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# BMJ Open

## Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan: A nationwide population-based retrospective cohort study

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3 **Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections**  
4 **in Taiwan: A nationwide population-based retrospective cohort study**

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4 35 **ABSTRACT**  
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7 36 **Objectives:** To estimate the clinical and economic impact of intensive care unit-acquired  
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10 37 bloodstream infections in Taiwan.

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13 38 **Design:** Retrospective cohort study.

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16 39 **Setting:** Nationwide Taiwanese population in the National Health Insurance Research  
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19 40 Database and the Taiwan Nosocomial Infections Surveillance (2007-2015) dataset.

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22 41 **Participants:** The first episodes of intensive care unit-acquired bloodstream infections in  
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25 42 patients  $\geq 20$  years of age in the datasets. Propensity score-matching (1:2) of demographic  
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28 43 data, comorbidities, and disease severity was performed to select a comparison cohort from a  
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31 44 pool of intensive care unit patients without intensive care unit-acquired infections from the  
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34 45 same datasets.

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37 46 **Primary and secondary outcome measures:** The 14-day mortality rate, length of  
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40 47 hospitalization, and healthcare cost.

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43 48 **Results:** After matching, the in-hospital mortality of 14,369 patients with intensive care  
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46 49 unit-acquired bloodstream infections was 44.38%, compared to 33.50% for 28,738 intensive  
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49 50 care unit patients without bloodstream infections. The 14-day mortality rate was also higher  
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53 51 in the bloodstream infections cohort (4,367, 30.39% vs. 6,860 deaths, 23.87%, respectively;  $p$   
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55 52  $< 0.001$ ). Furthermore, the patients with intensive care unit-acquired bloodstream infections  
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58 53 had a prolonged length of hospitalization after their index date (18 [IQR 7–39] vs. 10 days  
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4 54 [IQR 4–21], respectively;  $p < 0.001$ ) and a higher healthcare cost (16,086 [IQR 9,706–26,131]  
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7 55 vs. 10,731 US dollars [IQR 6,375–16,910], respectively;  $p < 0.001$ ). The excessive hospital  
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10 56 stay and healthcare cost per case were 12.77 days and 7,646 US dollars, respectively. Similar  
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13 57 results were observed in subgroup analyses of various World Health Organization’s priority  
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16 58 pathogens and *Candida* spp.

19 59 **Conclusions:** Intensive care unit-acquired bloodstream infections in critically ill patients  
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22 60 were associated with increased mortality, longer hospital stays, and higher healthcare costs.  
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31 63 **Keywords:** bloodstream infection; healthcare costs; hospital stay; intensive care unit;  
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34 64 mortality.  
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4 **66 STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 8 67 1. A large number of patients obtained from Nationwide Taiwanese population from two  
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10 68 datasets in Taiwan were included.  
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13 69 2. Propensity score-matching was performed to select a comparison cohort.  
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16 70 3. The 14-day mortality rate, length of hospitalization, and healthcare cost were analyzed.  
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19 71 4. Subgroup analyses of several drug-resistant pathogens were conducted.  
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22 72 5. The retrospective design may include some unmeasurable bias.  
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## 73 BACKGROUND

74 Critically ill patients in intensive care units (ICUs) are vulnerable to various infections,  
75 and these can lead to increased morbidity, mortality, and healthcare costs. Bloodstream  
76 infections (BSIs) are one of the most common infections acquired by ICU patients. It was  
77 reported that BSIs affected approximately 7 % of patients admitted to ICUs.[1] Previous  
78 studies have shown that ICU-acquired BSIs resulted in attributable mortality of 24.8%,[2]  
79 extended hospital stays by 13.5 days[3] and the cost of treatment was approximately 12,321  
80 US dollars per case. Moreover, despite advances in medical care and the development of new  
81 therapies, the outcome of BSIs in critically ill patients is adversely affected by a greater  
82 number of vulnerable hosts and the emergence of drug-resistant pathogens.

83 Discrepancies regarding the impact of pathogens on mortality have been reported.  
84 However, worse clinical outcome and higher economic burden have been reported for  
85 patients with BSI caused by resistant pathogens.[1, 4] For example, BSIs involving  
86 third-generation cephalosporin-resistant *Enterobacteriaceae* have been shown to significantly  
87 increase mortality risk compared to BSIs involving susceptible strains.[4] Moreover,  
88 candidemia has been associated with a 4-fold increase in mortality, while *Staphylococcus*  
89 *aureus* BSIs doubled the risk of mortality.[1] Meanwhile, the clinical impact of *Enterococci*  
90 remains a controversial topic.[5-7] Therefore, it is important not only to describe the clinical  
91 and economic impact of infections, but also to decipher the impact of individual pathogens.

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4 92 Due to the limited number of cases and the complex clinical characteristics of critically ill  
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7 93 patients, previous studies have reported either clinical or economic outcomes, have focused  
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10 94 on several species of pathogens, or have assessed only a limited number of pathogens. In the  
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13 95 present study, a health insurance database and a nationwide surveillance system for  
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16 96 healthcare-associated infections were used to estimate the clinical and economic  
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19 97 consequences of ICU-acquired BSIs caused by different pathogens in a large number of  
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22 98 patients in Taiwan. In addition, the impact of individual pathogens, especially  
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25 99 antibiotic-resistant bacteria on the World Health Organization (WHO) priority list,[8] were  
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28 100 investigated.  
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4 **102 METHODS**

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7 **103 Data sources**

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10 104 Two datasets, the National Health Insurance Research Database (NHIRD) and the  
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13 105 Taiwan Nosocomial Infection Surveillance (TNIS) dataset, were used in this study.  
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16 106 Demographic data, diagnoses (according to the International Classification of Diseases, 9th  
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19 107 Revision, Clinical Modification [ICD-9-CM]), procedures, and medications for patients  
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22 108 enrolled in Taiwan's national insurance system have been collected in the NHIRD since  
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25 109 1995.[9] In 2007, the TNIS was launched by the Taiwan Centers for Disease Control to  
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28 110 evaluate the epidemiologic trend of healthcare-associated infections in the ICUs in Taiwan.  
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31 111 The latter is a web-based surveillance system which collects clinical information of patients  
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34 112 with healthcare-associated infections from the ICUs of participating hospitals. This  
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37 113 information includes demographic data, infection foci, causative pathogens, and antimicrobial  
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40 114 susceptibility results.

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43 115 Both datasets were deposited in a database maintained by the Health and Welfare Data  
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46 116 Science Center, Ministry of Health and Welfare. Individual personal identification numbers  
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49 117 were encrypted so that data from the NHIRD and TNIS datasets could be interlinked. The  
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52 118 institutional review board of the National Health Research Institutes approved this study  
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55 119 (EC1051207-R4).

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## 121 **Study population, data collection, and propensity-score matching**

122 This retrospective cohort study enrolled adult patients who underwent ICU  
123 hospitalization between 2007 and 2015 in Taiwan. From the entries in the TNIS database, we  
124 identified all of the patients whose first episode of an ICU-acquired BSI occurred during the  
125 study period. Since coagulase-negative *Staphylococci* are often associated with contamination,  
126 these cases were not included in our analysis. We included species that constituted > 1 % of  
127 known bloodstream pathogens (Supplementary Table 1), which constituted 79.4% of all  
128 ICU-acquired BSI episodes. The index date for each case was defined as the date on which a  
129 positive blood culture result was obtained.

130 For comparison, we identified ICU patients who did not have ICU-acquired infections  
131 registered in TNIS database. In addition, patients with a discharge diagnosis of sepsis  
132 (ICD-9-CM: 038.X, 995.91), severe sepsis (ICD-9-CM: 995.92), or septic shock (ICD-9-CM:  
133 785.52) were also excluded. The pool of comparison patients was created for selection of  
134 those with the same admission date as any patient with ICU-acquired BSI. Because the  
135 comparison patients did not have index date of acquisition of infection, they were assigned “-  
136 pseudo-index dates” during hospitalization, which was selected from the index date of  
137 patients with the same day of hospitalization in the BSI group. We used 1:2 greedy  
138 matching[10] within a caliper width equal to 0.2 of the standard deviation of the logit of the  
139 propensity score. Propensity scores were then calculated for the likelihood of ICU-acquired

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4 140 BSIs by using baseline covariates and multivariate logistic regression analysis

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7 141 (Supplementary Table 2). Patient data from January 2005 were used to ensure that individuals

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10 142 were followed for at least two years prior to their selection for this study in order to confirm

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13 143 comorbidities[11] and for matching purposes.

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19 145 **Outcome measurements**

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22 146 Clinical outcomes included in-hospital mortality rate and 14-day mortality rate after the

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25 147 index date/pseudo-index date. Economic outcomes included hospitalization length after the

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28 148 index date/pseudo-index date and cost of overall hospitalization. Hospitalization length was

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31 149 defined as the duration of hospital stay after the index date/pseudo-index date. The overall

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34 150 cost of hospitalization was calculated. The costs were standardized and presented in values

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37 151 from 2017.

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43 153 **Subgroup analysis**

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46 154 To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different

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49 155 pathogens, we performed analyses on patients infected with single pathogen. For example,

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52 156 the impact of WHO priority bacteria and *Candida* were examined separately, as was the

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55 157 impact of drug resistance in these bacteria. We included patients whose first episode of an

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58 158 ICU-acquired BSI were caused by bacteria on the WHO priority list or *Candida*. Therefore,

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4 159 the clinical and economic outcomes of patients with *Acinetobacter baumannii*, *Pseudomonas*  
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7 160 *aeruginosa*, common *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*,  
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10 161 *Enterobacter* species, and *Serratia marcescens*), *S. aureus*, *Enterococcus* species, *Candida*  
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13 162 *albicans*, and non-*albicans Candida* (*Candida tropicalis*, *Candida parapsilosis*, and *Candida*  
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16 163 *glabrata*) were determined.

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19 164 The definition of multiple drug resistance (MDR) of WHO priority bacteria according to  
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22 165 the European Centre for Disease Prevention and Control (ECDC) was modified[12]  
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25 166 (Supplementary Table 3). In this study, non-susceptibility to at least one agent in at least  
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28 167 three antimicrobial categories in Gram-negative bacteria was defined as MDR. Oxacillin- and  
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31 168 vancomycin-non-susceptible *S. aureus* and vancomycin-non-susceptible *Enterococcus*  
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34 169 species were considered MDR Gram-positive bacteria.

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### 38 39 40 171 **Sensitivity analysis**

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43 172 To avoid competing risk between mortality and length of hospitalization/healthcare cost,  
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46 173 we included patients who survived to discharge. For these patients, length of hospitalization  
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49 174 after the index date/pseudo-index date and hospitalization costs were determined.

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### 53 54 55 176 **Statistical analysis**

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58 177 Descriptive statistics were used to examine baseline demographic and clinical  
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4 178 characteristics of the ICU patients included in this study. To account for potential  
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7 179 confounding biases among the study cohort, propensity score matching analysis was  
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10 180 performed. Propensity scores were calculated with multivariate logistic regression.  
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13 181 Standardized differences between the two groups with differences less than 0.1 were  
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16 182 confirmed in order to assess baseline characteristics. The Mann-Whitney U test was used to  
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19 183 evaluate economic outcomes and the Chi-squared test was used to evaluate mortality rate.  
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22 184 Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of  
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25 185 mortality in patients with BSI and the comparison cohort, while a generalized linear model  
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28 186 was used to calculate  $\beta$  values to estimate excess costs and length of hospitalization.  
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31 187 Variables with a *p*-value < 0.05 were eligible for inclusion in the model. *P*-values less than  
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34 188 0.05 were considered statistically significant. All analyses were performed by using SAS  
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37 189 statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA).  
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## 191 RESULTS

192 Among 38,659 episodes of ICU-acquired BSIs registered in TNIS during the 9-year  
193 study period, 28,495 patients were identified to have their first episode of a BSI. The NHIRD  
194 included 1,638,796 patients who underwent ICU hospitalization (Figure 1). After excluding  
195 patients whose data could not be interlinked with NHIRD or who did not have target  
196 pathogens, 14,369 patients with ICU-acquired BSIs were successfully matched to 28,738  
197 ICU patients without ICU-acquired infections (1:2). The demographic and clinical  
198 characteristics of the patients with BSI and comparison cohort are presented in Table 1. The  
199 groups had standardized differences that were  $< 10\%$  for all of the continuous and  
200 dichotomous categorical variables which were examined.

201 Table 2 lists the clinical and economic outcomes of the ICU patients with BSIs and the  
202 comparison cohort. The ICU patients with BSIs suffered a higher in-hospital mortality rate  
203 (44.38% vs. 33.50%, respectively;  $p < 0.001$ ) and a higher 14-day mortality rate (30.39% vs.  
204 23.87%, respectively;  $p < 0.001$ ). Logistic regression analyses showed that the OR of  
205 in-hospital mortality for the ICU patients with BSIs was 1.66 (95% confidence interval [CI],  
206 1.59–1.73;  $p < 0.001$ ), and it was 1.41 (95% CI, 1.34–1.47;  $p < 0.001$ ) for 14-day mortality.  
207 These significant associations were also observed in the subgroup analyses performed (Table  
208 3).

209 The ICU patients with BSIs had a longer length of hospitalization after the index date



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4 210 (18 vs. 10 days, respectively;  $p < 0.001$ ). Moreover, on average, their hospital stay was  
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7 211 extended by 12.77 days (95% CI, 12.02–13.52;  $p < 0.001$ ). The subgroup analyses performed  
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10 212 (Table 4) showed that all of the causative pathogens shared a similar trend. Compared with  
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13 213 the patients without ICU-acquired infections, the duration of hospitalization after the index  
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16 214 date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp.  
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19 215 was longer. In addition, hospitalization costs of the ICU patients with BSIs were higher  
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22 216 (16,086 vs. 10,731, respectively;  $p < 0.001$ ) (Table 2), with the excess cost being 7,646 US  
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25 217 dollars per patient (95% CI, 7,356–7,935;  $p < 0.001$ ). Table 4 presents the higher costs  
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28 218 associated with each of the various causative pathogen.

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31 219 For the ICU patients with BSIs who survived to discharge, their length of hospitalization  
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34 220 and healthcare costs were increased by 19.38 days and 8,829 US dollars, respectively,  
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37 221 (Supplementary Table 4) compared to the survivors without ICU-acquired infections.  
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4 **222 DISCUSSION**  
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7 **223** This study demonstrated that ICU patients with BSIs in Taiwan had significantly worse  
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10 **224** clinical outcomes and higher economic burden than ICU patients without ICU-acquired  
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13 **225** infections from the same population. For example, the patients with BSI exhibited 1.66-fold  
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16 **226** and 1.41-fold increases in in-hospital and 14-day mortality rates. Per case, the patients with  
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19 **227** BSI had an excess hospital stay of 12.77 days and cost of 7,646 US dollars. Furthermore, a  
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22 **228** similar clinical and economic impact was observed among all of the causative pathogens  
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25 **229** examined.  
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28 **230** BSIs have been associated with higher mortality and morbidity, contingent on the  
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31 **231** causative pathogen involved.[1,3,13-16] For example, worse clinical outcomes have been  
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34 **232** reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S.*  
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37 **233** *aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] In contrast,  
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40 **234** controversial results have been obtained regarding the mortality of patients affected by  
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43 **235** enterococcal bacteremia. While some authors have argued that *Enterococcus* spp. represents  
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46 **236** a low virulence pathogen[1] and is not associated with increased mortality unless in the  
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49 **237** presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] In  
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52 **238** the present study, significantly higher mortality was observed for patients with enterococcal  
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55 **239** bacteremia, and this may be due to vulnerability of the hosts examined, increased resistance,  
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58 **240** and a larger study population.  
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4 241 The high healthcare burden of BSIs reported in previous literature[3,13,20] and in the  
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7 242 present study underscores the importance of preventing ICU-acquired BSIs by infection  
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10 243 control measurements. Furthermore, the results of these studies help to assess cost  
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13 244 effectiveness of infection control measurements in the process of policy-making. For  
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16 245 example, patients with ICU-acquired BSIs during the 9-year period cost Taiwan an estimated  
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19 246 298 million US dollars and 495,222 days (supplementary Table 5). A policy that reduced the  
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22 247 rate of infection by 10%[21] would translate into a savings of 30 million US dollars and  
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25 248 4,952 patient-days saved.

