Open Forum Infectious Diseases

MAJOR ARTICLE

The Impact of Nosocomial Bloodstream Infections on Mortality: A Retrospective Propensity-Matched Cohort Study

Neta Petersiel,[1,a,b] Assa Sherman,[1,a] and Mical Paul[1,2]

[1]Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel, and [2]The Ruth and Bruce Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

Background. The mortality toll of nosocomial infections drives infection control efforts. We aimed to assess the contemporary mortality associated with nosocomial bloodstream infections (BSIs).

Methods. Retrospective propensity-matched cohort study conducted in 1 hospital in Israel between January 2010–December 2020. Adults >18 years old with nosocomial BSI were matched to controls using nearest neighbor matching of the propensity score for nosocomial BSI. We assessed all-cause mortality at 30 days, 90 days, and survival up to 1 year starting on the BSI day or matched hospital-day among controls; and the functional and cognitive change between admission and discharge using the Norton score among patients discharged alive. Residual differences between matched groups were addressed through Cox regression for 1-year survival.

Results. A total of 1361 patients with nosocomial BSI were matched to 1361 patients without BSI. Matching achieved similar patient groups, with small differences remaining in the Charlson score and albumin and hemoglobin levels. At 90 days, mortality was higher among patients with BSI (odds ratio [OR], 3.36 [95% confidence interval {CI}, 2.77–4.07]). ORs were higher when the BSI was caused by multidrug-resistant bacteria (OR, 5.22 [95% CI, 3.3–8.26]) and with inappropriate empirical antibiotics in the first 24 hours (OR, 3.85 [95% CI, 2.99–4.94]). Following full adjustment, the hazard ratio for 1-year mortality with nosocomial BSI was 2.28 (95% CI, 1.98–2.62). The Norton score declined more frequently among patients with BSI (OR, 2.27 [95% CI, 1.81–2.86]).

Conclusions. Nosocomial BSIs incur a highly significant mortality toll, particularly when caused by multidrug-resistant bacteria. Among hospital survivors, BSIs are associated with functional decline.

Keywords. attributable mortality; bacteremia; hospital-acquired infections; propensity score.

Healthcare-associated infections (HAIs) have a significant impact on patients' outcomes as well as on healthcare costs. The overall burden of bloodstream infections (BSIs) is difficult to define and is derived from studies describing the incidence and crude mortality following BSI to derive the attributable burden [1–4]. A systematic review based on surveillance systems estimated 15 000–36 000 deaths per year following nosocomial BSI in the United States (US), 2900–3600 in Canada, and 29 000–132 000 in Europe [4]. Using the European Antimicrobial Resistance Surveillance Network (EARS-Net) data, it was estimated that during 2015, there were 671 689 cases of infection with resistant bacteria (131 infections per 100 000 population), accounting for 33 110 attributable deaths (6.44 deaths per 100 000 population) and 874 541 disability-adjusted life-years (DALYs; 170 per 100 000 population). BSI accounted for 122/170 DALYs (71.7%) [5].

The burden to the individual patient was addressed with different study designs to estimate the morbidity and mortality burden that can be attributed to nosocomial BSIs. A retrospective cohort study including 5 European hospitals estimated hazard ratios (HRs) for hospital mortality ranging from nonsignificant for third generation–susceptible Enterobacterales to 2.88 (95% confidence interval [CI], 2.22–3.74) for third generation–resistant Enterobacterales compared to noninfected controls, showing the impact both of nosocomial BSI and of resistant nosocomial BSI [6]. A retrospective matched cohort study including 8 US hospitals estimated an adjusted odds ratio (OR) for 90-day mortality with nosocomial BSI of 2.08 (95% CI, 1.69–2.57) among elderly patients >65 years old [7]. Other studies in the intensive care

Received 23 August 2021; editorial decision 26 October 2021; accepted 5 November 2021; published online 6 November 2021.

[a]N. P. and A. S. contributed equally to this work.

[b]Present affiliation: Victorian Infectious Disease Service, the Royal Melbourne Hospital, and the University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia.

Correspondence: Neta Petersiel, MD, Infectious Diseases Institute. Rambam Health Care Campus, Haifa, Israel (neta.petersiel@unimelb.edu.au).

Open Forum Infectious Diseases®2021

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

https://doi.org/10.1093/ofid/ofab552

unit (ICU) or among elderly patients have not found a significant association between nosocomial BSI and mortality [8, 9].

Estimating the excess mortality and morbidity toll of nosocomial BSI to the individual patient is important to direct efforts to prevent nosocomial infections. We aimed to further examine the burden of all nosocomial BSIs on the individual patient, assessing long-term mortality and major determinants of the mortality burden relating to antibiotic resistance and empirical treatment.

