]. The final weight for each patient was the product of weights for all time points from the baseline to the last hospitalization for that patient. Weights were truncated at the 1st and 99th percentiles [25]. The covariates included for calculating IPW and summaries of the final stabilized weights are presented in [Supplementary Tables 1 and 2](#), respectively.

Finally, we fitted weighted pooled logistic MSMs, which asymptotically approximate Cox regression models with time-dependent covariates [29], to estimate the causal effects of bacteremia and sepsis on the first occurrence of a CV event [30, 31]. In addition to the composite outcome of any first CV event, we considered first stroke or TIA, and first MI for comparison.

To test the sensitivity of our results to potential misclassification of bacteremia and sepsis status in instances where the outcome and exposures occurred during the same hospitalization, we required an order for blood cultures within 24 hours of admission to consider bacteremia and sepsis status as positive if they occurred during the same hospitalization as a CV event. We performed a second sensitivity analysis, where we defined bacteremia to also include blood cultures positive for common skin contaminants to minimize the possibility of underestimating bacteremia. All statistical analyses were performed using R language and environment for statistical computing, version 3.2.0 (R Foundation, Vienna, Austria) via the “ipw” library [32].

RESULTS

The study included 156 380 hospitalizations for 47 009 patients. Bacteremia occurred during 4923 (3.1%) hospitalizations among 3932 (8.4%) patients. There was a total of 5544 (3.5%) hospitalizations (in 4474 patients [9.5%]) with a diagnosis of sepsis of any severity; specifically, 2600 (1.7%) hospitalizations with sepsis, 1192 (0.8%) with severe sepsis, and 1752 (1.1%) with septic shock, in 2281 (4.9%), 1125 (2.4%), and 1597 (3.4%) patients, respectively.

In the final study population, first CV events were observed in 3501 (2.2%) hospitalizations (7.4% of patients); thus, the

remaining 43 508 (92.6%) patients remained event-free during the study period. These included 1766 (1.1%) hospitalizations with stroke or TIA, 1834 (1.2%) hospitalizations with MI, and 99 (0.1%) hospitalizations with both stroke/TIA and MI. The proportion of patients who experienced a CV event and had at least 1 prior instance of bacteremia was 10.5% (414/3932), compared with 7.2% (3087/43 077) of patients without any prior instance of bacteremia. Among patients with at least 1 prior instance of sepsis of any severity, 12.0% (538/4474) experienced a CV event, compared with 7.0% (2963/42 535) without any prior instance of sepsis of any severity.

The characteristics of the study population are presented in [Table 1](#). Hospitalizations in which bacteremia or any sepsis occurred were more frequent among patients with comorbidities ([Table 1](#)). Except for alcohol abuse, hospitalizations in which sepsis developed had a statistically significantly higher burden of comorbidities. There was no statistically significant difference in the frequency of hospitalizations with bacteremia or sepsis in patients who were residents of St Louis City/County and those who were potentially referred from outside the area to this tertiary care center.

[Table 2](#) presents the estimates of the marginal causal effects, expressed as odds ratios and adjusted for all confounders and comorbidities by IPW ([Supplementary Table 1](#)), of bacteremia and sepsis for CV events. Bacteremia and sepsis of any severity resulted in higher odds of experiencing all CV events. The causal odds of experiencing a CV event was 1.52-fold (95% confidence interval [CI], 1.21- to 1.90-fold) higher in patients with prior instances of bacteremia compared to those without ([Table 2](#)). Prior development of sepsis with any severity resulted in a 2.39-fold (95% CI, 1.88- to 3.03-fold) increase in the odds of experiencing a CV event, with the highest odds ratio of 6.91 (95% CI, 5.34–8.93) for the development of MI in patients with prior instances of septic shock ([Table 2](#)).