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28 249 Drug resistance has been found to be correlated with higher medical costs due to the  
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31 250 need for second-line antimicrobials for treatment, as well as additional diagnostic and  
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34 251 treatment tools.[22, 23] In the present study, the costs for MDR bacteria included extra 85  
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37 252 million US dollars and 140,923 days over nine years (Supplementary Table 5). However, cost  
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40 253 differences between susceptible and resistant strains were not determined in the present  
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43 254 study. Drug-susceptible strains were not included as controls due to differences in testing  
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46 255 methods, drugs, and breakpoints for these strains which could lead to mis-assignments of  
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49 256 drug-resistant pathogens as susceptible pathogens.

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52 257 Candidemia poses a great threat to ICU patients due to its excessive medical  
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55 258 burdens,[16,18,20] and *C. albicans* is the most common pathogen. However, in some  
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58 259 countries, the prevalence of non-*albicans* *Candida* exceeds that of *C. albicans*.[24] For those  
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4 260 infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization  
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7 261 stays, and increased hospital costs have been described;[25-27] although other studies have  
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10 262 reported contradicting findings.[28,29] These discrepancies may be due to host factors and  
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13 263 differences in the virulence and resistance patterns[24] of non-*albicans Candida*. In the  
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16 264 present study, the crude 14-day and in-hospital mortality rates of 958 patients infected with  
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19 265 *C. albicans* were 38.10% and 56.16%, respectively. In comparison, among 704 patients  
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22 266 infected with non-*albicans Candida*, these rates were 34.94% and 52.98%, respectively.  
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25 267 While the hospital costs and length of stay were higher in the non-*albicans Candida* group  
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28 268 compared to the *C. albicans* group, the 95% CI overlapped for the two groups (Table 4).  
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31 269 These data suggested that the clinical and economic outcomes of these two groups did not  
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34 270 greatly differ. However, the present study was not designed to specifically compare the  
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37 271 outcomes of those infected with *C. albicans* versus non-*albicans Candida*. Therefore,  
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40 272 additional studies with a larger number of patients, adjustment for host factors, and  
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43 273 consideration of antifungal drugs, incubation time, and treatment duration are needed to  
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46 274 clarify the impact of each *Candida* species.

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49 275 The large number of patients examined in this study and the use of propensity score  
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52 276 matching represent two major strengths of the present study. These aspects also allowed the  
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55 277 impact of each pathogen group to be discerned. However, there were also several limitations  
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58 278 associated with the present study which merit discussion. First, the exact cost after the index  
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4 279 date could not be retrieved from the NHIRD. Therefore, the high total cost shown in this  
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7 280 study may be due to costs incurred prior to the onset of a BSI. It is possible that matching of  
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10 281 the duration before the index date and comorbidity may have reduced overestimations of  
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13 282 healthcare costs due to time-dependent bias.[30] Second, confounding factors associated with  
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16 283 clinical impact, such as APACHE II or Pitt Bacteremia scores, were not included in this  
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19 284 study. Instead, other clinical risk factors (Charlson Comorbidity Index score, number of  
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22 285 organ failures, use of inotropic agents, and receipt of invasive procedures) were incorporated  
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25 286 in our model. Third, our study is inherently limited by its retrospective design, which  
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28 287 includes a dependence on the accuracy of the ICD codes used and unmeasurable bias.[31,32]  
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31 288 In addition, the prolonged hospitalization may have been due to a change in patient  
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34 289 management in response to a BSI, rather than increased morbidity due to a BSI.[15]  
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## 38 39 40 291 **CONCLUSIONS**

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43 292 ICU-acquired BSIs have a negative clinical and economic impact on affected patients  
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46 293 regardless of the causative pathogens involved. Awareness of these negative affects is  
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49 294 important for promoting infection control measurements and for policy-making.  
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4 296 **LIST OF ABBREVIATIONS**  
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7 297 BSI = bloodstream infection;  
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10 298 CI = confidence interval;  
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13 299 ECDC = European Centre for Disease Prevention and Control;  
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16 300 ICD-9-CM = international classification of diseases, 9th revision, clinical modification;  
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19 301 ICU = intensive care unit;  
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22 302 IQR = interquartile range;  
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25 303 MDR = multiple drug resistance;  
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28 304 NHIRD = National Health Insurance Research Database;  
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31 305 OR = odds ratio;  
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34 306 TNIS = Taiwan Nosocomial Infection Surveillance;  
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37 307 WHO = World Health Organization;  
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4 **309 DECLARATIONS**

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7 **310 Ethics approval and consent to participate**

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10 311 The institutional review board of the National Health Research Institutes approved this study  
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13 312 (EC1051207-R4).  
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19 **314 Consent for publication**

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22 315 Not applicable.  
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28 **317 Availability of data and materials**

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31 318 The data that support the findings of this study are available from Ministry of Health and

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34 319 Welfare, Taiwan but restrictions apply to the availability of these data, which were used

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37 320 under license for the current study, and so are not publicly available. Data are however

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40 321 available from the authors upon reasonable request and with permission of Ministry of Health

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43 322 and Welfare, Taiwan.  
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49 **324 Competing interests**

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52 325 The authors declare that they have no competing interests.  
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13 331 interpretation of data; writing of the report; or the decision to submit the article for  
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19 333

22 334 **Author contributions**

25 335 Conceptualization: CAH, SCK

28 336 Data curation: YTC, CAH, SCK

31 337 Formal analysis: SMS, YTC

34 338 Funding acquisition: YCW, SCK

37 339 Investigation: YCW, SCK

40 340 Methodology: YTC, CAH, SCK

43 341 Project administration: YCW, CAH, SCK

46 342 Resources: YTC, CAH, SCK

49 343 Software: SMS, YTC

52 344 Supervision: SMS, YTC

55 345 Validation: CAH, SCK

58 346 Visualization: YCW, SMS



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348 Writing—review & editing: YCW, CAH, SCK

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355 **REFERENCES**

- 356 1. Prowle JR, Echeverri JE, Ligabo EV, et al. Acquired bloodstream infection in the  
357 intensive care unit: incidence and attributable mortality. *Crit Care* 2011; **15**: R100.
- 358 2. Garrouste-Orgeas M, Timsit JF, Tafflet M, et al. Excess risk of death from intensive  
359 care unit-acquired nosocomial bloodstream infections: a re-appraisal. *Clin Infect Dis*  
360 2006; **42**: 1118-26.
- 361 3. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired  
362 bloodstream infections. *J Hosp Infect* 2006; **63**: 124-32.
- 363 4. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of  
364 bloodstream infections caused by antimicrobial-susceptible and non-susceptible  
365 Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011:  
366 a multicentre retrospective cohort study. *Euro Surveill* 2016; **21**: pii=30319.
- 367 5. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to  
368 nosocomial enterococcal bacteremia: a controlled study. *Am J Infect Control* 1989;  
369 **17**: 323-9.
- 370 6. Ong DS, Bonten MJ, Safdari K, et al. Epidemiology, management, and risk-adjusted  
371 mortality of ICU-acquired enterococcal bacteremia. *Clin Infect Dis* 2015; **61**:  
372 1413-20.
- 373 7. Kramer TS, Remschmidt C, Werner S, et al. The importance of adjusting for

- 1  
2  
3  
4 374 Enterococcus species when assessing the burden of vancomycin resistance: a cohort  
5  
6  
7 375 study including over 1000 cases of enterococcal bloodstream infections. *Antimicrob*  
8  
9  
10 376 *Resist Infect Control* 2018; **7**: 133.
- 11  
12  
13 377 8. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of  
14  
15  
16 378 new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis.  
17  
18  
19 379 *Lancet Infect Dis* 2018; **18**: 318-27.
- 20  
21  
22 380 9. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan.  
23  
24  
25 381 *London J Prim Care (Abingdon)* 2010; **3**: 115-9.
- 26  
27  
28 382 10. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in  
29  
30  
31 383 Ontario. *N Engl J Med* 2007; **357**: 1393-402.
- 32  
33  
34 384 11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with  
35  
36  
37 385 ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-9.
- 38  
39  
40 386 12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively  
41  
42  
43 387 drug-resistant and pandrug-resistant bacteria: an international expert proposal for  
44  
45  
46 388 interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**:  
47  
48  
49 389 268-81.
- 50  
51  
52 390 13. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill  
53  
54  
55 391 patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;  
56  
57  
58 392 **271**: 1598-601.
- 59  
60

- 1  
2  
3  
4 393 14. Laupland KB, Zygun DA, Davies HD, et al. Population-based assessment of intensive  
5  
6  
7 394 care unit-acquired bloodstream infections in adults: incidence, risk factors, and  
8  
9  
10 395 associated mortality rate. *Crit Care Med* 2002; **30**: 2462-7.  
11  
12  
13 396 15. Barnett AG, Page K, Campbell M, et al. The increased risks of death and extra lengths  
14  
15  
16 397 of hospital and ICU stay from hospital-acquired bloodstream infections: a  
17  
18  
19 398 case-control study. *BMJ Open* 2013; **3**: e003587.  
20  
21  
22 399 16. Marra AR, Camargo LF, Pignatari AC, et al. Nosocomial bloodstream infections in  
23  
24  
25 400 Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide  
26  
27  
28 401 surveillance study. *J Clin Microbiol* 2011; **49**: 1866-71.  
29  
30  
31 402 17. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in  
32  
33  
34 403 patients with *Acinetobacter baumannii* infection: systematic review and  
35  
36  
37 404 meta-analysis. *Clin Microbiol Infect* 2014; **20**: 416-23.  
38  
39  
40 405 18. Schwab F, Geffers C, Behnke M, et al. ICU mortality following ICU-acquired  
41  
42  
43 406 primary bloodstream infections according to the type of pathogen: a prospective  
44  
45  
46 407 cohort study in 937 Germany ICUs (2006-2015). *PloS One* 2018; **13**: e0194210.  
47  
48  
49 408 19. Caballero-Granado FJ, Becerril B, Cuberos L, et al. Attributable mortality rate and  
50  
51  
52 409 duration of hospital stay associated with enterococcal bacteremia. *Clin Infect Dis*  
53  
54  
55 410 2001; **32**: 587-94.  
56  
57  
58 411 20. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically  
59  
60

- 1  
2  
3  
4 412 ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis*  
5  
6  
7 413 2005; **41**: 1591-8.  
8  
9  
10 414 21. Tseng SH, Lee CM, Lin TY, et al. Combating antimicrobial resistance: antimicrobial  
11  
12  
13 415 stewardship program in Taiwan. *J Microbiol Immunol Infect* 2012; **45**: 79-89.  
14  
15  
16 416 22. Howard D, Cordell R, McGowan JE, Jr., et al. Measuring the economic costs of  
17  
18  
19 417 antimicrobial resistance in hospital settings: summary of the Centers for Disease  
20  
21  
22 418 Control and Prevention-Emory Workshop. *Clin Infect Dis* 2001; **33**: 1573-8.  
23  
24  
25 419 23. Mauldin PD, Salgado CD, Hansen IS, et al. Attributable hospital cost and length of  
26  
27  
28 420 stay associated with health care-associated infections caused by antibiotic-resistant  
29  
30  
31 421 gram-negative bacteria. *Antimicrob Agents Chemother* 2010; **54**: 109-15.  
32  
33  
34 422 24. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia  
35  
36  
37 423 in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin*  
38  
39  
40 424 *Infect Dis* 2009; **48**: 1695-703.  
41  
42  
43 425 25. Dimopoulos G, Ntziora F, Rachiotis G, et al. *Candida albicans* versus non-*albicans*  
44  
45  
46 426 intensive care unit-acquired bloodstream infections: differences in risk factors and  
47  
48  
49 427 outcome. *Anesth Analg* 2008; **106**: 523-9.  
50  
51  
52 428 26. Moran C, Grussemeier CA, Spalding JR, et al. Comparison of costs, length of stay,  
53  
54  
55 429 and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream  
56  
57  
58 430 infections. *Am J Infect Control* 2010; **38**: 78-80.  
59  
60

- 1  
2  
3  
4 431 27. Gong X, Luan T, Wu X, et al. Invasive candidiasis in intensive care units in China:  
5  
6  
7 432 risk factors and prognoses of *Candida albicans* and non-*albicans* *Candida* infections.  
8  
9  
10 433 *Am J Infect Control* 2016; **44**: e59-63.  
11  
12  
13 434 28. Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia  
14  
15  
16 435 in 3648 patients: data from the prospective antifungal therapy (PATH Alliance®)  
17  
18  
19 436 registry, 2004-2008. *Diagn Microbiol Infect Dis* 2012; **74**: 323-31.  
20  
21  
22 437 29. Barchiesi F, Orsetti E, Gesuita R, et al.; Candidemia Study Group. Epidemiology,  
23  
24  
25 438 clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy  
26  
27  
28 439 from 2010 to 2014. *Infection* 2016; **44**: 205-13.  
29  
30  
31 440 30. Nelson RE, Samore MH, Jones M, et al. Reducing time-dependent bias in estimates of  
32  
33  
34 441 the attributable cost of health care-associated Methicillin-resistant *Staphylococcus*  
35  
36  
37 442 aureus infections: a comparison of three estimation strategies. *Med Care* 2015; **53**:  
38  
39  
40 443 827-34.  
41  
42  
43 444 31. Kuo SC, Shih SM, Hsieh LY, et al. Antibiotic restriction policy paradoxically  
44  
45  
46 445 increased private drug consumptions outside Taiwan's National Health Insurance. *J*  
47  
48  
49 446 *Antimicrob Chemother* 2017; **72**: 1544-5.  
50  
51  
52 447 32. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative  
53  
54  
55 448 data. *JAMA* 2012; **307**: 1433-5.  
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450 **Table 1. Characteristics of the intensive care unit patients with bloodstream infections**  
 451 **and the matched comparison cohort.**

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,369	28,738	
Males	9,060 (63.05)	18,059 (62.84)	0.004
Age, years, mean (SD)	65.21 (21.58)	65.41 (20.24)	0.010
Length of stay before index date/ pseudo-index date, days, mean (SD)	15.81 (12.51)	15.32 (12.21)	0.039
Monthly income, USD			
Dependent	2,438 (16.97)	4,837 (16.83)	0.004
< 657.33	4,794 (33.36)	9,601 (33.41)	0.001
657.33–1504.60	6,370 (44.33)	12,805 (44.56)	0.005
> 1504.60	753 (5.24)	1,465 (5.10)	0.006
Urbanization level			
1 (urban)	3,681 (25.62)	7,292 (25.37)	0.006
2	4,004 (27.87)	8,028 (27.94)	0.002
3	2,246 (15.63)	4,541 (15.80)	0.005
4 (rural)	4,427 (30.81)	8,849 (30.79)	0
Charlson Comorbidity Index score, mean (SD)	3.09 (2.80)	3.12 (2.93)	0.013
0	2,968 (20.66)	6,198 (21.57)	0.022
1	1,947 (13.55)	3,995 (13.90)	0.010
2	2,313 (16.10)	4,418 (15.37)	0.020