METHODS

Study Design

This was a retrospective propensity-matched cohort study conducted at Rambam Health Care Campus (RHCC), Haifa, Israel. The study was approved by the local ethics committee, with a waiver of informed consent, using anonymized data.

Inclusion Criteria

We included patients >18 years old with nosocomial bacteremia and matched controls. Patients were identified from a database of all hospitalized patients between January 2010 and December 2020. Each patient was included once for the first hospital admission during the study period. We excluded patients with community-onset BSIs, fungal BSI, and all patients with hospitalization <48 hours. Data were unavailable from the surgical ICU that uses a different medical record system, but data from other ICUs (medical, cardiac, thoracic surgery, and neurosurgical) were included. From the remaining cohort, we matched patients with nosocomial BSI to controls without BSI by the propensity score for nosocomial BSI. Nosocomial BSI was defined when caused by clinically significant bacteria and excluding BSI by common commensal bacteria, using the National Healthcare Safety Network definitions [10]. Nosocomial acquisition was defined when the first positive blood culture was taken >48 hours after admission.

Outcomes

The outcomes examined were 30-day mortality, 90-day mortality, and survival until 1 year. Follow-up started on the day of the first positive blood culture for patients with nosocomial BSI, and on the same day after admission for the matched control patient (index day). Matched pairs in whom the control patient died before the BSI hospital-day were excluded from this analysis (index day analysis). As sensitivity analysis, we analyzed outcomes starting from admission both for patients with BSI and controls, including controls who did not survive to the index day. As secondary outcome, we assessed the functional and cognitive change between admission and discharge among patients discharged alive. We used the Norton score [11] (total and its components), assessed and documented routinely in real time by the department nurses on admission and on the day of discharge.

Data Collection

The data for this study were collected retrospectively using MDClone, a big-data query tool for healthcare data-driven studies. MDClone is linked at RHCC to the electronic patient file (Prometheus), which is operating fully in the hospital since 2010, and to the hospital's demographic records and laboratory data. Postdischarge mortality data are updated in Prometheus automatically from the national Ministry of Health, recording all deaths. We collected a large dataset of variables reflecting risk factors for BSI, risk factors for acquisition of multidrug resistance [12, 13] and risk factors for mortality among inpatients (list of variables provided in Supplement 1). The Charlson-age comorbidity index and its individual components were collected [14]. Risk factors for BSI (eg, neutropenia, surgery, mechanical ventilation) were considered only if occurring after admission and before index day (BSI date or matched hospital-day for controls).

Power

In the 10-year study span, we observed 1361 patients with nosocomial BSI. Assuming a 30-day mortality rate of 10% for controls without BSI, a correlation coefficient for mortality between matched cases and controls of 0.3 and 1 control per patient with BSI, the study was powered >80% to detect an OR for mortality among BSI patients relative to controls of 1.3 or higher ($\alpha = .05$).

Analysis

Bivariate comparisons were conducted using a χ^2 test and computing the Mantel-Haenzel OR with 95% CIs. Means are presented with standard deviation (SD) and medians with 25th–75th percentile ranges (interquartile range [IQR]). Continuous variables that were normally distributed were compared using a *t* test and skewed variables were compared using the Mann-Whitney *U* test. Survival analyses were performed using Kaplan-Meier curves.

In the full cohort of hospitalized patients, we compared between patients with and without nosocomial BSI and computed the propensity score for nosocomial BSI using binary logistic regression, selecting for the model nonduplicating variables significant on univariate analysis ($P < .05$). Variables used for the propensity score are presented in Supplementary Table 1. Missing data for albumin in the non-BSI group were imputed using multiple imputation (missing for 115/1361 patients). Calibration of the model was assessed using a receiver operating characteristic (ROC) curve. We matched patients with BSI to a control patient without BSI with the closest propensity score (nearest neighbor matching) at a 1:1 ratio, targeting a maximal caliper of 0.001. We assessed the quality of the matching by comparing the patient characteristics in the matched cohort and report on the final caliper achieved. Outcomes were compared between patients with and without nosocomial BSI in the propensity score–matched cohort. We adjusted for residual

confounders despite the matching using Cox regression computing the HRs for survival until end of follow-up.

We performed preplanned subgroup analyses for multidrug-resistant (MDR) and non-MDR nosocomial BSIs and nosocomial BSIs treated with appropriate or inappropriate antibiotic therapy in the first 24 hours after collection day of the first positive blood culture. MDR bacteria included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Appropriateness of antibiotic therapy was defined by the in vitro coverage. Statistical significance of the difference between subgroups was assessed using the Breslow-Day statistic. Analyses were performed using SPSS version 24.