There were 620 (0.4%) and 1062 (0.7%) hospitalizations in which bacteremia and sepsis of any severity developed concurrent with a CV event, respectively. To increase the likelihood that exposures preceded a CV event, we considered 69 (0.04%) and 76 (0.05%) hospitalizations in patients who developed bacteremia and sepsis of any severity without a physician’s order for blood culture within 24 hours of admission as negative for bacteremia in our sensitivity analysis, respectively. The results of the first sensitivity analysis suggested the same conclusion (ie, same direction) as the results of the primary analysis, except for the effect of nonsevere sepsis and bacteremia on the development of stroke or TIA that did not reach statistical significance ([Supplementary Table 3](#)). In the second sensitivity analysis, we considered an additional 3920 (2.5%) hospitalizations in patients with a positive blood culture for a common skin contaminant as having bacteremia. Including these patients resulted in bacteremia occurring during 8843 (5.7%) hospitalizations among 6646 (14.1%) patients in the second sensitivity analysis. The results of the second

Table 1. Characteristics of the Study Population (N = 156 380)

Characteristic	Hospitalizations With Bacteremia (n = 4923)	Hospitalizations Without Bacteremia (n = 151 457)	P Value	Hospitalizations With Sepsis (n = 5544)	Hospitalizations Without Sepsis (n = 150 836)	P Value
Age, y, mean, median, IQR	56.1, 57.0, 21.0	53.9, 55.0, 26.0	<.01	57.8, 59.0, 20.0	53.9, 55.0, 26.0	<.01
Male sex	2682 (54.5)	69 368 (45.8)	<.01	2983 (53.8)	69 067 (45.8)	<.01
Race/ethnicity						
African American	1794 (36.4)	57 568 (38.0)	.03	1859 (33.5)	57 503 (38.1)	<.01
Asian	48 (0.98)	1182 (0.78)	.15	45 (0.81)	1185 (0.79)	.89
Other	54 (1.10)	2295 (1.52)	.02	68 (1.2)	2281 (1.5)	.10
White	3027 (61.5)	90 412 (59.7)	.01	3572 (64.4)	89 867 (59.6)	<.01
SIRS	4002 (81.3)	53 707 (35.5)	<.01	4975 (89.7)	52 734 (35.0)	<.01
Length of stay, d, mean, median, IQR	16.5, 10.0, 16.0	5.2, 3.0, 4.0	<.01	17.0, 10.6, 16.2	5.2, 3.0, 4.0	<.01
ICU admitted or transferred	2053 (41.7)	18 905 (12.5)	<.01	3847 (69.4)	17 111 (11.3)	<.01
Surgery	858 (17.4)	28 467 (18.8)	.02	1081 (19.5)	28 244 (18.7)	.15
Prior 30-day admission	1853 (37.6)	38 372 (25.3)	<.01	2264 (40.8)	37 961 (25.2)	<.01
St Louis City/County resident	1236 (25.1)	36 730 (24.3)	.17	1346 (24.3)	36 620 (24.3)	1.00
Risk factors for CV disease and sepsis						
Diabetes	1459 (29.6)	37 182 (24.5)	<.01	1616 (29.1)	37 025 (24.5)	<.01
Hypertension	3303 (67.1)	93 568 (61.8)	<.01	3851 (69.5)	93 020 (61.7)	<.01
Congestive heart failure	962 (19.5)	24 672 (16.3)	<.01	1322 (23.8)	24 312 (16.1)	<.01
Cardiac arrhythmias	1145 (23.3)	23 624 (15.6)	<.01	1766 (31.9)	23 003 (15.3)	<.01
Valvular heart disease	390 (7.9)	8891 (5.9)	<.01	485 (8.7)	8796 (5.8)	<.01
Pulmonary circulation disorders	414 (8.4)	7690 (5.1)	<.01	568 (10.2)	7536 (5.0)	<.01
Peripheral vascular disorders	322 (6.5)	8556 (5.6)	.01	449 (8.1)	8429 (5.6)	<.01
Chronic pulmonary disease	1193 (24.2)	36 065 (23.8)	.51	1484 (26.8)	35 774 (23.7)	<.01
Renal failure	1189 (24.2)	24 305 (16.0)	<.01	1457 (26.3)	24 037 (15.9)	<.01
Liver disease	630 (12.8)	10 229 (6.8)	<.01	898 (16.2)	9961 (6.6)	<.01
Coagulopathy	965 (19.6)	8575 (5.7)	<.01	1348 (24.3)	8192 (5.4)	<.01
AIDS/HIV	140 (2.8)	1639 (1.1)	<.01	86 (1.6)	1693 (1.1)	<.01
Metastatic cancer	514 (10.4)	13 620 (9.0)	<.01	554 (10.0)	13 580 (9.0)	.01
Lymphoma	406 (8.2)	5744 (3.8)	<.01	486 (8.8)	5664 (3.8)	<.01
Obesity	400 (8.1)	13 495 (8.9)	.06	549 (9.9)	13 346 (8.8)	<.01
Alcohol abuse	289 (5.9)	8408 (5.6)	.35	298 (5.4)	8399 (5.6)	.56
Medication use						
ACE inhibitors	946 (19.2)	33 230 (21.9)	<.01	895 (16.1)	33 281 (22.1)	<.01
ARBs	225 (4.6)	10 516 (6.9)	<.01	208 (3.8)	10 533 (7.0)	<.01
β-blockers	488 (9.9)	15 094 (10.0)	.92	569 (10.3)	15 013 (10.0)	.46
CCBs	1078 (21.9)	31 011 (20.5)	.02	1149 (20.7)	30 940 (20.5)	.71
Diuretics	2406 (48.9)	50 069 (33.1)	<.01	3000 (54.1)	49 475 (32.8)	<.01
Hydralazine	717 (14.6)	17 352 (11.5)	<.01	770 (13.9)	17 299 (11.5)	<.01
Nitrates	108 (2.2)	2873 (1.9)	.15	142 (2.6)	2839 (1.9)	<.01
NSAIDs	4395 (89.3)	128 548 (84.9)	<.01	4784 (86.3)	128 159 (85.0)	<.01
Statins	1015 (20.6)	37 694 (24.9)	<.01	1129 (20.4)	37 580 (24.9)	<.01
Vasopressors	1604 (32.6)	13 214 (8.7)	<.01	2979 (53.7)	11 839 (7.8)	<.01