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4	≥ 3	7,141 (49.70)	14,127 (49.16)	0.011
5				
6	Comorbidities			
7				
8	Diabetes mellitus	4,901 (34.11)	9,848 (34.27)	0.003
9				
10	Cerebrovascular disease	3,592 (25.00)	7,192 (25.03)	0.001
11				
12	Hypertension	8,156 (56.76)	16,334 (56.84)	0.002
13				
14	Myocardial infarction	530 (3.69)	1,110 (3.86)	0.009
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16	Heart failure	2,574 (17.91)	5,276 (18.36)	0.012
17				
18	Peripheral vascular disease	755 (5.25)	1,524 (5.30)	0.002
19				
20	Liver disease	2,765 (19.24)	5,573 (19.39)	0.004
21				
22	Chronic kidney disease	3,905 (27.18)	8,003 (27.85)	0.015
23				
24	Dyslipidemia	2,787 (19.40)	5,558 (19.34)	0.001
25				
26	Cancer	2,799 (19.48)	5,689 (19.80)	0.008
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30	Number of dysfunctional organs,			
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32	mean (SD)	1.02 (0.81)	1.03 (0.86)	0.014
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34	0	4,047 (28.16)	8,465 (29.46)	0.029
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36	1	6,498 (45.22)	12,396 (43.13)	0.042
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38	2	3,324 (23.13)	6,460 (22.48)	0.016
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40	≥ 3	500 (3.48)	1,417 (4.93)	0.072
41				
42	Use of inotropic agents	11,529 (80.24)	23,153 (80.57)	0.008
43				
44	Use of steroid	10 (0.07)	19 (0.07)	0.001
45				
46	Use of ventilator (> 3 days)	11,798 (82.11)	23,578 (82.04)	0.002
47				
48	Emergent renal replacement			
49	therapy	2,680 (18.65)	5,523 (19.22)	0.014
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51	Propensity score (SD)	0.13 (0.11)	0.13 (0.11)	0.014
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58	452	Abbreviations: BSI = bloodstream infection; SD = standard deviation.		
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453 **Table 2. Clinical and economic outcomes among patients with bloodstream infections and the matched comparison cohort.**

Outcomes	Full cohort			Matched cohort		
	ICU patients	Comparison	<i>P</i> -value	ICU patients	Comparison	<i>P</i> -value
	with BSI	cohort		with BSI	cohort	
No. of patients	17,834	713,518		14,369	28,738	
Clinical outcomes						
In-hospital mortality, n (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,377 (44.48)	9,627 (33.50)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,367 (30.39)	6,860 (23.87)	< 0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median (IQR)	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 34)	10 (4, 21)	< 0.0001

Cost of hospitalization (USD) <sup>a</sup> , median	18,457	4,971	< 0.0001	16,086	10,731	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,706, 26,431)	(6,375, 16,910)	

454 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

455 <sup>a</sup>The costs are standardized and presented as the values in 2017.

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456 **Table 3. Clinical outcomes for the various pathogen groups.**

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)	
	In-hospital mortality	14-days mortality
MDR Gram-negative bacteria (2,255)	1.97 (1.76, 2.21)	1.65 (1.47, 1.85)
MDR Gram-positive bacteria (1,440)	1.90 (1.64, 2.19)	1.32 (1.14, 1.53)
<i>Acinetobacter baumannii</i> (1,775)	1.48 (1.30, 1.68)	1.39 (1.21, 1.59)
<i>Pseudomonas aeruginosa</i> (861)	1.62 (1.35, 1.95)	1.74 (1.43, 2.11)
Enterobacteriaceae <sup>b</sup> (3,581)	1.53 (1.40, 1.68)	1.28 (1.16, 1.41)
<i>Staphylococcus aureus</i> (1,733)	1.69 (1.47, 1.94)	1.15 (0.99, 1.33)
<i>Enterococcus species</i> <sup>c</sup> (1,287)	1.75 (1.50, 2.04)	1.50 (1.28, 1.76)
<i>Candida albicans</i> (958)	2.39 (2.00, 2.85)	1.84 (1.54, 2.20)
Non- <i>albicans Candida</i> <sup>d</sup> (704)	1.95 (1.59, 2.38)	1.47 (1.19, 1.81)

457 Abbreviations: MDR = multiple drug resistance.

458 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this  
459 analysis.

460 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter*  
461 *cloacae*, *Enterobacter aerogenes*, and *Serratia marcescens*.

462 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other  
463 *Enterococcus species*.

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4 464 <sup>d</sup>Non-*albicans* *Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida*

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7 465 *glabrata*.

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468 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Beta (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.76 (8.82, 12.70)	7,317 (6,514, 8,279)
MDR Gram-positive bacteria	13.36 (10.46, 16.25)	5,605 (4,706, 6,504)
<i>Acinetobacter baumannii</i>	10.14 (8.49, 11.80)	7,311 (6,401, 8,261)
<i>Pseudomonas aeruginosa</i>	9.68 (7.49, 11.88)	6,117 (5,043, 7,330)
Enterobacteriaceae <sup>b</sup>	14.96 (13.29, 16.63)	7,312 (6,784, 7,960)
<i>Staphylococcus aureus</i>	14.96 (12.81, 17.10)	4,817 (4,147, 5,547)
<i>Enterococcus species</i> <sup>c</sup>	10.57 (7.78, 13.35)	7,314 (6,387, 8,321)
<i>Candida albicans</i>	11.01 (8.6, 13.42)	9,115 (7,929, 10,361)

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4 Non-*albicans Candida*<sup>d</sup> 14.19 (10.31, 18.08) 11,344 (9,850, 12,838)  
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7 469 Abbreviations: MDR = multiple drug resistance.  
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10 470 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this analysis.  
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12  
13 471 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Serratia*  
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16 472 *marcescens*.  
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19 473 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.  
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22 474 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.  
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4 478 **FIGURE LEGENDS**

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7 479 **Figure 1. Flow diagram of the study design.**

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16 482 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National

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19 483 Health Insurance Research Database.

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4 490 **SUPPLEMENTARY FILES:**  
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7 491 Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before  
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10 492 enrollment and the number of patients infected after matching.  
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16 494 Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched  
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19 495 comparison cohort.  
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25 497 Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.  
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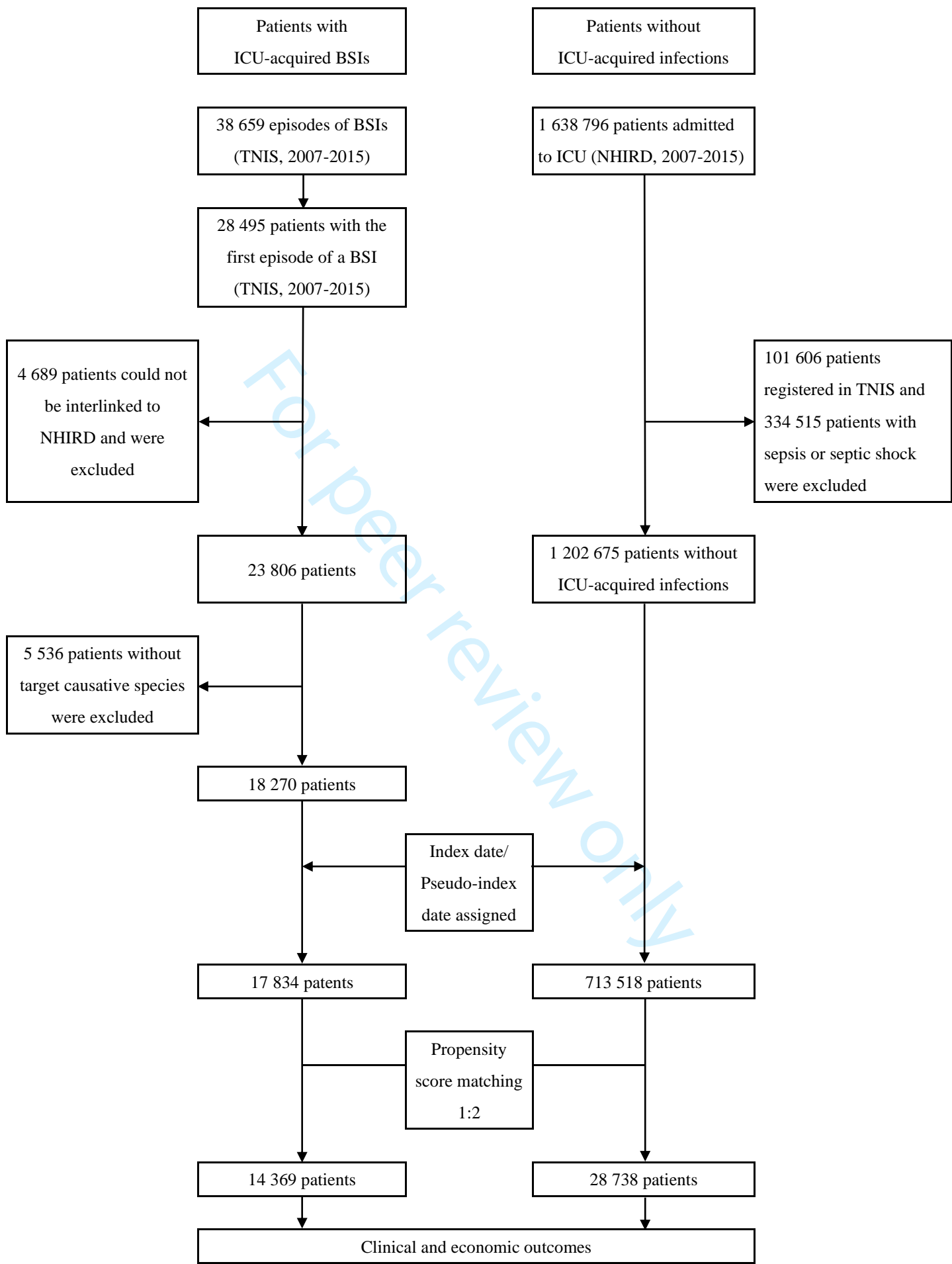
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31 499 Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the  
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1 **Supplementary Table 1. The number of episodes of intensive care unit-acquired**  
 2 **bloodstream infections caused by common pathogens before enrollment and the**  
 3 **number of patients infected after matching.**

	No. of BSI episodes before enrollment <sup>a</sup>	No. of patients after matching <sup>b</sup>
<i>Acinetobacter baumannii</i>	5,214	1,775
<i>Staphylococcus aureus</i>	4,382	1,733
<i>Klebsiella pneumoniae</i>	3,965	1,376
<i>Pseudomonas aeruginosa</i>	2,619	861
<i>Candida albicans</i>	2,554	958
<i>Escherichia coli</i>	2,287	850
<i>Enterobacter cloacae</i>	1,982	755
<i>Enterococcus faecium</i>	1,950	653
<i>Stenotrophomonas maltophilia</i>	1,599	465
<i>Enterococcus faecalis</i>	1,427	422
<i>Serratia marcescens</i>	1,239	437
<i>Candida tropicalis</i>	890	332
<i>Burkholderia cepacia</i>	808	252
Other <i>Enterococcus</i> species <sup>c</sup>	688	212
<i>Elizabethkingia meningoseptica</i>	659	177
<i>Chryseobacterium indologenes</i>	553	154
<i>Candida parapsilosis</i>	534	177
<i>Candida glabrata</i>	461	195
<i>Enterobacter aerogenes</i>	419	163

4 Abbreviations: BSI= bloodstream infection.

5 <sup>a</sup>The number of episodes of bloodstream infections with known pathogens was 38,659.

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3 6 Coagulase-negative staphylococci was excluded from analyses due to possibility of  
4  
5 7 contamination. One episode may have multiple pathogens. There were 30,697 episodes of  
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7 8 bloodstream infections caused by the pathogens listed above.

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9 9 <sup>b</sup>The number of patients enrolled case was 14,369 (Table 1) but only patients with  
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11 10 bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it  
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13 11 was 11,947. There were 2,422 patients with bloodstream infections caused by multiple  
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15 12 pathogens.

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17 13 <sup>c</sup>*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis*.  
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15 **Supplementary Table 2. Propensity score model results of probability of bloodstream**  
 16 **infections among intensive care unit patients and matched comparison cohort.**

Parameter	Estimate	Odds ratios	95% Confidence interval		P-value
			Lower	Upper	
			Age, years	-0.002	
Length of stay before index date/pseudo-index date, days	0.010	1.010	0.997	1.023	0.131
Year of index date					
2007	--	1.000	--	--	--
2008	0.313	1.367	1.251	1.494	< 0.0001
2009	0.474	1.606	1.468	1.758	< 0.0001
2010	0.450	1.569	1.432	1.718	< 0.0001
2011	0.553	1.739	1.579	1.915	< 0.0001
2012	0.440	1.552	1.402	1.719	< 0.0001
2013	0.335	1.398	1.254	1.558	< 0.0001
2014	0.193	1.212	1.082	1.359	0.001
2015	0.144	1.155	1.025	1.301	0.018
Month of index date					
Jan	--	1.000	--	--	--
Feb	0.015	1.015	0.919	1.122	0.768
Mar	-0.014	0.986	0.895	1.087	0.782
Apr	-0.021	0.979	0.887	1.080	0.670
May	0.034	1.034	0.936	1.142	0.507
Jun	0.083	1.087	0.983	1.202	0.104

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3	Jul	0.054	1.056	0.955	1.167	0.287
4						
5	Aug	0.097	1.101	0.997	1.217	0.058
6						
7	Sep	0.112	1.118	1.010	1.238	0.032
8						
9						
10	Oct	-0.012	0.988	0.892	1.094	0.816
11						
12	Nov	-0.020	0.981	0.885	1.087	0.708
13						
14	Dec	-0.106	0.900	0.812	0.997	0.044
15						
16						
17	Male	0.016	1.017	0.973	1.062	0.463
18						
19	Monthly income, USD					
20						
21	Dependent	--	1.000	--	--	--
22						
23	<657.33	0.026	1.026	0.958	1.100	0.461
24						
25	657.33–1504.60	-0.013	0.987	0.920	1.059	0.721
26						
27	>1504.60	0.089	1.093	0.979	1.220	0.114
28						
29						
30	Urbanization level					
31						
32	1 (urban)		1.000			
33						
34	2	-0.016	0.984	0.929	1.042	0.584
35						
36	3	-0.042	0.959	0.894	1.028	0.239
37						
38	4 (rural)	-0.019	0.982	0.927	1.039	0.522
39						
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41						
42	Hospital level					
43						
44	Level I (Medical center)	--	1.000	--	--	--
45						
46	Level II (Regional					
47	hospital)	-0.018	0.982	0.931	1.036	0.512
48						
49	Level III (Local hospital)	-0.016	0.985	0.836	1.160	0.852
50						
51						
52	Charlson Comorbidity Index					
53						
54	score					
55						
56	0	--	1.000	--	--	--
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3	1	0.107	1.113	1.032	1.201	0.006
4						
5	2	0.240	1.272	1.176	1.375	< 0.0001
6						
7	$\geq 3$	0.293	1.340	1.222	1.469	< 0.0001
8						
9						
10	Comorbidities					
11						
12	Diabetes mellitus	0.002	1.002	0.951	1.056	0.926
13						
14	Cerebrovascular disease	-0.029	0.972	0.902	1.046	0.447
15						
16	Hypertension	-0.001	0.999	0.950	1.049	0.953
17						
18	Myocardial infarction	0.015	1.015	0.829	1.243	0.885
19						
20	Heart failure	-0.037	0.964	0.883	1.052	0.408
21						
22	Peripheral vascular					
23	disease	-0.018	0.982	0.891	1.082	0.713
24						
25	Liver disease	-0.043	0.958	0.891	1.030	0.247
26						
27	Chronic kidney disease	-0.070	0.932	0.862	1.009	0.082
28						
29	Dyslipidemia	-0.017	0.984	0.919	1.053	0.634
30						
31	Cancer	-0.122	0.885	0.831	0.943	< 0.0001
32						
33						
34						
35						
36						
37						
38	Number of dysfunctional					
39	organs					
40						
41	0	--	1.000	--	--	--
42						
43	1	0.136	1.146	0.991	1.324	0.066
44						
45	2	0.192	1.211	0.921	1.593	0.170
46						
47	$\geq 3$	-0.167	0.846	0.555	1.291	0.438
48						
49						
50						
51	Use of inotropic agents	0.103	1.109	0.883	1.393	0.374
52						
53	Use of steroid	-0.001	0.999	0.454	2.197	0.998
54						
55	Use of ventilator (> 3 days)	0.190	1.209	0.851	1.719	0.290
56						
57	Emergent renal replacement	0.051	1.053	0.915	1.211	0.472
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18 **Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and**  
 19 **antimicrobial agents used to define drug resistance.**