RESULTS

Between January 2010 and December 2020, 248 826 patients were admitted to RHCC (first admission in the study period), of whom 181 868 had a hospital length of stay (LOS) >48 hours and did not have fungal BSI. Of them, 1361 patients had clinically significant nosocomial BSI (Figure 1). Nosocomial BSI occurred at a median of 11 days in hospital (IQR, 6–21 days). Of the 1361 BSIs, 341 (25.1%) were due to gram-positive bacteria, 970 (71.3%) were due to gram-negative bacteria, and 50 (3.7%) were due to anaerobes (Supplementary Table 1). MDR bacteria were isolated in 223 (16.4%): 84/197 (42.6%) MRSA of all *S aureus*, 12/125 (9.6%) VRE of *Enterococcus* spp, 36/633 (5.7%) CRE of all Enterobacterales, 61/85 (71.8%) CRAB of all *Acinetobacter baumannii*, and 30/171 (17.5%) CRPA of all *P aeruginosa* BSIs. Inappropriate antibiotic therapy in the first 24 hours was prescribed to 761/1361 (55.9%) of patients with nosocomial BSI.

Propensity Score Derivation

The variables associated with nosocomial BSI used to the derive the propensity score are described in Supplementary Table 2. Highly significant differences were observed in nearly all variables relating to patients' demographics, baseline functional status, comorbidities, and variables related to the index admission, including the department type, laboratory tests, and devices/procedures. The final regression model to predict nosocomial BSI achieved excellent calibration with an area under the ROC curve of 0.90 (95% CI, .89–.91; Supplementary Table 3 and Supplementary Figure 1).

Matched Cohort

Following the 1:1 match, 1361 patients with nosocomial BSI were matched to 1361 patients without BSI. The median caliper was 2×10^{-6} (IQR, 1.5×10^{-7} to 1.295×10^{-5}). The resulting patient groups were similar in the predictors available for mortality (Table 1). Statistically significant, but clinically minor differences remained in the Charlson score and albumin and hemoglobin levels. The mean age of the patients in our matched

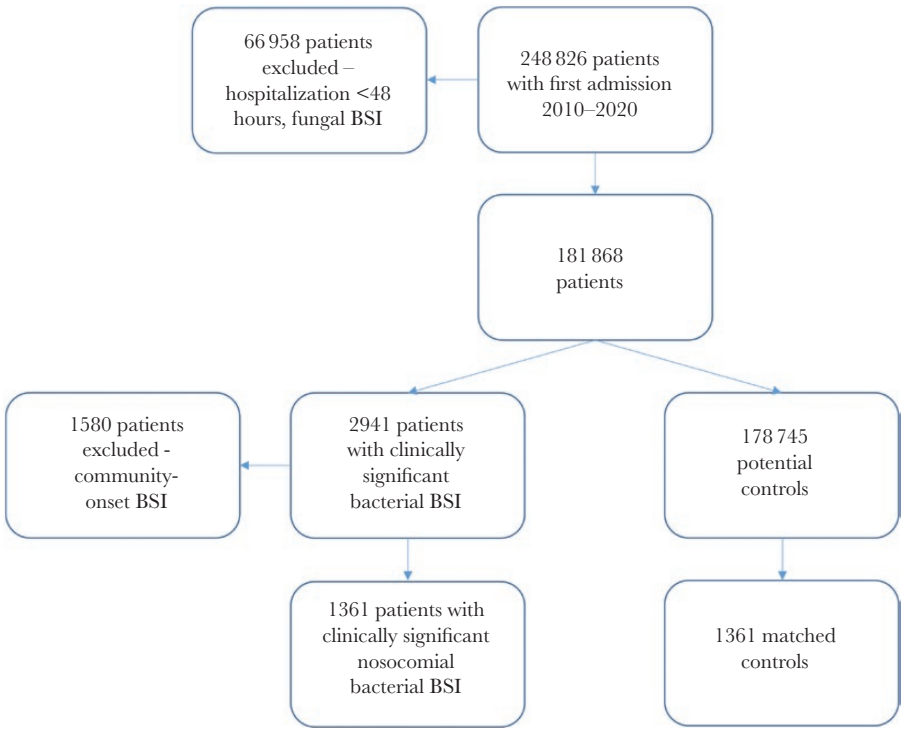

Figure 1. Patient flowchart. Abbreviation: BSI, bloodstream infection.