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; n, number of hospitalizations; NSAID, nonsteroidal anti-inflammatory drug; SIRS, systemic inflammatory response syndrome.

sensitivity analysis also indicated the same conclusions as the results of the primary analysis; however, the estimates for the causal odds ratios were marginally higher in the sensitivity analysis (Supplementary Table 4).

DISCUSSION

We found that development of either bacteremia or sepsis resulted in a 1.52- to 6.91-fold increase in the odds of developing

subsequent CV events, with the largest effect observed for septic shock and its impact on subsequent MI. This elevated risk of developing a subsequent CV event was consistent across all sepsis severity levels as well as with confirmed bacteremia, and, with the exception of nonsevere sepsis or bacteremia and stroke/TIA, was robust to the sensitivity analyses.

These findings are important, given reports indicating that the incidence of CV events is sometimes insufficiently explained

Table 2. Estimates of the Causal Odds Ratio, Adjusted for Measured Confounders and Comorbidities by the Inverse Probability Weighting, of Bacteremia and Sepsis for Subsequent Any Cardiovascular Event, Stroke or Transient Ischemic Attack, and Myocardial Infarction

Exposure	Causal Odds Ratio ^a (95% CI)		
	Any CV Event	Stroke or TIA	MI
Bacteremia	1.52 (1.21–1.90)	1.00 (.70–1.44)	2.00 (1.55–2.60)
Any sepsis	2.39 (1.88–3.03)	1.24 (.86–1.79)	3.29 (2.49–4.36)
Sepsis	1.99 (1.50–2.63)	1.15 (.75–1.77)	2.63 (1.89–3.65)
Severe sepsis	3.60 (2.59–5.00)	1.53 (1.06–2.21)	4.99 (3.35–7.45)
Septic shock	4.55 (3.58–5.78)	1.64 (1.03–2.63)	6.91 (5.34–8.93)

Abbreviations: CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; TIA, transient ischemic attack.