Pathogens	Antimicrobial categories	Antimicrobial agents	
<i>Acinetobacter baumannii</i> <sup>a</sup>	Aminoglycosides	Gentamicin	
		Tobramycin	
		Amikacin	
		Netilmicin	
	Carbapenems	Imipenem	
		Meropenem	
		Doripenem	
	Fluoroquinolones	Ciprofloxacin	
		Levofloxacin	
		Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid	
		Cefotaxime	
		Cefepime	
		Extended-spectrum cephalosporins	Cefpirome
Ceftazidime			
Ceftriaxone			
<i>Pseudomonas aeruginosa</i> <sup>a</sup>	Aminoglycosides	Gentamicin	
		Tobramycin	
		Amikacin	
		Netilmicin	
	Carbapenems	Imipenem	
		Meropenem	



		Doripenem
		Ciprofloxacin
	Fluoroquinolones	Levofloxacin
	Antipseudomonal penicillins +	Piperacillin-tazobactam
	$\beta$ -lactamase inhibitors	Ticarcillin-clavulanic acid
		Cefepime
	Antipseudomonal cephalosporins	Cefpirome
		Ceftazidime
		Gentamicin
		Tobramycin
	Aminoglycosides	Amikacin
		Netilmicin
		Imipenem
		Meropenem
	Carbapenems	Doripenem
		Ertapenem
<i>Enterobacteriaceae<sup>a</sup></i>		Ciprofloxacin
<i>(Escherichia coli,</i>	Fluoroquinolones	Levofloxacin
<i>Klebsiella pneumoniae,</i>	Antipseudomonal penicillins +	Piperacillin-tazobactam
<i>Enterobacter cloacae</i>	$\beta$ -lactamase inhibitors	Ticarcillin-clavulanic acid
<i>Enterobacter</i>		Cefotaxime
<i>aerogenes, or Serratia</i>	Extended-spectrum cephalosporins	Cefepime
<i>marcescens)</i>		Cefpirome
		Ceftazidime

		Ceftriaxone
<i>Staphylococcus aureus</i> <sup>b</sup>	Glycopeptides	Vancomycin
	$\beta$ -lactamase-resistant penicillins	Oxacillin
<i>Enterococcus faecium</i> , <i>Enterococcus faecalis</i> , or other <i>Enterococcus</i> <i>species</i> <sup>b</sup>	Glycopeptides	Vancomycin

<sup>a</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories.

<sup>b</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent.

23 **Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to**  
 24 **the discharge.<sup>a</sup>**

Clinical outcomes	beta (95% Confidence interval) <sup>b</sup>	<i>P</i> -value
Length of hospitalization after the index date/pseudo-index date, days	19.38 (18.57, 20.2)	< 0.0001
Cost of hospitalization, USD	8,829 (8,428, 9,231)	< 0.0001

30 <sup>a</sup>A total of 7,992 of patients with intensive care unit-acquired bloodstream infections and 19,111 comparators survived to the discharge.

31 <sup>b</sup>Adjusted imbalanced variables in Table 1.

33 **Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.**

34

Pathogen groups (Numbers of patients) <sup>a</sup>	9-year excessive hospitalization or healthcare cost	
	Length of hospitalization after the index date	Cost of hospitalization (USD) <sup>b, c</sup>
	(days) <sup>b</sup>	
All pathogens (38,659)	495,222	297,515,798
MDR Gram-negative bacteria (6,825)	87,428	52,524,518
MDR Gram-positive bacteria (4,176)	53,495	32,138,078
<i>Acinetobacter baumannii</i> (5,214)	66,791	40,126,423
<i>Pseudomonas aeruginosa</i> (2,619)	33,549	20,155,562
<i>Enterobacteriaceae</i> <sup>d</sup> (9,486)	121,516	73,003,307
<i>Staphylococcus aureus</i> (4,382)	56,133	33,723,434
<i>Enterococcus species</i> <sup>e</sup> (4,045)	51,816	31,129,916
<i>Candida albicans</i> (2,554)	32,717	19,655,329
<i>Non-albicans Candida</i> <sup>f</sup> (1,872)	23,980	14,406,725

35 Abbreviations: MDR= multiple drug resistance.

<sup>a</sup>The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The inclusion and exclusion criteria in the method section were not applied in this Table (see Figure 1).

<sup>b</sup>The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s) and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was that in matched control group.

$Ave_{\text{Hospitalization per case}} = [(\text{sum of hospitalization length}) / \text{the number of patients}]$ .

$\text{Excessive } Ave_{\text{Hospitalization per person}} = (Ave_{\text{Hospitalization in bloodstream infection group}}) - (Ave_{\text{Hospitalization in comparison group}})$ .

$\text{Total excessive hospitalization length over 9 years} = (\text{excessive } Ave_{\text{Hospitalization per person}}) \times (\text{total number of episodes over 9 years})$

The 9-year excessive healthcare cost was calculated similarly.

<sup>c</sup>The costs are standardized and presented the values in 2017.

<sup>d</sup>*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa*, and *Serratia marcescens*.

<sup>e</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

<sup>f</sup>*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(b) For matched studies, give matching criteria and number of exposed and unexposed	#9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	#11-12
		(b) Describe any methods used to examine subgroups and interactions	#10-11
		(c) Explain how missing data were addressed	#8-10
		(d) If applicable, explain how loss to follow-up was addressed	#8-10
		(e) Describe any sensitivity analyses	#11
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#13
		(b) Give reasons for non-participation at each stage	#13
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#13-14
		(b) Indicate number of participants with missing data for each variable of interest	#13-14
		(c) Summarise follow-up time (eg, average and total amount)	#13-14
Outcome data	15*	Report numbers of outcome events or summary measures over time	#13-14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#13-14
		(b) Report category boundaries when continuous variables were categorized	#13-14
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#13-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#13-14
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	#15
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	#17-18
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#20-21

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan: A nationwide population-based retrospective cohort study

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Intensive care
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, MICROBIOLOGY, INFECTIOUS DISEASES, HEALTH ECONOMICS, INTENSIVE & CRITICAL CARE

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3 **Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections**  
4 **in Taiwan: A nationwide population-based retrospective cohort study**

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27 **Running title:** Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan

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4 **35 ABSTRACT**

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7 **36 Objectives:** To estimate the clinical and economic impact of intensive care unit-acquired  
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10 **37** bloodstream infections in Taiwan.

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13 **38 Design:** Retrospective cohort study.

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16 **39 Setting:** Nationwide Taiwanese population in the National Health Insurance Research  
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19 **40** Database and the Taiwan Nosocomial Infections Surveillance (2007-2015) dataset.

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22 **41 Participants:** The first episodes of intensive care unit-acquired bloodstream infections in  
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25 **42** patients  $\geq 20$  years of age in the datasets. Propensity score-matching (1:2) of demographic  
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28 **43** data, comorbidities, and disease severity was performed to select a comparison cohort from a  
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31 **44** pool of intensive care unit patients without intensive care unit-acquired infections from the  
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34 **45** same datasets.

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37 **46 Primary and secondary outcome measures:** The 14-day mortality rate, length of  
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40 **47** hospitalization, and healthcare cost.

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43 **48 Results:** After matching, the in-hospital mortality of 14,234 patients with intensive care  
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46 **49** unit-acquired bloodstream infections was 44.23%, compared to 33.48% for 28,468 intensive  
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49 **50** care unit patients without bloodstream infections. The 14-day mortality rate was also higher  
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52 **51** in the bloodstream infections cohort (4,323, 30.37% *vs.* 6,766 deaths, 23.77%, respectively; *p*  
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55 **52**  $< 0.001$ ). Furthermore, the patients with intensive care unit-acquired bloodstream infections  
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58 **53** had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] *vs.* 10  
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4 54 days [IQR 4–21], respectively;  $p < 0.001$ ) and a higher healthcare cost (16,038 US dollars  
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7 55 [IQR 9,667–25,946] vs. 10,372 US dollars [IQR 6,289–16,932], respectively;  $p < 0.001$ ). The  
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10 56 excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars,  
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12  
13 57 respectively. Similar results were observed in subgroup analyses of various World Health  
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16 58 Organization’s priority pathogens and *Candida* spp.

19 59 **Conclusions:** Intensive care unit-acquired bloodstream infections in critically ill patients  
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22 60 were associated with increased mortality, longer hospital stays, and higher healthcare costs.  
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31 63 **Keywords:** bloodstream infection; healthcare costs; hospital stay; intensive care unit;  
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34 64 mortality.  
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4 **66 STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 8 67 1. A large number of patients obtained from Nationwide Taiwanese population from two  
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10 68 datasets in Taiwan were included.  
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13 69 2. Propensity score-matching was performed to select a comparison cohort.  
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16 70 3. The 14-day and 28-day mortality rate, length of hospitalization, and healthcare cost were  
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18 71 analyzed.  
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22 72 4. Subgroup analyses of several drug-resistant pathogens were conducted.  
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25 73 5. The retrospective design may include some unmeasurable bias.  
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## 74 BACKGROUND

75 Critically ill patients in intensive care units (ICUs) are vulnerable to various infections,  
76 and these can lead to increased morbidity, mortality, and healthcare costs. Bloodstream  
77 infections (BSIs) are one of the most common infections acquired by ICU patients. It was  
78 reported that BSIs affected approximately 7 % of patients admitted to ICUs.[1] Previous  
79 studies have shown that ICU-acquired BSIs resulted in attributable mortality of 24.8%,[2]  
80 extended hospital stays by 13.5 days[3] and the cost of treatment was approximately 12,321  
81 US dollars per case. Moreover, despite advances in medical care and the development of new  
82 therapies, the outcome of BSIs in critically ill patients is adversely affected by a greater  
83 number of vulnerable hosts and the emergence of drug-resistant pathogens.

84 Discrepancies regarding the impact of pathogens on mortality have been reported.  
85 However, worse clinical outcome and higher economic burden have been reported for  
86 patients with BSI caused by resistant pathogens.[1, 4] For example, BSIs involving  
87 third-generation cephalosporin-resistant *Enterobacteriaceae* have been shown to significantly  
88 increase mortality risk compared to BSIs involving susceptible strains.[4] Moreover,  
89 candidemia has been associated with a 4-fold increase in mortality, while *Staphylococcus*  
90 *aureus* BSIs doubled the risk of mortality.[1] Meanwhile, the clinical impact of *Enterococci*  
91 remains a controversial topic.[5-7] Therefore, it is important not only to describe the clinical  
92 and economic impact of infections, but also to decipher the impact of individual pathogens.

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4 93 Due to the limited number of cases and the complex clinical characteristics of critically ill  
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7 94 patients, previous studies have reported either clinical or economic outcomes, have focused  
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10 95 on several species of pathogens, or have assessed only a limited number of pathogens. In the  
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13 96 present study, a health insurance database and a nationwide surveillance system for  
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16 97 healthcare-associated infections were used to estimate the clinical and economic  
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19 98 consequences of ICU-acquired BSIs caused by different pathogens in a large number of  
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22 99 patients in Taiwan. In addition, the impact of individual pathogens, especially  
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25 100 antibiotic-resistant bacteria on the World Health Organization (WHO) priority list,[8] were  
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28 101 investigated.  
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## 102 **METHODS**

### 103 **Data sources**

104 Two datasets, the National Health Insurance Research Database (NHIRD) and the  
105 Taiwan Nosocomial Infection Surveillance (TNIS) dataset, were used in this study.  
106 Demographic data, diagnoses (according to the International Classification of Diseases, 9th  
107 Revision, Clinical Modification [ICD-9-CM]), procedures, and medications for patients  
108 enrolled in Taiwan's national insurance system have been collected in the NHIRD since  
109 1995.[9] In 2007, the TNIS was launched by the Taiwan Centers for Disease Control to  
110 evaluate the epidemiologic trend of healthcare-associated infections in the ICUs in Taiwan.  
111 The latter is a web-based surveillance system which collects clinical information of patients  
112 with healthcare-associated infections from the ICUs of participating hospitals. This  
113 information includes demographic data, infection foci, causative pathogens, and antimicrobial  
114 susceptibility results. Participation in TNIS is essential for the hospital accreditation in  
115 Taiwan.

116 Both datasets were deposited in a database maintained by the Health and Welfare Data  
117 Science Center, Ministry of Health and Welfare. Individual personal identification numbers  
118 were encrypted so that data from the NHIRD and TNIS datasets could be interlinked. The  
119 institutional review board of the National Health Research Institutes approved this study  
120 (EC1051207-R4).

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4 1217 122 **Study population, data collection, and propensity-score matching**

10 123 This retrospective cohort study enrolled adult patients who underwent ICU  
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13 124 hospitalization between 2007 and 2015 in Taiwan. From the entries in the TNIS database, we  
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16 125 identified all of the patients whose first episode of an ICU-acquired BSI occurred during the  
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19 126 study period. Coagulase-negative *Staphylococci* are often been identified in the ICUs but a  
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22 127 certain proportion is associated with contamination; therefore, these cases were not included  
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25 128 in our analysis. We included species that constituted > 1 % of known bloodstream pathogens  
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28 129 (Supplementary Table 1), which constituted 79.4% of all ICU-acquired BSI episodes. The  
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31 130 index date for each case was defined as the date on which a positive blood culture result was  
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34 131 obtained. The encrypted personal identification numbers of included patients were interlinked  
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37 132 with NHIRD to retrieve their demographic data, comorbidities, procedures, and medications.