Table 1. Characteristics of Patients With and Those Without Nosocomial Bloodstream Infection in the Propensity-Matched Cohort

Variable	Nosocomial BSI (n = 1361)	Control (n = 1361)	*P* Value
Demography			
Age, y, mean (SD; range)	63.6 (17.7; 18–101)	64.1 (19.7; 18–104)	.555
Sex (female)	509 (37.4)	516 (37.9)	.782
Country of birth (Israel)	641 (47.1)	582 (42.8)	.023
Ethnicity (Jew)	654 (48.1)	706 (51.9)	.46
Health maintenance organization (Clalit)	878 (64.5)	872 (64.1)	.81
Long-term care facility resident	376 (27.6)	377 (27.7)	.966
Chronic medical conditions			
Norton total on admission, median (IQR)	13 (8–19)	12 (8–19)	.297
Charlson score (total), median (IQR)	5 (3–7), n = 1308	5 (2–7), n = 1327	.015
Chronic kidney disease	136 (10)	156 (11.5)	.215
Dialysis	20 (1.5)	28 (2.1)	.224
Cerebrovascular accident	188 (13.8)	190 (14)	.912
Hemiplegia	40 (2.9)	42 (3.1)	.823
Dementia	38 (2.8)	38 (2.8)	1
Chronic obstructive pulmonary disease	626 (46)	644 (47.3)	.489
Cirrhosis	21 (1.5)	25 (1.8)	.552
Malignancy	254 (18.7)	270 (19.8)	.437
Diabetes	411 (30.2)	403 (29.6)	.738
Ischemic heart disease	338 (24.8)	340 (25)	.929
Congestive heart failure	194 (14.3)	184 (13.5)	.579
Peripheral vascular disease	41 (3)	40 (2.9)	.91
HIV	3 (0.2)	5 (0.4)	.479
Index admission characteristics			
Period Oct 2009–Nov 2011	339 (24.1)	341 (25.1)	.82
Period Dec 2011–May 2014	341 (25.1)	340 (25)	
Period Jun 2014–Feb 2017	332 (24.4)	349 (25.6)	
Period Mar 2017–Dec 2020	349 (25.6)	331 (24.3)	
Internal departments	686 (50.4)	693 (50.9)	.891
Surgical departments	579 (42.5)	578 (42.5)	
Hematological departments	96 (7.1)	90 (6.6)	
Nasogastric tube[a]	650 (47.8)	630 (46.3)	.442
Mechanical ventilation[a]	247 (18.1)	227 (16.7)	.312
Surgery[a]	619 (45.5)	591 (43.4)	.28
Laboratory values on admission			
Albumin, g/dL			
≤2.5	385 (28.3)	355 (26.1)	.021
2.5–3.499	671 (49.3)	742 (54.5)	
≥3.5	305 (22.4)	264 (19.4)	
Creatinine, mg/dL, median (IQR)	1 (.8–1.45)	1 (.8–1.45)	.791
Hemoglobin, g/dL, mean (SD)	12.03 (2.5)	12.25 (2.4), n = 1360	.018
WBC × 10^9 cells/L, median (IQR)	10.7 (7.65–15.46)	10.89 (8.08–14.99), n = 1360	.406
Neutropenia[a] <500 × 10^9 cells/L	70 (5.1)	61 (4.5)	.42

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

Abbreviations: BSI, bloodstream infection; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; WBC, white blood cell count.

[a]Before index day for patients with BSI and without BSI.

cohort was 63.8 years (SD, 18.7), and 1025 (37.7%) were female. Following the exclusion of control patients not surviving to the matched BSI day after admission, 1188 BSI patients and 1188 controls remained for the main analysis, from the index day.

Outcomes

Mortality data until end of follow-up were available for all patients. Survival from the index day was significantly lower with nosocomial BSI (log-rank $P < .001$; HR, 2.36 [95% CI, 2.04–2.67]). Survival curves separated from the start of follow-up, widening until about day 100, and remained separated until end of follow-up at 1 year from the index day (Figure 2A). The survival curves starting from the day of admission crossed on day 35 to favor the control patients, violating the proportional hazard assumption; thus, further statistics on survival from admission were not performed (Figure 2B).