^a Covariates included for calculating inverse probability weighting are presented in Supplementary Table 1.

by traditional risk factors, which may be lacking in some populations such as adults ≤ 45 years of age [33]. Prevention or rigorous monitoring for sepsis and bacteremia therefore represents an additional area for targeted interventions, to prevent CV events especially in high-risk groups such as elderly persons, patients receiving immunosuppressant drugs, or transplant recipients. The added burden of CV events as outcomes of sepsis should be taken into account for defining strategies and policies to prevent sepsis. The downstream effects of sepsis not only manifest in increased rates of disability and cognitive impairment, but also may have untoward effects on CV and neurological health, as we have shown, which could have a significant impact on public health in the United States.

One distinct feature of this study is that we accounted for the contribution of all instances of bacteremia or sepsis prior to a CV event, rather than restricting the analysis to the first or the last instance of exposure. We appropriately adjusted for the time-varying confounding effects of evolving comorbidities and covariates [24, 26]. We included a large patient population that was not limited to an ICU, which allowed us to classify CV events as stroke/TIA and MI in addition to studying the composite outcome of any CV event. In addition to the explicit *ICD-9-CM* codes for sepsis, our study included bacteremia based on positive blood cultures, which, despite its imperfect accuracy, is not subject to the inherent inaccuracy of medical coding in administrative billing data [34, 35].

Some past studies have suggested an association between infection and stroke and coronary syndromes [15, 16]. Walkey et al reported a 2.7-fold increase in the odds of in-hospital stroke in patients with severe sepsis who developed atrial fibrillation [10]. Donzé et al reported a 3.3- and 5.7-fold increase in the odds of postoperative thromboses in patients with preoperative sepsis and severe sepsis, respectively [13]. Community-acquired bacteremia has been reported to increase the risk of short-term CV events by 20.9-fold [12]. Unlike the longitudinal design in our study, other studies used case-crossover [5–9],

case-control [3, 5], or cohort [4, 8, 10–13] designs that are less suitable to study the long-term and cumulative effects of bacteremia and sepsis on subsequent CV events.

Our work can be extended, for example, to study the effects of specific infectious agents or specific clinical conditions such as pneumonia, urinary tract infection, or postsurgical infection on more specific outcomes such as stroke type. Another important area of research is to identify the specific causal pathways that lead bacteremia and sepsis to exert their long-term effects on CV events through a causal mediation analysis [36]. Moreover, it is important to identify factors such as genetic factors or comorbid conditions that may have mechanistic interactions with bacteremia and sepsis for occurrences of CV events, especially those factors that may act as sufficient causes [37, 38].

Our study had some limitations. We relied on administrative data for identification of comorbidities and CV events; however, we used validated algorithms [1, 20] whenever possible to minimize potential misclassification bias. Our analytic approach was not directed to and could not compare the timing of (early vs late) CV events after a specific episode of bacteremia or sepsis. It was not possible to compare the risk of CV events following a single episode with those with multiple episodes of bacteremia or sepsis. Validity of estimates in MSMs relies on the correct specification of exposure, censoring, and final structural models to satisfy the conditional exchangeability (ie, no unmeasured confounding), consistency (ie, well-defined treatment), and positivity (ie, positive probability of exposure at every level of confounders) assumptions [25]. Similar to the traditional regression models for outcomes, our analytic approach is not robust to model misspecification and unmeasured confounders [39]. Potential unmeasured confounders such as proinflammatory markers or imperfect adherence to outpatient-administered medications could bias the risk estimates. Even though we used the existing consensus definition, the consistency assumption may be harder to conceptualize for a clinical condition such as sepsis. We could not rule out previous CV events prior to the first hospitalization at our hospital. Our study population was limited to our tertiary care academic center. However, we theoretically adjusted for the fact that some patients might have developed sepsis or bacteremia or experienced CV events in (or were referred to) other healthcare facilities using IPW for censoring. Finally, we note that our study is a single-center study that is not subject to the random variations and clustering effects (eg, differential care quality in academic/specialty vs community hospitals) that could inherently arise in a multicenter observational study.

Supplementary Data

Supplementary materials are available at <http://cid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Author contributions. S. R. J. and B. S. T. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S. R. J., B. S. T., and V. J. F. conceptualized and designed the study. S. R. J. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. V. J. F., J. G., and D. K. W. supervised the study.

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