40 133 For comparison, we identified ICU patients who did not have ICU-acquired infections  
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43 134 registered in TNIS database. In addition, patients with a discharge diagnosis of sepsis  
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46 135 (ICD-9-CM: 038.X, 995.91), severe sepsis (ICD-9-CM: 995.92), or septic shock (ICD-9-CM:  
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49 136 785.52) in the comparison cohort, but not in the BSI group, were also excluded. The pool of  
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52 137 comparison patients was created for selection of those with the same admission date as any  
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55 138 patient with ICU-acquired BSI. Because the comparison patients did not have index date of  
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58 139 acquisition of infection, they were assigned “pseudo-index dates” during hospitalization,

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4 140 which was selected from the index date of patients with the same day of hospitalization in the  
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7 141 BSI group. Baseline variables and those associated with ICU-acquired BSIs were first  
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10 142 selected. Propensity scores were then calculated for the likelihood of ICU-acquired BSIs by  
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13 143 multivariate logistic regression analysis. Variables were removed from the multivariable  
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16 144 model in a stepwise fashion. We used 1:2 greedy matching[10] within a caliper width equal  
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19 145 to 0.1 of the standard deviation of the logit of the propensity score. Propensity scores were  
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22 146 then calculated for the likelihood of ICU-acquired BSIs by using baseline covariates and  
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25 147 multivariate logistic regression analysis (Supplementary Table 2). Patient data from January  
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28 148 2005 were used to ensure that individuals were followed for at least two years prior to their  
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31 149 selection for this study in order to confirm comorbidities[11] and for matching purposes.  
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### 37 151 **Patient and Public Involvement**

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40 152 Patients and the public were not directly involved in the planning of this study.  
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### 46 154 **Outcome measurements**

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49 155 Clinical outcomes included in-hospital, 14-day, and 28-day mortality rate after the index  
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52 156 date/pseudo-index date. Economic outcomes included hospitalization length after the index  
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55 157 date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined  
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58 158 as the duration of hospital stay after the index date/pseudo-index date. The overall cost of  
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4 159 hospitalization was calculated. The costs were standardized and presented in values from  
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7 160 2017.  
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### 13 162 **Subgroup analysis**

16 163 To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different  
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19 164 pathogens, we performed analyses on patients infected with single pathogen. For example,  
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22 165 the impact of WHO priority bacteria and *Candida* were examined separately, as was the  
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25 166 impact of drug resistance in these bacteria. We included patients whose first episode of an  
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28 167 ICU-acquired BSI were caused by bacteria on the WHO priority list or *Candida*. Therefore,  
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31 168 the clinical and economic outcomes of patients with *Acinetobacter baumannii*, *Pseudomonas*  
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34 169 *aeruginosa*, common *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*,  
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37 170 *Enterobacter* species, and *Serratia marcescens*), *S. aureus*, *Enterococcus* species, *Candida*  
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40 171 *albicans*, and non-*albicans Candida* (*Candida tropicalis*, *Candida parapsilosis*, and *Candida*  
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43 172 *glabrata*) were determined.

46 173 The definition of multiple drug resistance (MDR) of WHO priority bacteria according to  
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49 174 the European Centre for Disease Prevention and Control (ECDC) was modified[12]  
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52 175 (Supplementary Table 3). In this study, non-susceptibility to at least one agent in at least  
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55 176 three antimicrobial categories in Gram-negative bacteria was defined as MDR. Oxacillin- and  
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58 177 vancomycin-non-susceptible *S. aureus* and vancomycin-non-susceptible *Enterococcus*  
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4 178 species were considered MDR Gram-positive bacteria.  
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### 10 180 **Sensitivity analysis**

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13 181 To avoid competing risk between mortality and length of hospitalization/healthcare cost,  
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16 182 we included patients who survived to discharge. For these patients, length of hospitalization  
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19 183 after the index date/pseudo-index date and hospitalization costs were determined.  
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### 25 185 **Statistical analysis**

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28 186 Descriptive statistics were used to examine baseline demographic and clinical  
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31 187 characteristics of the ICU patients included in this study. To account for potential  
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34 188 confounding biases among the study cohort, propensity score matching analysis was  
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37 189 performed. Propensity scores were calculated with multivariate logistic regression.  
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40 190 Standardized differences between the two groups with differences less than 0.1 were  
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43 191 confirmed in order to assess baseline characteristics. The Mann-Whitney U test was used to  
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46 192 evaluate economic outcomes and the Chi-squared test was used to evaluate mortality rate.  
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49 193 Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of  
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52 194 mortality in patients with BSI and the comparison cohort, while a generalized linear model  
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55 195 was used to calculate  $\beta$  values to estimate excess costs and length of hospitalization.  
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58 196 Variables with a  $p$ -value  $< 0.05$  were eligible for inclusion in the model.  $P$ -values less than  
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4 197 0.05 were considered statistically significant. All analyses were performed by using SAS

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7 198 statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA).

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## 200 RESULTS

201 Among 38,659 episodes of ICU-acquired BSIs registered in TNIS during the 9-year  
202 study period, 28,495 patients were identified to have their first episode of a BSI. The NHIRD  
203 included 1,638,796 patients who underwent ICU hospitalization (Figure 1). After excluding  
204 patients whose data could not be interlinked with NHIRD or who did not have target  
205 pathogens, 14,234 patients with ICU-acquired BSIs were successfully matched to 28,468  
206 ICU patients without ICU-acquired infections (1:2). The demographic and clinical  
207 characteristics of the patients with BSI and comparison cohort are presented in Table 1. The  
208 groups had standardized differences that were  $< 10\%$  for all of the continuous and  
209 dichotomous categorical variables which were examined.

210 Table 2 lists the clinical and economic outcomes of the ICU patients with BSIs and the  
211 comparison cohort. The ICU patients with BSIs suffered a higher in-hospital mortality rate  
212 (44.23% vs. 33.48%, respectively;  $p < 0.001$ ), a higher 14-day mortality rate (30.37% vs.  
213 23.77%, respectively;  $p < 0.001$ ), and a higher 28-day mortality (39.48% vs. 32.28%,  
214 respectively;  $p < 0.001$ ). Logistic regression analyses showed that the OR of in-hospital  
215 mortality for the ICU patients with BSIs was 1.67 (95% confidence interval [CI], 1.59–1.75;  
216  $p < 0.001$ ), and it was 1.42 (95% CI, 1.35–1.49;  $p < 0.001$ ) for for 14-day mortality and 1.41  
217 (95% CI, 1.34–1.47;  $p < 0.001$ ) for 28-day mortality. These significant associations were also  
218 observed in the subgroup analyses performed (Table 3).

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4 219 The ICU patients with BSIs had a longer length of hospitalization after the index date  
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7 220 (18 vs. 10 days, respectively;  $p < 0.001$ ). Moreover, on average, their hospital stay was  
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10 221 extended by 12.69 days (95% CI, 11.92–13.47;  $p < 0.001$ ). The subgroup analyses performed  
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13 222 (Table 4) showed that all of the causative pathogens shared a similar trend. Compared with  
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16 223 the patients without ICU-acquired infections, the duration of hospitalization after the index  
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19 224 date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp.  
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22 225 was longer. In addition, hospitalization costs of the ICU patients with BSIs were higher  
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25 226 (16,038 vs. 10,372, respectively;  $p < 0.001$ ) (Table 2), with the excess cost being 7,669 US  
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28 227 dollars per patient (95% CI, 7,380–7,958;  $p < 0.001$ ). Table 4 presents the higher costs  
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31 228 associated with each of the various causative pathogen.

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34 229 For the ICU patients with BSIs who survived to discharge, their length of hospitalization  
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37 230 and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively,  
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40 231 (Supplementary Table 4) compared to the survivors without ICU-acquired infections.  
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4 232 **DISCUSSION**  
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7 233 This study demonstrated that ICU patients with BSIs in Taiwan had significantly worse  
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10 234 clinical outcomes and higher economic burden than ICU patients without ICU-acquired  
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13 235 infections from the same population. For example, the patients with BSI exhibited 1.67-,  
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16 236 1.42-, and 1.41-fold increases in in-hospital, 14-day, and 28-day mortality rates, respectively.  
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19 237 Per case, the patients with BSI had an excess hospital stay of 12.69 days and cost of 7,669 US  
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22 238 dollars. Furthermore, a similar clinical and economic impact was observed among all of the  
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25 239 causative pathogens examined.  
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28 240 BSIs have been associated with higher mortality and morbidity, contingent on the  
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31 241 causative pathogen involved.[1,3,13-16] For example, worse clinical outcomes have been  
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34 242 reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S.*  
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37 243 *aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] In contrast,  
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40 244 controversial results have been obtained regarding the mortality of patients affected by  
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43 245 enterococcal bacteremia. While some authors have argued that *Enterococcus* spp. represents  
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46 246 a low virulence pathogen[1] and is not associated with increased mortality unless in the  
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49 247 presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] In  
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52 248 the present study, significantly higher mortality was observed for patients with enterococcal  
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55 249 bacteremia, and this may be due to vulnerability of the hosts examined, increased resistance,  
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58 250 and a larger study population.  
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4 251 The high healthcare burden of BSIs reported in previous literature[3,13,20] and in the  
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7 252 present study underscores the importance of preventing ICU-acquired BSIs by infection  
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10 253 control measurements. Furthermore, the results of these studies help to assess cost  
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13 254 effectiveness of infection control measurements in the process of policy-making. For example,  
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16 255 patients with ICU-acquired BSIs during the 9-year period cost Taiwan an estimated 297  
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19 256 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate  
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22 257 of infection by 10%[21] would translate into a savings of 30 million US dollars and 49,213  
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25 258 patient-days saved.

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28 259 Drug resistance has been found to be correlated with higher medical costs due to the  
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31 260 need for second-line antimicrobials for treatment, as well as additional diagnostic and  
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34 261 treatment tools.[22, 23] In the present study, the costs for MDR bacteria included extra 84  
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37 262 million US dollars and 140,043 days over nine years (Supplementary Table 5). However, cost  
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40 263 differences between susceptible and resistant strains were not determined in the present study.  
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43 264 Drug-susceptible strains were not included as controls due to differences in testing methods,  
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46 265 drugs, and breakpoints for these strains which could lead to mis-assignments of drug-resistant  
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49 266 pathogens as susceptible pathogens.

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52 267 Candidemia poses a great threat to ICU patients due to its excessive medical  
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55 268 burdens,[16,18,20] and *C. albicans* is the most common pathogen. However, in some  
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58 269 countries, the prevalence of non-*albicans* *Candida* exceeds that of *C. albicans*.[24] For those  
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4 270 infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization  
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7 271 stays, and increased hospital costs have been described;[25-27] although other studies have  
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10 272 reported contradicting findings.[28,29] These discrepancies may be due to host factors and  
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13 273 differences in the virulence and resistance patterns[24] of non-*albicans Candida*. In the  
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16 274 present study, the crude 14-day and in-hospital mortality rates of 951 patients infected with *C.*  
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19 275 *albicans* were 37.96% and 55.94%, respectively. In comparison, among 703 patients infected  
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22 276 with non-*albicans Candida*, these rates were 34.99% and 53.06%, respectively. While the  
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25 277 hospital costs and length of stay were higher in the non-*albicans Candida* group compared to  
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28 278 the *C. albicans* group, the 95% CI overlapped for the two groups (Table 4). These data  
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31 279 suggested that the clinical and economic outcomes of these two groups did not greatly differ.  
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34 280 However, the present study was not designed to specifically compare the outcomes of those  
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37 281 infected with *C. albicans* versus non-*albicans Candida*. Therefore, additional studies with a  
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40 282 larger number of patients, adjustment for host factors, and consideration of antifungal drugs,  
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43 283 incubation time, and treatment duration are needed to clarify the impact of each *Candida*  
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46 284 species.

49 285 The large number of patients examined in this study and the use of propensity score  
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52 286 matching represent two major strengths of the present study. These aspects also allowed the  
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55 287 impact of each pathogen group to be discerned. However, there were also several limitations  
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58 288 associated with the present study which merit discussion. First, the exact cost after the index  
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4 289 date could not be retrieved from the NHIRD. Therefore, the high total cost shown in this  
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7 290 study may be due to costs incurred prior to the onset of a BSI. It is possible that matching of  
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10 291 the duration before the index date and comorbidity may have reduced overestimations of  
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13 292 healthcare costs due to time-dependent bias.[30] Second, confounding factors associated with  
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16 293 clinical impact, such as APACHE II or Pitt Bacteremia scores, were not included in this study.  
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19 294 Instead, other clinical risk factors (Charlson Comorbidity Index score, number of organ  
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22 295 failures, use of inotropic agents, and receipt of invasive procedures) were incorporated in our  
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25 296 model. Third, our study is inherently limited by its retrospective design, which includes a  
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28 297 dependence on the accuracy of the ICD codes used and unmeasurable bias.[31,32] Fourth, the  
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31 298 prolonged hospitalization may have been due to a change in patient management in response  
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34 299 to a BSI, rather than increased morbidity due to a BSI.[15] In addition, the number of  
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37 300 participating hospitals varied during study period and therefore was considered in propensity  
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40 301 score matching. Finally, the collection of personal identification numbers is not mandatory in  
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43 302 TNIS, which resulted in failure of interlink (missing data). Their impact on the outcome was  
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## 305 **CONCLUSIONS**

306 ICU-acquired BSIs have a negative clinical and economic impact on affected patients  
307 regardless of the causative pathogens involved. Awareness of these negative affects is

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308 important for promoting infection control measurements and for policy-making.

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4 **310 LIST OF ABBREVIATIONS**  
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7 311 BSI = bloodstream infection;  
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10 312 CI = confidence interval;  
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13 313 ECDC = European Centre for Disease Prevention and Control;  
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16 314 ICD-9-CM = international classification of diseases, 9th revision, clinical modification;  
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19 315 ICU = intensive care unit;  
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22 316 IQR = interquartile range;  
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25 317 MDR = multiple drug resistance;  
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28 318 NHIRD = National Health Insurance Research Database;  
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31 319 OR = odds ratio;  
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34 320 TNIS = Taiwan Nosocomial Infection Surveillance;  
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37 321 WHO = World Health Organization;  
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4 **323 DECLARATIONS**

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7 **324 Ethics approval and consent to participate**

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10 325 The institutional review board of the National Health Research Institutes approved this study  
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13 326 (EC1051207-R4).  
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19 **328 Consent for publication**

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22 329 Not applicable.  
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28 **331 Availability of data and materials**

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31 332 The data that support the findings of this study are available from Ministry of Health and

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34 333 Welfare, Taiwan but restrictions apply to the availability of these data, which were used

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37 334 under license for the current study, and so are not publicly available. Data are however

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40 335 available from the authors upon reasonable request and with permission of Ministry of Health

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43 336 and Welfare, Taiwan.  
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52 339 The authors declare that they have no competing interests.  
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23  
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26  
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28 350 Data curation: YTC, CAH, SCK

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30  
31 351 Formal analysis: SMS, YTC

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40 354 Methodology: YTC, CAH, SCK

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43 355 Project administration: YCW, CAH, SCK

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46 356 Resources: YTC, CAH, SCK

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49 357 Software: SMS, YTC

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52 358 Supervision: SMS, YTC

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55 359 Validation: CAH, SCK

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58 360 Visualization: YCW, SMS

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369 **REFERENCES**

- 370 1. Prowle JR, Echeverri JE, Ligabo EV, et al. Acquired bloodstream infection in the  
371 intensive care unit: incidence and attributable mortality. *Crit Care* 2011; **15**: R100.
- 372 2. Garrouste-Orgeas M, Timsit JF, Tafflet M, et al. Excess risk of death from intensive  
373 care unit-acquired nosocomial bloodstream infections: a re-appraisal. *Clin Infect Dis*  
374 2006; **42**: 1118-26.
- 375 3. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired  
376 bloodstream infections. *J Hosp Infect* 2006; **63**: 124-32.
- 377 4. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of  
378 bloodstream infections caused by antimicrobial-susceptible and non-susceptible  
379 Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011:  
380 a multicentre retrospective cohort study. *Euro Surveill* 2016; **21**: pii=30319.
- 381 5. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to  
382 nosocomial enterococcal bacteremia: a controlled study. *Am J Infect Control* 1989;  
383 **17**: 323-9.
- 384 6. Ong DS, Bonten MJ, Safdari K, et al. Epidemiology, management, and risk-adjusted  
385 mortality of ICU-acquired enterococcal bacteremia. *Clin Infect Dis* 2015; **61**:  
386 1413-20.
- 387 7. Kramer TS, Remschmidt C, Werner S, et al. The importance of adjusting for