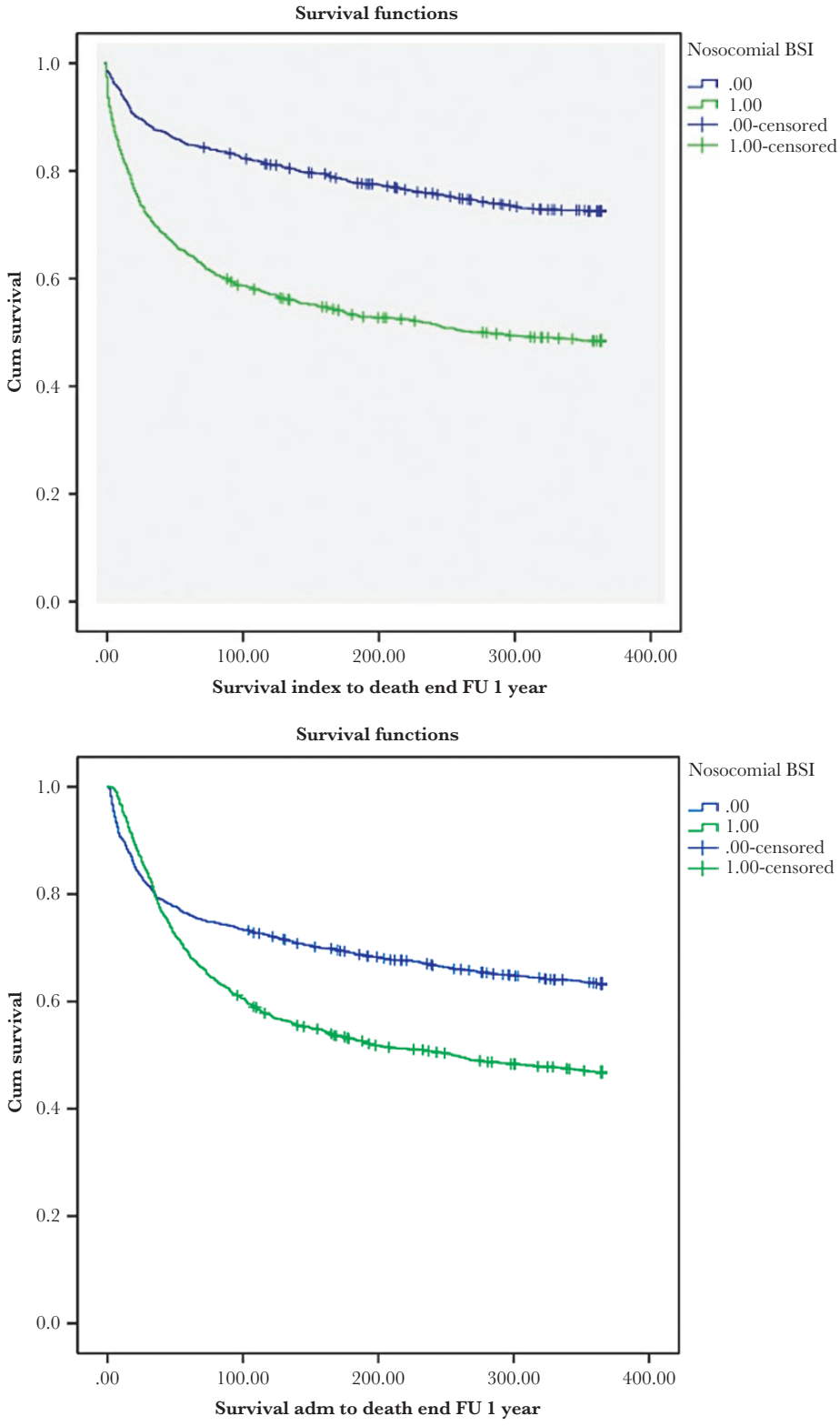

Figure 2. Survival curves for patients with nosocomial bloodstream infection (BSI) vs propensity score–matched controls. *A*, Survival from the index day (day 0 = hospital-day of BSI and matched day of control). *B*, Survival from the day of admission (day 0 = hospital admission day). Abbreviations: BSI, bloodstream infection; CI, confidence interval; HR, hazard ratio.

Thirty-day mortality from the index day was 28.3% (336/1188) among patients with nosocomial BSI and 11.4% (135/1188) among controls (propensity score–matched OR, 3.08 [95% CI, 2.47–3.83]; $P < .001$; Table 2). The difference was similar at 90 days (40.3% [479/1188] vs 16.8% [199/1188], respectively; OR, 3.35 [95% CI, 2.77–4.06]; $P < .001$). The Charlson score and

Table 2. Outcomes for Patients With and Those Without Nosocomial Bloodstream Infection in the Propensity Score–Matched Cohort

Outcome	With BSI	Without BSI	OR (95% CI)	*P* Value
All patients				
30-day mortality from index day	336/1188 (28.3%)	135/1188 (11.4%)	3.076 (2.471–3.830)	<.001
90-day mortality from index day	479/1188 (40.3%)	199/1188 (16.8%)	3.358 (2.773–4.066)	<.001
30-day mortality from admission	233/1361 (17.1%)	254/1361 (18.7%)	0.900 (.740–1.095)	.294
90-day mortality from admission	522/1361 (38.4%)	353/1361 (25.9%)	1.777 (1.509–2.092)	<.001
Norton: functional decline[a]	293/738 (39.7%)	171/738 (23.2%)	2.183 (1.742–2.736)	<.001
Norton: cognitive decline[a]	36/738 (4.9%)	24/738 (3.3%)	1.526 (.901–2.584)	.073
Norton: total score decline[a]	281/738 (38.1%)	157/738 (21.3%)	2.275 (1.807–2.865)	<.001
Norton: total score, change from baseline, median (IQR)	0 (–1 to 3), n = 738	0 (0–3), n = 738	…	<.001
MDR subgroup[b]				
30-day mortality from index day	78/190 (41.1%)	28/190 (14.7%)	4.029 (2.458–6.606)	<.001
90-day mortality from index day	106/190 (55.8%)	37/190 (19.5%)	5.218 (3.297–8.260)	<.001
Non-MDR subgroup[b]				
30-day mortality from index day	258/998 (25.9%)	107/998 (10.7%)	2.903 (2.271–3.711)[a]	<.001
90-day mortality from index day	373/998 (37.4%)	162/998 (16.2%)	3.080 (2.493–3.805)[a]	<.001
Inappropriate empirical antibiotics subgroup[c]				
30-day mortality from index day	215/668 (32.2%)	80/668 (12%)	3.488 (2.625–4.636)	<.001
90-day mortality from index day	302/668 (45.2%)	118/668 (17.7%)	3.846 (2.994–4.941)	<.001
Appropriate empirical antibiotics subgroup[c]				
30-day mortality from index day	121/520 (23.3%)	55/520 (10.6%)	2.564 (1.815–3.623)[b]	<.001
90-day mortality from index day	177/520 (34.0%)	81/520 (15.6%)	2.797 (2.075–3.769)[b]	<.001

Abbreviations: BSI, bloodstream infection; CI, confidence interval; IQR, interquartile range; MDR, multidrug resistant; OR, odds ratio.

[a]Decline of the Norton score component or total score by at least 1 point, comparing admission and discharge scores, among patients discharged alive.

[b]Difference between MDR and non-MDR subgroups: $P = .244$ for 30-day mortality and $P = .041$ for 90-day mortality.

[c]Difference between appropriate and inappropriate empirical subgroups: $P = .177$ for 30-day mortality and $P = .109$ for 90-day mortality.

albumin and hemoglobin levels were associated with survival; adjusted to these, nosocomial BSI remained significantly associated with death at end of follow-up (HR, 2.28 [95% CI, 1.98–2.62]) from the index day (Table 3).

The Norton score was available for 738 matched pairs of patients discharged alive. The change from baseline was significantly more negative among patients with nosocomial BSI, with a decline in the total score among 281/738 (38.1%) patients with BSI compared to 157/738 (21.3%) matched patients without BSI ($P < .001$; Table 2 and Supplementary Figure 2). The difference in the total Norton scale was driven mainly by a change in functional status, with a decline from admission to discharge documented in 293/738 (39.7%) of patients with BSI vs 171/728 (23.2%) of controls ($P < .001$). Cognitive decline was documented more rarely and a small difference between groups was nonsignificant (Table 2).

Table 3. Survival Analysis in Propensity Score–Matched Cohorts Until 1 Year of Follow-up

Variable	HR (95% CI) for Death	*P* Value
Analysis from index day (n = 2306[a])		
Nosocomial BSI	2.277 (1.983–2.615)	<.001
Charlson score (per point increment)	1.183 (1.161–1.205)	<.001
Albumin (g/dL)		
≤2.5	2.198 (1.790–2.698)	<.001
3.499–2.5	1.497 (1.233–1.816)	<.001
≥3.5	Reference	
Hemoglobin (per 1 g/dL increment)	0.969 (.942–.996)	.024

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Patients with missing Charlson score and hemoglobin were excluded from the analysis.

Subgroup Analyses

Mortality from the index date was significantly higher among patients with nosocomial BSI compared to their matched controls in all subgroup analyses (Table 2). The magnitude of the difference was larger among patients with MDR bacteria compared to non-MDRs and among those treated with inappropriate empirical antibiotics compared to those given appropriate empirical antibiotics, reaching statistical significance in the 90-day mortality subgroup analysis by MDR status (OR, 5.22 [95% CI, 3.3–8.26] for patients with MDR bacteria vs 3.08 [95% CI, 2.49–3.8] for patients with non-MDR bacteria, both compared to their matched controls; $P = .04$ for subgroup difference).

DISCUSSION

In this propensity-matched cohort study, we estimated the burden of nosocomial bacteremia outside the ICU as reflected by patient's mortality and functional status. Mortality rates by 30 and 90 days, were higher for patients with nosocomial BSI than for controls. Mortality was higher whether patients were treated with early empirical appropriate antibiotics or not. This

difference was more pronounced for patients with MDR BSI. The propensity-adjusted ORs for 90-day mortality translate to an absolute increase of 236 (95% CI, 191–283) deaths per 1000 patients following an episode of nosocomial BSI and 363 (95% CI, 249–472) deaths per 1000 patients following nosocomial BSI with MDR bacteria. Developing nosocomial BSI was also associated with poorer functional status at discharge, an often-overlooked important outcome for the individual patient.