- 1  
2  
3  
4 388 Enterococcus species when assessing the burden of vancomycin resistance: a cohort  
5  
6  
7 389 study including over 1000 cases of enterococcal bloodstream infections. *Antimicrob*  
8  
9  
10 390 *Resist Infect Control* 2018; **7**: 133.  
11  
12  
13 391 8. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of  
14  
15  
16 392 new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis.  
17  
18  
19 393 *Lancet Infect Dis* 2018; **18**: 318-27.  
20  
21  
22 394 9. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan.  
23  
24  
25 395 *London J Prim Care (Abingdon)* 2010; **3**: 115-9.  
26  
27  
28 396 10. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in  
29  
30  
31 397 Ontario. *N Engl J Med* 2007; **357**: 1393-402.  
32  
33  
34 398 11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with  
35  
36  
37 399 ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-9.  
38  
39  
40 400 12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively  
41  
42  
43 401 drug-resistant and pandrug-resistant bacteria: an international expert proposal for  
44  
45  
46 402 interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**:  
47  
48  
49 403 268-81.  
50  
51  
52 404 13. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill  
53  
54  
55 405 patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;  
56  
57  
58 406 **271**: 1598-601.  
59  
60

- 1  
2  
3  
4 407 14. Laupland KB, Zygun DA, Davies HD, et al. Population-based assessment of intensive  
5  
6  
7 408 care unit-acquired bloodstream infections in adults: incidence, risk factors, and  
8  
9  
10 409 associated mortality rate. *Crit Care Med* 2002; **30**: 2462-7.  
11  
12  
13 410 15. Barnett AG, Page K, Campbell M, et al. The increased risks of death and extra lengths  
14  
15  
16 411 of hospital and ICU stay from hospital-acquired bloodstream infections: a  
17  
18  
19 412 case-control study. *BMJ Open* 2013; **3**: e003587.  
20  
21  
22 413 16. Marra AR, Camargo LF, Pignatari AC, et al. Nosocomial bloodstream infections in  
23  
24  
25 414 Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide  
26  
27  
28 415 surveillance study. *J Clin Microbiol* 2011; **49**: 1866-71.  
29  
30  
31 416 17. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in  
32  
33  
34 417 patients with *Acinetobacter baumannii* infection: systematic review and  
35  
36  
37 418 meta-analysis. *Clin Microbiol Infect* 2014; **20**: 416-23.  
38  
39  
40 419 18. Schwab F, Geffers C, Behnke M, et al. ICU mortality following ICU-acquired  
41  
42  
43 420 primary bloodstream infections according to the type of pathogen: a prospective  
44  
45  
46 421 cohort study in 937 Germany ICUs (2006-2015). *PloS One* 2018; **13**: e0194210.  
47  
48  
49 422 19. Caballero-Granado FJ, Becerril B, Cuberos L, et al. Attributable mortality rate and  
50  
51  
52 423 duration of hospital stay associated with enterococcal bacteremia. *Clin Infect Dis*  
53  
54  
55 424 2001; **32**: 587-94.  
56  
57  
58 425 20. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically  
59  
60

- 1  
2  
3  
4 426 ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis*  
5  
6  
7 427 2005; **41**: 1591-8.  
8  
9  
10 428 21. Tseng SH, Lee CM, Lin TY, et al. Combating antimicrobial resistance: antimicrobial  
11  
12  
13 429 stewardship program in Taiwan. *J Microbiol Immunol Infect* 2012; **45**: 79-89.  
14  
15  
16 430 22. Howard D, Cordell R, McGowan JE, Jr., et al. Measuring the economic costs of  
17  
18  
19 431 antimicrobial resistance in hospital settings: summary of the Centers for Disease  
20  
21  
22 432 Control and Prevention-Emory Workshop. *Clin Infect Dis* 2001; **33**: 1573-8.  
23  
24  
25 433 23. Mauldin PD, Salgado CD, Hansen IS, et al. Attributable hospital cost and length of  
26  
27  
28 434 stay associated with health care-associated infections caused by antibiotic-resistant  
29  
30  
31 435 gram-negative bacteria. *Antimicrob Agents Chemother* 2010; **54**: 109-15.  
32  
33  
34 436 24. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia  
35  
36  
37 437 in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin*  
38  
39  
40 438 *Infect Dis* 2009; **48**: 1695-703.  
41  
42  
43 439 25. Dimopoulos G, Ntziora F, Rachiotis G, et al. *Candida albicans* versus non-*albicans*  
44  
45  
46 440 intensive care unit-acquired bloodstream infections: differences in risk factors and  
47  
48  
49 441 outcome. *Anesth Analg* 2008; **106**: 523-9.  
50  
51  
52 442 26. Moran C, Grussemyer CA, Spalding JR, et al. Comparison of costs, length of stay,  
53  
54  
55 443 and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream  
56  
57  
58 444 infections. *Am J Infect Control* 2010; **38**: 78-80.  
59  
60

- 1  
2  
3  
4 445 27. Gong X, Luan T, Wu X, et al. Invasive candidiasis in intensive care units in China:  
5  
6  
7 446 risk factors and prognoses of *Candida albicans* and non-*albicans* *Candida* infections.  
8  
9  
10 447 *Am J Infect Control* 2016; **44**: e59-63.  
11  
12  
13 448 28. Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia  
14  
15  
16 449 in 3648 patients: data from the prospective antifungal therapy (PATH Alliance®)  
17  
18  
19 450 registry, 2004-2008. *Diagn Microbiol Infect Dis* 2012; **74**: 323-31.  
20  
21  
22 451 29. Barchiesi F, Orsetti E, Gesuita R, et al.; Candidemia Study Group. Epidemiology,  
23  
24  
25 452 clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy  
26  
27  
28 453 from 2010 to 2014. *Infection* 2016; **44**: 205-13.  
29  
30  
31 454 30. Nelson RE, Samore MH, Jones M, et al. Reducing time-dependent bias in estimates of  
32  
33  
34 455 the attributable cost of health care-associated Methicillin-resistant *Staphylococcus*  
35  
36  
37 456 *aureus* infections: a comparison of three estimation strategies. *Med Care* 2015; **53**:  
38  
39  
40 457 827-34.  
41  
42  
43 458 31. Kuo SC, Shih SM, Hsieh LY, et al. Antibiotic restriction policy paradoxically  
44  
45  
46 459 increased private drug consumptions outside Taiwan's National Health Insurance. *J*  
47  
48  
49 460 *Antimicrob Chemother* 2017; **72**: 1544-5.  
50  
51  
52 461 32. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative  
53  
54  
55 462 data. *JAMA* 2012; **307**: 1433-5.  
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464 **Table 1. Characteristics of the intensive care unit patients with bloodstream infections**  
 465 **and the matched comparison cohort.**

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (63.03%)	17,861 (62.74%)	0.006
Age, years, mean (SD)	65.12 (21.62)	65.08 (20.60)	0.002
Length of stay before index date/ pseudo-index date, days, mean (SD)	15.69 (12.14)	15.29 (11.96)	0.033

## Monthly income, USD

Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001

## Urbanization level

1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002

## Hospital level

Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007

## Charlson Comorbidity Index

score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019

## Comorbidities

Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005
Hypertension	525 (3.69%)	1,124 (3.95%)	0.014
Myocardial infarction	2,532 (17.79%)	5,173 (18.17%)	0.01



Heart failure	742 (5.21%)	1,509 (5.3%)	0.004
Peripheral vascular disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Liver disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Chronic kidney disease	2,766 (19.43%)	5,683 (19.96%)	0.013
Dyslipidemia	2,753 (19.34%)	5,635 (19.79%)	0.011
Cancer	4,840 (34%)	9,642 (33.87%)	0.003
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (4.86%)	0.074
Use of inotropic agents	11,398 (80.08%)	22,858 (80.29%)	0.005
Use of steroid	9 (0.06%)	20 (0.07%)	0.003
Use of ventilator	12,493 (87.77%)	25,075 (88.08%)	0.01
Use of ventilator (> 3 days)	11,668 (81.97%)	23,458 (82.4%)	0.011
Emergent renal replacement therapy	2615 (18.37%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

466 Abbreviations: BSI = bloodstream infection; SD = standard deviation.

467 **Table 2. Clinical and economic outcomes among patients with bloodstream infections and the matched comparison cohort.**

Outcomes	Full cohort			Matched cohort		
	ICU patients	Comparison	<i>P</i> -value	ICU patients	Comparison	<i>P</i> -value
	with BSI	cohort		with BSI	cohort	
No. of patients	17,834	713,518		14,234	28,468	
Clinical outcomes						
In-hospital mortality, n (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.2%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.3%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.4%)	9,189 (32.28%)	< 0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 30)	10 (4, 21)	< 0.0001

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	(IQR)					
Cost of hospitalization (USD) <sup>a</sup> , median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,246)	(6,289, 16,932)	

468 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

469 <sup>a</sup>The costs are standardized and presented as the values in 2017.

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470 **Table 3. Clinical outcomes for the various pathogen groups.**

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
<i>Acinetobacter baumannii</i> (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
<i>Pseudomonas aeruginosa</i> (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae <sup>b</sup> (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
<i>Staphylococcus aureus</i> (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
<i>Enterococcus species</i> <sup>c</sup> (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
<i>Candida albicans</i> (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non- <i>albicans Candida</i> <sup>d</sup> (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

471 Abbreviations: MDR = multiple drug resistance.

472 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this  
473 analysis.

474 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*,  
475 *Enterobacter aerogenes*, and *Serratia marcescens*.

476 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other

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477 *Enterococcus species.*

478 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida*

479 *glabrata.*

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482 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,372 (5,500, 7,184)
<i>Acinetobacter baumannii</i>	9.4 (7.65, 11.14)	6,777 (5,823, 7,632)
<i>Pseudomonas aeruginosa</i>	10.01 (7.83, 12.19)	6,791 (5,609, 7,913)
Enterobacteriaceae <sup>b</sup>	15.05 (13.33, 16.76)	7,474 (6,881, 8,007)
<i>Staphylococcus aureus</i>	14.72 (12.63, 16.81)	5,271 (4,528, 5,894)
<i>Enterococcus species</i> <sup>c</sup>	10.66 (7.85, 13.48)	7,279 (6,305, 8,132)
<i>Candida albicans</i>	11.37 (8.82, 13.92)	8,698 (7,512, 9,864)

Non- <i>albicans Candida</i> <sup>d</sup>	15.13 (11.77, 18.49)	11,446 (10,025, 12,927)
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483 Abbreviations: MDR = multiple drug resistance.

484 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this analysis.

485 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Serratia marcescens*.

486 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

487 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

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4 491 **FIGURE LEGENDS**  
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7 492 **Figure 1. Flow diagram of the study design.**  
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16 495 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National  
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4 **503 SUPPLEMENTARY FILES:**  
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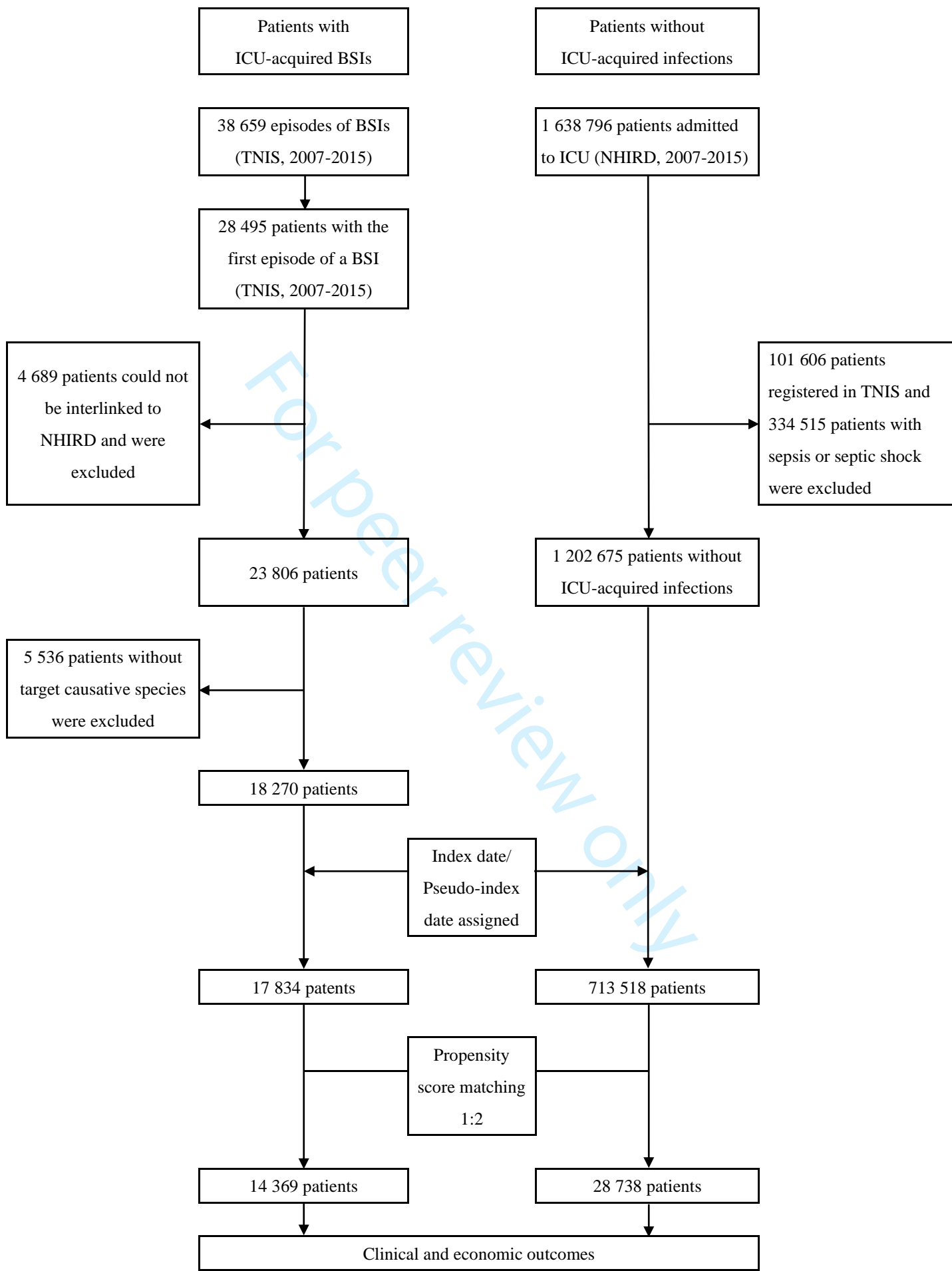
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7 504 Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before  
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10 505 enrollment and the number of patients infected after matching.

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13 506 Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched  
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16 507 comparison cohort.

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19 508 Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

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22 509 Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the  
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28 511 Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.  
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1 **Supplementary Table 1. The number of episodes of intensive care unit-acquired**  
 2 **bloodstream infections caused by common pathogens before enrollment and the number**  
 3 **of patients infected after matching.**

	No. of BSI episodes before enrollment <sup>a</sup>	No. of patients after matching <sup>b</sup>
<i>Acinetobacter baumannii</i>	5,214	1,761
<i>Staphylococcus aureus</i>	4,382	1,721
<i>Klebsiella pneumoniae</i>	3,965	1,357
<i>Pseudomonas aeruginosa</i>	2,619	853
<i>Candida albicans</i>	2,554	951
<i>Escherichia coli</i>	2,287	843
<i>Enterobacter cloacae</i>	1,982	746
<i>Enterococcus faecium</i>	1,950	647
<i>Stenotrophomonas maltophilia</i>	1,599	454
<i>Enterococcus faecalis</i>	1,427	419
<i>Serratia marcescens</i>	1,239	439
<i>Candida tropicalis</i>	890	329
<i>Burkholderia cepacia</i>	808	251
Other <i>Enterococcus</i> species <sup>c</sup>	688	211
<i>Elizabethkingia meningoseptica</i>	659	173
<i>Chryseobacterium indologenes</i>	553	152
<i>Candida parapsilosis</i>	534	177
<i>Candida glabrata</i>	461	197
<i>Enterobacter aerogenes</i>	419	163

4 Abbreviations: BSI= bloodstream infection.

5 <sup>a</sup>The number of episodes of bloodstream infections with known pathogens was 38,659.

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3 6 Coagulase-negative staphylococci was excluded from analyses due to possibility of  
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5 7 contamination. One episode may have multiple pathogens. There were 30,697 episodes of  
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7 8 bloodstream infections caused by the pathogens listed above.

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9 9 <sup>b</sup>The number of patients enrolled case was 14,234 (Table 1) but only patients with  
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11 10 bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it  
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13 11 was 11,844. There were 2,390 patients with bloodstream infections caused by multiple  
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15 12 pathogens.

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17 13 <sup>c</sup>*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis*.  
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15 **Supplementary Table 2. Propensity score model results of probability of bloodstream**  
 16 **infections among intensive care unit patients and matched comparison cohort.**

Parameter	Estimate	Odds ratios	95% Confidence interval		P-value
			Lower	Upper	
			Age, years	-0.0014	
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

Dependent	--	1.000	--	--	--
<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
Urbanization level					
1 (urban)		1.000			
2	0.0093	1.0094	0.9516	1.0706	0.7560
3	-0.0006	0.9994	0.9293	1.0748	0.9872
4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
Hospital level					
Level I (Medical center)	--	1.000	--	--	--
Level II (Regional hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
Charlson Comorbidity Index score					
0	--	1.000	--	--	--
1	0.1421	1.1527	1.0681	1.2439	0.0003
2	0.2932	1.3407	1.2390	1.4508	<0.0001
≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
Comorbidities					
Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292

Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

18 **Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and**  
 19 **antimicrobial agents used to define drug resistance.**

Pathogens	Antimicrobial categories	Antimicrobial agents	
<i>Acinetobacter baumannii</i> <sup>a</sup>	Aminoglycosides	Gentamicin	
		Tobramycin	
		Amikacin	
		Netilmicin	
	Carbapenems	Imipenem	
		Meropenem	
		Doripenem	
	Fluoroquinolones	Ciprofloxacin	
		Levofloxacin	
		Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid	
		Extended-spectrum cephalosporins	Cefotaxime
			Cefepime
			Cefpirome
<i>Pseudomonas aeruginosa</i> <sup>a</sup>	Aminoglycosides	Ceftazidime	
		Ceftriaxone	
		Gentamicin	
		Tobramycin	
	Carbapenems	Amikacin	
		Meropenem	



		Doripenem
		Ciprofloxacin
	Fluoroquinolones	Levofloxacin
		Piperacillin-tazobactam
	Antipseudomonal penicillins + $\beta$ -lactamase inhibitors	Ticarcillin-clavulanic acid
		Cefepime
	Antipseudomonal cephalosporins	Cefpirome
		Ceftazidime
		Gentamicin
		Tobramycin
	Aminoglycosides	Amikacin
		Netilmicin
		Imipenem
		Meropenem
	Carbapenems	Doripenem
		Ertapenem
		Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + $\beta$ -lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
		Cefotaxime
		Cefepime
	Extended-spectrum cephalosporins	Cefpirome
		Ceftazidime
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33	<i>Enterobacteriaceae</i> <sup>a</sup>	
34	( <i>Escherichia coli</i> ,	
35	<i>Klebsiella pneumoniae</i> ,	
36	<i>Enterobacter cloacae</i>	
37	<i>Enterobacter</i>	
38	<i>aerogenes</i> , or <i>Serratia</i>	
39	<i>marcescens</i> )	
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		Ceftriaxone
	Glycopeptides	Vancomycin
<i>Staphylococcus aureus</i> <sup>b</sup>	$\beta$ -lactamase-resistant penicillins	Oxacillin
<i>Enterococcus faecium</i> ,		
<i>Enterococcus faecalis</i> ,	Glycopeptides	Vancomycin
or other <i>Enterococcus</i>		
<i>species</i> <sup>b</sup>		

<sup>a</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories.

<sup>b</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent.

23 **Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to**  
 24 **the discharge.<sup>a</sup>**

		25
<b>Clinical outcomes</b>	<b>Excess costs or length of hospitalization (95% Confidence interval)<sup>b</sup></b>	<b>P-value</b>
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	< 0.0001 <sub>29</sub>
Cost of hospitalization, USD	8,871 (8,475, 9,268)	< 0.0001 <sub>30</sub>
		31

32 <sup>a</sup>A total of 7,939 of patients with intensive care unit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

33 <sup>b</sup>Adjusted imbalanced variables in Table 1.

34

35 **Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.**

36

9-year excessive hospitalization or healthcare cost		
Pathogen groups	Length of hospitalization after the index date	Cost of hospitalization (USD) <sup>b, c</sup>
(Numbers of patients) <sup>a</sup>	(days) <sup>b</sup>	
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
<i>Acinetobacter baumannii</i> (5,214)	66,374	40,003,372
<i>Pseudomonas aeruginosa</i> (2,619)	33,340	20,093,754
<i>Enterobacteriaceae</i> <sup>d</sup> (9,486)	120,757	72,779,438
<i>Staphylococcus aureus</i> (4,382)	55,783	33,620,019
<i>Enterococcus species</i> <sup>e</sup> (4,045)	51,493	31,034,454
<i>Candida albicans</i> (2,554)	32,512	19,595,054
<i>Non-albicans Candida</i> <sup>f</sup> (1,872)	23,831	14,362,546

37 Abbreviations: MDR= multiple drug resistance.

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3 38 <sup>a</sup>The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The  
4  
5 39 inclusion and exclusion criteria in the method section were not applied in this Table (see Figure 1).

6  
7  
8 40 <sup>b</sup>The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s)  
9  
10 41 and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was  
11  
12 42 difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average  
13  
14 43 hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was  
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17 44 that in matched control group.

18  
19 45  $Ave_{Hospitalization}$  per case = [(sum of hospitalization length)/the number of patients].

20  
21 46 Excessive  $Ave_{Hospitalization}$  per person = ( $Ave_{Hospitalization}$  in bloodstream infection group) - ( $Ave_{Hospitalization}$  in comparison group).

22  
23 47 Total excessive hospitalization length over 9 years = (excessive  $Ave_{Hospitalization}$  per person) × (total number of episodes over 9 years)

24  
25 48 The 9-year excessive healthcare cost was calculated similarly.

26  
27 49 <sup>c</sup>The costs are standardized and presented the values in 2017.

28  
29 50 <sup>d</sup>*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa*, and *Serratia*  
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32 51 *marcescens*.

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34 52 <sup>e</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

35  
36 53 <sup>f</sup>*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	#1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(b) For matched studies, give matching criteria and number of exposed and unexposed	#9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	#11-12
		(b) Describe any methods used to examine subgroups and interactions	#10-11
		(c) Explain how missing data were addressed	#8-10
		(d) If applicable, explain how loss to follow-up was addressed	#8-10
		(e) Describe any sensitivity analyses	#11
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#13
		(b) Give reasons for non-participation at each stage	#13
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#13-14
		(b) Indicate number of participants with missing data for each variable of interest	#13-14
		(c) Summarise follow-up time (eg, average and total amount)	#13-14
Outcome data	15*	Report numbers of outcome events or summary measures over time	#13-14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#13-14
		(b) Report category boundaries when continuous variables were categorized	#13-14
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#13-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#13-14
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	#15
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	#17-18
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#20-21

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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# BMJ Open

## Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan: A nationwide population-based retrospective cohort study

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3 **Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections**  
4 **in Taiwan: A nationwide population-based retrospective cohort study**

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27 **Running title:** Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan

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31 **Word count:**

32 **Abstract: 269 words**

33 **Text: 2692 words**

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4 35 **ABSTRACT**

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7 36 **Objectives:** To estimate the clinical and economic impact of intensive care unit-acquired  
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10 37 bloodstream infections in Taiwan.

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13 38 **Design:** Retrospective cohort study.

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16 39 **Setting:** Nationwide Taiwanese population in the National Health Insurance Research  
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19 40 Database and the Taiwan Nosocomial Infections Surveillance (2007-2015) dataset.

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22 41 **Participants:** The first episodes of intensive care unit-acquired bloodstream infections in  
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25 42 patients  $\geq 20$  years of age in the datasets. Propensity score-matching (1:2) of demographic  
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28 43 data, comorbidities, and disease severity was performed to select a comparison cohort from a  
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31 44 pool of intensive care unit patients without intensive care unit-acquired infections from the  
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34 45 same datasets.

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37 46 **Primary and secondary outcome measures:** The mortality rate, length of hospitalization,  
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40 47 and healthcare cost.

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43 48 **Results:** After matching, the in-hospital mortality of 14,234 patients with intensive care  
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46 49 unit-acquired bloodstream infections was 44.23%, compared to 33.48% for 28,468 intensive  
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49 50 care unit patients without bloodstream infections. The 14-day mortality rate was also higher  
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53 51 in the bloodstream infections cohort (4,323, 30.37% vs. 6,766 deaths, 23.77%, respectively;  $p$   
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55 52  $< 0.001$ ). Furthermore, the patients with intensive care unit-acquired bloodstream infections  
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58 53 had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] vs. 10  
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4 54 days [IQR 4–21], respectively;  $p < 0.001$ ) and a higher healthcare cost (16,038 US dollars  
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7 55 [IQR 9,667–25,946] vs. 10,372 US dollars [IQR 6,289–16,932], respectively;  $p < 0.001$ ). The  
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10 56 excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars,  
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13 57 respectively. Similar results were observed in subgroup analyses of various World Health  
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16 58 Organization's priority pathogens and *Candida* spp.

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19 59 **Conclusions:** Intensive care unit-acquired bloodstream infections in critically ill patients  
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22 60 were associated with increased mortality, longer hospital stays, and higher healthcare costs.  
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31 63 **Keywords:** bloodstream infection; healthcare costs; hospital stay; intensive care unit;  
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34 64 mortality.  
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4 **66 STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 8 67 1. A large number of patients obtained from Nationwide Taiwanese population from two  
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10 68 datasets in Taiwan were included.  
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13 69 2. Propensity score-matching was performed to select a comparison cohort.  
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16 70 3. The mortality rate, length of hospitalization, and healthcare cost were analyzed.  
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19 71 4. Subgroup analyses of several drug-resistant pathogens were conducted.  
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22 72 5. The retrospective design may include some unmeasurable bias.  
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## 73 BACKGROUND

74 Critically ill patients in intensive care units (ICUs) are vulnerable to various infections,  
75 and these can lead to increased morbidity, mortality, and healthcare costs. Bloodstream  
76 infections (BSIs) are one of the most common infections acquired by ICU patients. It was  
77 reported that BSIs affected approximately 7 % of patients admitted to ICUs.[1] Previous  
78 studies have shown that ICU-acquired BSIs resulted in attributable mortality of 24.8%,[2]  
79 extended hospital stays by 13.5 days[3] and the cost of treatment was approximately 12,321  
80 US dollars per case. Moreover, despite advances in medical care and the development of new  
81 therapies, the outcome of BSIs in critically ill patients is adversely affected by a greater  
82 number of vulnerable hosts and the emergence of drug-resistant pathogens.

83 Discrepancies regarding the impact of pathogens on mortality have been reported.  
84 However, worse clinical outcome and higher economic burden have been reported for  
85 patients with BSI caused by resistant pathogens.[1, 4] For example, BSIs involving  
86 third-generation cephalosporin-resistant *Enterobacteriaceae* have been shown to significantly  
87 increase mortality risk compared to BSIs involving susceptible strains.[4] Moreover,  
88 candidemia has been associated with a 4-fold increase in mortality, while *Staphylococcus*  
89 *aureus* BSIs doubled the risk of mortality.[1] Meanwhile, the clinical impact of *Enterococci*  
90 remains a controversial topic.[5-7] Therefore, it is important not only to describe the clinical  
91 and economic impact of infections, but also to decipher the impact of individual pathogens.

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4 92 Due to the limited number of cases and the complex clinical characteristics of critically ill  
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7 93 patients, previous studies have reported either clinical or economic outcomes, have focused  
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10 94 on several species of pathogens, or have assessed only a limited number of pathogens. In the  
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13 95 present study, a health insurance database and a nationwide surveillance system for  
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16 96 healthcare-associated infections were used to estimate the clinical and economic  
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19 97 consequences of ICU-acquired BSIs caused by different pathogens in a large number of  
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22 98 patients in Taiwan. In addition, the impact of individual pathogens, especially  
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25 99 antibiotic-resistant bacteria on the World Health Organization (WHO) priority list,[8] were  
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28 100 investigated.



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4 **101 METHODS**

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7 **102 Data sources**

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10 103 Two datasets, the National Health Insurance Research Database (NHIRD) and the  
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13 104 Taiwan Nosocomial Infection Surveillance (TNIS) dataset, were used in this study.  
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16 105 Demographic data, diagnoses (according to the International Classification of Diseases, 9th  
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19 106 Revision, Clinical Modification [ICD-9-CM]), procedures, and medications for patients  
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22 107 enrolled in Taiwan's national insurance system have been collected in the NHIRD since  
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25 108 1995.[9] In 2007, the TNIS was launched by the Taiwan Centers for Disease Control to  
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28 109 evaluate the epidemiologic trend of healthcare-associated infections in the ICUs in Taiwan.  
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31 110 The latter is a web-based surveillance system which collects clinical information of patients  
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34 111 with healthcare-associated infections from the ICUs of participating hospitals. This  
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37 112 information includes demographic data, infection foci, causative pathogens, and antimicrobial  
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40 113 susceptibility results. Participation in TNIS is essential for the hospital accreditation in  
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46 115 Both datasets were deposited in a database maintained by the Health and Welfare Data  
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49 116 Science Center, Ministry of Health and Welfare. Individual personal identification numbers  
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52 117 were encrypted so that data from the NHIRD and TNIS datasets could be interlinked. The  
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55 118 institutional review board of the National Health Research Institutes approved this study  
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58 119 (EC1051207-R4).  
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4 1207 121 **Study population, data collection, and propensity-score matching**

122 This retrospective cohort study enrolled adult patients who underwent ICU  
123 hospitalization between 2007 and 2015 in Taiwan. From the entries in the TNIS database, we  
124 identified all of the patients whose first episode of an ICU-acquired BSI occurred during the  
125 study period. Coagulase-negative *Staphylococci* are often identified in the ICUs but a certain  
126 proportion is associated with contamination; therefore, these cases were not included in our  
127 analysis. We included species that constituted > 1 % of known bloodstream pathogens  
128 (Supplementary Table 1), which constituted 79.4% of all ICU-acquired BSI episodes. The  
129 index date for each case was defined as the date on which a positive blood culture result was  
130 obtained. The encrypted personal identification numbers of included patients were interlinked  
131 with NHIRD to retrieve their demographic data, comorbidities, procedures, and medications.