Several studies have estimated the impact of nosocomial BSI on mortality. Some of these studies performed a population analysis evaluating the effects of nosocomial BSI on patients' outcome [1, 2, 15]. These have the advantage of examining large databases but lack patient-specific data, such as the clinical and laboratory variables representing sepsis presentation. Studies similar to ours, attempting to define the mortality burden to the individual patient due to nosocomial BSIs, used variable methods [3, 6–9, 16, 17]. Most matched infected to noninfected patients and varied by the population assessed, the matching variables, and the follow-up duration. A critical factor to consider in these analyses is the immortal time of patients BSI, until the BSI occurs. Most studies matched by LOS, requiring that controls' LOS will be at least as long as the time until BSI of the matched case. We found it difficult to match by exposure time in addition to other important predictors of mortality, since many BSIs were acquired late during hospitalization (up to 183 days). Empirical studies assessing the need to match by exposure time have not shown a significant impact of this factor on the mortality burden attributed to nosocomial BSIs [18, 19], unlike an effect on LOS and costs increment estimates [19]. However, we excluded case-control pairs in which the control died before the BSI hospital-day of the matched case and started patients' follow-up on the BSI or matched hospital-day for cases and controls, respectively. On sensitivity analysis, we also started the follow-up from admission for both groups, as the most conservative estimate of BSI burden due to the immortal time bias. The Kaplan-Meier curve starting from the day of admission shows the immortal time of the nosocomial BSI patients; the survival curves crossed on day 35 to favor the control patients (Figure 2B). Our results fall within the range of estimates from previous studies. Studies including a large percentage of patients with coagulase-negative staphylococcal bacteremia tended to find lower and nonsignificant associations between nosocomial BSI and mortality [8, 9]. Studies in ICUs and those assessing MDR bacteria tended to find higher associations between BSI and mortality, as in our study [3, 16].

Not many studies incorporated the factor of the appropriateness of empirical antibiotic treatment for the bacteremia, when examining the impact on mortality. Inappropriate empirical antibiotic treatment has been associated with mortality in most studies examining risk factors for death among patients with bacteremia [20], and is thus a possible factor affecting the burden of BSI. In a matched case-control study conducted in 12 ICUs in France, the ORs for death in patients with nosocomial BSI compared to controls were 2.69 (95% CI, 1.79–4.05) for patients receiving appropriate antibiotics in the first day compared to 4.11 (95% CI, 2.20–7.66) for patients receiving inappropriate empirical antibiotic treatment [16]. In our study, the mortality burden was higher in patient-pairs where the BSI was not treated empirically appropriately (OR, 3.85 [95% CI, 2.99–4.94]) compared to patients-pairs where it was (2.8 [95% CI, 2.07–3.77]), although without statistical significance. These results stress the importance of early appropriate antibiotics, but show the burden of BSI independent of the appropriateness of empirical antibiotics. Different studies have examined outcomes other than mortality, including LOS and costs. We are not aware of previous studies assessing functional and cognitive outcomes, highly relevant for surviving patients. We found functional decline from admission to discharge among patients with nosocomial BSI, significantly more common than the change observed among cases.

The association between nosocomial BSI and higher mortality rates highlights the need to prevent such infections. It is estimated that some of these infections can be prevented through infection prevention and control programs such as the ones published by the Centers for Disease Control and Prevention, the European Centre for Disease Prevention and Control, and the World Health Organization [21–23]. A systematic review of interventional studies to reduce HAI, estimated between 10% and 70% reduction effect, depending on the type of infection, with central line–associated bloodstream infections (CLABSIs) being the most preventable [24]. Additionally, in the US, performance standards in HAI prevention, linked to payment through the Affordable Care Act, have had some success in decreasing the incidence of CLABSIs, while only marginally influencing other infections such as surgical site infections and catheter-associated urinary tract infections [25, 26].

Our study has several limitations. Because this was a retrospective study, we did not have access to data that were not routinely collected. Accordingly, we did not have reliable data on the source of the BSI, since this was not collected as a discrete variable until recently. We did not use consensus definitions for multidrug resistance [27], but defined as MDR bacteria that lead to change in patients' management in our center (use of non-β-lactam antibiotics, contact isolation requirements, possible delay in appropriate antibiotics). Despite the development of a propensity score predicting nosocomial BSI with excellent calibration, few differences remained between cases and controls in major confounders. We, therefore, performed further adjustment on the propensity score–matched cohort, finding associations similar to those of the crude propensity score–matched analysis. We had postdischarge mortality data but did not follow the functional and cognitive outcomes after discharge. The strengths of this study are the relatively large cohort, matching on multiple factors using the propensity score, a long

follow-up for survival, and the analyses addressing MDR bacteria and the appropriateness of empirical antibiotic treatment.

In conclusion, our study demonstrates a strong association between nosocomial BSI and increased risk of death, persisting up to 1 year after the event. The ORs for 90-day mortality ranged between 2.8 and 5.2 for nosocomial BSIs. The mortality burden of nosocomial BSI was not significantly attenuated by appropriate empirical antibiotic treatment but was significantly higher among patients with BSI caused by MDR bacteria. Our results emphasize the need to adhere to infection control measures in order to prevent such infections and the spread of MDR bacteria in hospitals.

Notes

Patient consent. The study was approved by the local ethics committee with a waiver of informed consent given the noninterventional study design.

Financial support. The study was funded in part by the Israeli Ministry of Science and Technology grant 3-14834.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Søgaard M, Nørgaard M, Dethlefsen C, Schønheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. Clin Infect Dis **2011**; 52:61–9.
2. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
3. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA **1994**; 271:1598–601.
4. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect **2013**; 19:501–9.
5. Cassini A, Högberg LD, Plachouras D, et al; Burden of AMR Collaborative Group. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis **2019**; 19:56–66.
6. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and *Staphylococcus aureus* in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill **2016**; 21:30319.
7. Kaye KS, Marchaim D, Chen TY, et al. Effect of nosocomial bloodstream infections on mortality, length of stay, and hospital costs in older adults. J Am Geriatr Soc **2014**; 62:306–11.
8. Digiovine B, Chenoweth C, Watts C, Higgins M. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. Am J Respir Crit Care Med **1999**; 160:976–81.
9. Reunes S, Rombaut V, Vogelaers D, et al. Risk factors and mortality for nosocomial bloodstream infections in elderly patients. Eur J Intern Med **2011**; 22:e39–44.
10. Centers for Disease Control and Prevention. Bloodstream infection event (central line-associated bloodstream infection and non-central line associated bloodstream infection). https://www.cdc.gov/nhsn/psc/bsi/index.html. Accessed July 2021.
11. Norton D, Exton-Smith AN, McLaren R. *An Investigation of Geriatric Nursing Problems in Hospital.* Edinburgh: Churchill Livingstone; **1975**.
12. Tacconelli E, Cataldo MA, Dancer SJ, et al; European Society of Clinical Microbiology. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant gram-negative bacteria in hospitalized patients. Clin Microbiol Infect **2014**; 20(Suppl 1):1–55.
13. Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. J Infect Dis **2017**; 215:28–36.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
15. AL-Rawajfah OM, Stetzer F, Hewitt JB. Incidence of and risk factors for nosocomial bloodstream infections in adults in the United States, 2003. Infect Control Hosp Epidemiol **2009**; 30:1036–44.
16. Garrouste-Orgeas M, Timsit JF, Tafflet M, et al; OUTCOMEREA Study Group. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. Clin Infect Dis **2006**; 42:1118–26.
17. Orsi GB, Di Stefano L, Noah N. Hospital-acquired, laboratory-confirmed bloodstream infection: increased hospital stay and direct costs. Infect Control Hosp Epidemiol **2002**; 23:190–7.
18. Blot S, De Bacquer D, Hoste E, et al. Influence of matching for exposure time on estimates of attributable mortality caused by nosocomial bacteremia in critically ill patients. Infect Control Hosp Epidemiol **2005**; 26:352–6.
19. Watson D, Spaulding AB, Dreyfus J. Risk-set matching to assess the impact of hospital-acquired bloodstream infections. Am J Epidemiol **2019**; 188:461–6.
20. Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother **2010**; 54:4851–63.
21. European Centre for Disease Prevention and Control. Core competencies for infection control and hospital hygiene professionals in the European Union. **2013**. https://www.ecdc.europa.eu/en/publications-data/core-competencies-infection-control-and-hospital-hygiene-professionals-european. Accessed July 2021.
22. Office of Disease Prevention and Health Promotion, US Department of Health and Human Services. National action plan to prevent health care-associated infections: road map to elimination. Phase 1: acute-care hospitals. **2013**. https://health.gov/our-work/health-care-quality/health-care-associated-infections/national-hai-action-plan#P1. Accessed July 2021.
23. World Health Organization. Core competencies for infection prevention and control professionals. **2020**. https://apps.who.int/iris/handle/10665/335821. Accessed July 2021.
24. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Infect **2003**; 54:258–66; quiz 321.
25. Srinivasan A, Craig M, Cardo D. The power of policy change, federal collaboration, and state coordination in healthcare-associated infection prevention. Clin Infect Dis **2012**; 55:426–31.
26. Centers for Disease Control and Prevention. Winnable battles final report: healthcare-associated infections. **2017**. https://www.cdc.gov/winnablebattles/report/index.html. Accessed July 2021.
27. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect **2012**; 18:268–81.