132 For comparison, we identified ICU patients who did not have ICU-acquired infections  
133 registered in TNIS database. In addition, patients with a discharge diagnosis of sepsis  
134 (ICD-9-CM: 038.X, 995.91), severe sepsis (ICD-9-CM: 995.92), or septic shock (ICD-9-CM:  
135 785.52) in the comparison cohort, but not in the BSI group, were also excluded. The pool of  
136 comparison patients was created for selection of those with the same admission date as any  
137 patient with ICU-acquired BSI. Because the comparison patients did not have index date of  
138 acquisition of infection, they were assigned “pseudo-index dates” during hospitalization,

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4 139 which was selected from the index date of patients with the same day of hospitalization in the  
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7 140 BSI group. Baseline variables and those associated with ICU-acquired BSIs were first  
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10 141 selected. Propensity scores were then calculated for the likelihood of ICU-acquired BSIs by  
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13 142 multivariate logistic regression analysis. Variables were removed from the multivariable  
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16 143 model in a stepwise fashion. We used 1:2 greedy matching [10] within a caliper width equal  
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19 144 to 0.1 of the standard deviation of the logit of the propensity score (Supplementary Table 2).  
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22 145 Patient data from January 2005 were used to ensure that individuals were followed for at least  
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25 146 two years prior to their selection for this study in order to confirm comorbidities[11] and for  
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28 147 matching purposes.  
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### 34 149 **Patient and Public Involvement**

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37 150 Patients and the public were not directly involved in the planning of this study.  
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### 43 152 **Outcome measurements**

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46 153 Clinical outcomes included in-hospital, 14-day, and 28-day mortality rate after the index  
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49 154 date/pseudo-index date. Economic outcomes included hospitalization length after the index  
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52 155 date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined  
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55 156 as the duration of hospital stay after the index date/pseudo-index date. The overall cost of  
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58 157 hospitalization was calculated. The costs were standardized and presented in values from  
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10 160 **Subgroup analysis**

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13 161 To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different  
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16 162 pathogens, we performed analyses on patients infected with single pathogen. For example,  
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19 163 the impact of WHO priority bacteria and *Candida* were examined separately, as was the  
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22 164 impact of drug resistance in these bacteria. We included patients whose first episode of an  
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25 165 ICU-acquired BSI were caused by bacteria on the WHO priority list or *Candida*. Therefore,  
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28 166 the clinical and economic outcomes of patients with *Acinetobacter baumannii*, *Pseudomonas*  
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31 167 *aeruginosa*, common *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*,  
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34 168 *Enterobacter* species, and *Serratia marcescens*), *S. aureus*, *Enterococcus* species, *Candida*  
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37 169 *albicans*, and non-*albicans Candida* (*Candida tropicalis*, *Candida parapsilosis*, and *Candida*  
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40 170 *glabrata*) were determined.

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43 171 The definition of multiple drug resistance (MDR) of WHO priority bacteria according to  
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46 172 the European Centre for Disease Prevention and Control (ECDC) was modified[12]  
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49 173 (Supplementary Table 3). In this study, non-susceptibility to at least one agent in at least  
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52 174 three antimicrobial categories in Gram-negative bacteria was defined as MDR. Oxacillin- and  
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55 175 vancomycin-non-susceptible *S. aureus* and vancomycin-non-susceptible *Enterococcus*  
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58 176 species were considered MDR Gram-positive bacteria.

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7 178 **Sensitivity analysis**

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10 179 To avoid competing risk between mortality and length of hospitalization/healthcare cost,  
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13 180 we included patients who survived to discharge. For these patients, length of hospitalization  
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16 181 after the index date/pseudo-index date and hospitalization costs were determined.  
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22 183 **Statistical analysis**

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25 184 Descriptive statistics were used to examine baseline demographic and clinical  
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28 185 characteristics of the ICU patients included in this study. To account for potential  
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31 186 confounding biases among the study cohort, propensity score matching analysis was  
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34 187 performed. Propensity scores were calculated with multivariate logistic regression.  
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37 188 Standardized differences between the two groups with differences less than 0.1 were  
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40 189 confirmed in order to assess baseline characteristics. The Mann-Whitney U test was used to  
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43 190 evaluate economic outcomes and the Chi-squared test was used to evaluate mortality rate.  
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46 191 Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of  
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49 192 mortality in patients with BSI and the comparison cohort, while a generalized linear model  
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52 193 was used to calculate  $\beta$  values to estimate excess costs and length of hospitalization.  
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55 194 Variables with a  $p$ -value  $< 0.05$  were eligible for inclusion in the model.  $P$ -values less than  
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58 195 0.05 were considered statistically significant. All analyses were performed by using SAS  
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4 196 statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA).  
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## 198 RESULTS

199 Among 38,659 episodes of ICU-acquired BSIs registered in TNIS during the 9-year  
200 study period, 28,495 patients were identified to have their first episode of a BSI. The NHIRD  
201 included 1,638,796 patients who underwent ICU hospitalization (Figure 1). After excluding  
202 patients whose data could not be interlinked with NHIRD or who did not have target  
203 pathogens, 14,234 patients with ICU-acquired BSIs were successfully matched to 28,468  
204 ICU patients without ICU-acquired infections (1:2). The demographic and clinical  
205 characteristics of the patients with BSI and comparison cohort are presented in Table 1. The  
206 groups had standardized differences that were  $< 10\%$  for all of the continuous and  
207 dichotomous categorical variables which were examined.

208 Table 2 lists the clinical and economic outcomes of the ICU patients with BSIs and the  
209 comparison cohort. The ICU patients with BSIs suffered a higher in-hospital mortality rate  
210 (44.23% vs. 33.48%, respectively;  $p < 0.001$ ), a higher 14-day mortality rate (30.37% vs.  
211 23.77%, respectively;  $p < 0.001$ ), and a higher 28-day mortality (39.48% vs. 32.28%,  
212 respectively;  $p < 0.001$ ). Logistic regression analyses showed that the OR of in-hospital  
213 mortality for the ICU patients with BSIs was 1.67 (95% confidence interval [CI], 1.59–1.75;  
214  $p < 0.001$ ), and it was 1.42 (95% CI, 1.35–1.49;  $p < 0.001$ ) for 14-day mortality and 1.41  
215 (95% CI, 1.34–1.47;  $p < 0.001$ ) for 28-day mortality. These significant associations were also  
216 observed in the subgroup analyses performed (Table 3).

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4 217 The ICU patients with BSIs had a longer length of hospitalization after the index date  
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7 218 (18 vs. 10 days, respectively;  $p < 0.001$ ). Moreover, on average, their hospital stay was  
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10 219 extended by 12.69 days (95% CI, 11.92–13.47;  $p < 0.001$ ). The subgroup analyses performed  
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13 220 (Table 4) showed that all of the causative pathogens shared a similar trend. Compared with  
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16 221 the patients without ICU-acquired infections, the duration of hospitalization after the index  
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19 222 date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp.  
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22 223 was longer. In addition, hospitalization costs of the ICU patients with BSIs were higher  
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25 224 (16,038 vs. 10,372, respectively;  $p < 0.001$ ) (Table 2), with the excess cost being 7,669 US  
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28 225 dollars per patient (95% CI, 7,380–7,958;  $p < 0.001$ ). Table 4 presents the higher costs  
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31 226 associated with each of the various causative pathogen.

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34 227 For the ICU patients with BSIs who survived to discharge, their length of hospitalization  
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37 228 and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively,  
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40 229 (Supplementary Table 4) compared to the survivors without ICU-acquired infections.  
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## 230 DISCUSSION

231 This study demonstrated that ICU patients with BSIs in Taiwan had significantly worse  
232 clinical outcomes and higher economic burden than ICU patients without ICU-acquired  
233 infections from the same population. For example, the patients with BSI exhibited 1.67-,  
234 1.42-, and 1.41-fold increases in in-hospital, 14-day, and 28-day mortality rates, respectively.  
235 Per case, the patients with BSI had an excess hospital stay of 12.69 days and cost of 7,669 US  
236 dollars. Furthermore, a similar clinical and economic impact was observed among all of the  
237 causative pathogens examined.

238 BSIs have been associated with higher mortality and morbidity, contingent on the  
239 causative pathogen involved.[1,3,13-16] For example, worse clinical outcomes have been  
240 reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S.*  
241 *aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] In contrast,  
242 controversial results have been obtained regarding the mortality of patients affected by  
243 enterococcal bacteremia. While some authors have argued that *Enterococcus* spp. represents  
244 a low virulence pathogen[1] and is not associated with increased mortality unless in the  
245 presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] In  
246 the present study, significantly higher mortality was observed for patients with enterococcal  
247 bacteremia, and this may be due to vulnerability of the hosts examined, increased resistance,  
248 and a larger study population.

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4 249 The high healthcare burden of BSIs reported in previous literature[3,13,20] and in the  
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7 250 present study underscores the importance of preventing ICU-acquired BSIs by infection  
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10 251 control measurements. Furthermore, the results of these studies help to assess cost  
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13 252 effectiveness of infection control measurements in the process of policy-making. For example,  
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16 253 patients with ICU-acquired BSIs during the 9-year period cost Taiwan an estimated 297  
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19 254 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate  
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22 255 of infection by 10%[21] would translate into a savings of 30 million US dollars and 49,213  
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25 256 patient-days saved.

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28 257 Drug resistance has been found to be correlated with higher medical costs due to the  
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31 258 need for second-line antimicrobials for treatment, as well as additional diagnostic and  
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34 259 treatment tools.[22, 23] In the present study, the costs for MDR bacteria included extra 84  
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37 260 million US dollars and 140,043 days over nine years (Supplementary Table 5). However, cost  
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40 261 differences between susceptible and resistant strains were not determined in the present study.  
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43 262 Drug-susceptible strains were not included as controls due to differences in testing methods,  
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46 263 drugs, and breakpoints for these strains which could lead to mis-assignments of drug-resistant  
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49 264 pathogens as susceptible pathogens.

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52 265 Candidemia poses a great threat to ICU patients due to its excessive medical  
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55 266 burdens,[16,18,20] and *C. albicans* is the most common pathogen. However, in some  
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58 267 countries, the prevalence of non-*albicans* *Candida* exceeds that of *C. albicans*.[24] For those  
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4 268 infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization  
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7 269 stays, and increased hospital costs have been described;[25-27] although other studies have  
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10 270 reported contradicting findings.[28,29] These discrepancies may be due to host factors and  
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13 271 differences in the virulence and resistance patterns[24] of non-*albicans Candida*. In the  
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16 272 present study, the crude 14-day and in-hospital mortality rates of 951 patients infected with *C.*  
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19 273 *albicans* were 37.96% and 55.94%, respectively. In comparison, among 703 patients infected  
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22 274 with non-*albicans Candida*, these rates were 34.99% and 53.06%, respectively. While the  
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25 275 hospital costs and length of stay were higher in the non-*albicans Candida* group compared to  
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28 276 the *C. albicans* group, the 95% CI overlapped for the two groups (Table 4). These data  
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31 277 suggested that the clinical and economic outcomes of these two groups did not greatly differ.  
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34 278 However, the present study was not designed to specifically compare the outcomes of those  
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37 279 infected with *C. albicans* versus non-*albicans Candida*. Therefore, additional studies with a  
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40 280 larger number of patients, adjustment for host factors, and consideration of antifungal drugs,  
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43 281 incubation time, and treatment duration are needed to clarify the impact of each *Candida*  
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46 282 species.

49 283 The large number of patients examined in this study and the use of propensity score  
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52 284 matching represent two major strengths of the present study. These aspects also allowed the  
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55 285 impact of each pathogen group to be discerned. However, there were also several limitations  
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58 286 associated with the present study which merit discussion. First, the exact cost after the index  
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4 287 date could not be retrieved from the NHIRD. Therefore, the high total cost shown in this  
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7 288 study may be due to costs incurred prior to the onset of a BSI. It is possible that matching of  
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10 289 the duration before the index date and comorbidity may have reduced overestimations of  
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13 290 healthcare costs due to time-dependent bias.[30] Second, confounding factors associated with  
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16 291 clinical impact, such as APACHE II or Pitt Bacteremia scores, were not included in this study.  
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19 292 Instead, other clinical risk factors (Charlson Comorbidity Index score, number of organ  
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22 293 failures, use of inotropic agents, and receipt of invasive procedures) were incorporated in our  
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25 294 model. Third, our study is inherently limited by its retrospective design, which includes a  
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28 295 dependence on the accuracy of the ICD codes used and unmeasurable bias.[31,32] Fourth, the  
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31 296 prolonged hospitalization may have been due to a change in patient management in response  
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34 297 to a BSI, rather than increased morbidity due to a BSI.[15] In addition, the number of  
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37 298 participating hospitals varied during study period and therefore was considered in propensity  
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40 299 score matching. Finally, the collection of personal identification numbers is not mandatory in  
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43 300 TNIS, which resulted in failure of interlink (missing data). In 2007-2015 TNIS dataset,  
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46 301 27,603 of 132,118 (20.9%) patients lacked personal identification numbers, compared to  
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49 302 4689 of 28495 (16.5%) patients with ICU-acquired BSI in this study. Patients without  
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52 303 personal identification numbers were excluded from the analyses and therefore no further  
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55 304 methods were applied to account for excluded data. However, their impact on the outcome  
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58 305 was unknown.  
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7 307 **CONCLUSIONS**8  
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10 308 ICU-acquired BSIs have a negative clinical and economic impact on affected patients11  
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13 309 regardless of the causative pathogens involved. Awareness of these negative affects is14  
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16 310 important for promoting infection control measurements and for policy-making.17  
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4 **312 LIST OF ABBREVIATIONS**  
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7 313 BSI = bloodstream infection;  
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10 314 CI = confidence interval;  
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13 315 ECDC = European Centre for Disease Prevention and Control;  
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16 316 ICD-9-CM = international classification of diseases, 9th revision, clinical modification;  
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19 317 ICU = intensive care unit;  
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22 318 IQR = interquartile range;  
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25 319 MDR = multiple drug resistance;  
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28 320 NHIRD = National Health Insurance Research Database;  
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31 321 OR = odds ratio;  
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34 322 TNIS = Taiwan Nosocomial Infection Surveillance;  
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37 323 WHO = World Health Organization;  
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4 **325 DECLARATIONS**

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7 **326 Ethics approval and consent to participate**

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10 327 The institutional review board of the National Health Research Institutes approved this study  
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13 328 (EC1051207-R4).  
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19 **330 Consent for publication**

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22 331 Not applicable.  
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28 **333 Availability of data and materials**

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31 334 The data that support the findings of this study are available from Ministry of Health and  
32  
33  
34 335 Welfare, Taiwan but restrictions apply to the availability of these data, which were used  
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36  
37 336 under license for the current study, and so are not publicly available. Data are however  
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40 337 available from the authors upon reasonable request and with permission of Ministry of Health  
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43 338 and Welfare, Taiwan.  
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49 **340 Competing interests**

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52 341 The authors declare that they have no competing interests.  
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19 349

22 350 **Author contributions**

25 351 Conceptualization: CAH, SCK

28 352 Data curation: YTC, CAH, SCK

31 353 Formal analysis: SMS, YTC

34 354 Funding acquisition: YCW, SCK

37 355 Investigation: YCW, SCK

40 356 Methodology: YTC, CAH, SCK

43 357 Project administration: YCW, CAH, SCK

46 358 Resources: YTC, CAH, SCK

49 359 Software: SMS, YTC

52 360 Supervision: SMS, YTC

55 361 Validation: CAH, SCK

58 362 Visualization: YCW, SMS



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363 Writing—original draft: YCW, SMS, SCK

364 Writing—review & editing: YCW, CAH, SCK

365 All authors approved the final version of the manuscript.

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371 **REFERENCES**

- 372 1. Prowle JR, Echeverri JE, Ligabo EV, et al. Acquired bloodstream infection in the  
373 intensive care unit: incidence and attributable mortality. *Crit Care* 2011; **15**: R100.
- 374 2. Garrouste-Orgeas M, Timsit JF, Tafflet M, et al. Excess risk of death from intensive  
375 care unit-acquired nosocomial bloodstream infections: a re-appraisal. *Clin Infect Dis*  
376 2006; **42**: 1118-26.
- 377 3. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired  
378 bloodstream infections. *J Hosp Infect* 2006; **63**: 124-32.
- 379 4. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of  
380 bloodstream infections caused by antimicrobial-susceptible and non-susceptible  
381 Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011:  
382 a multicentre retrospective cohort study. *Euro Surveill* 2016; **21**: pii=30319.
- 383 5. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to  
384 nosocomial enterococcal bacteremia: a controlled study. *Am J Infect Control* 1989;  
385 **17**: 323-9.
- 386 6. Ong DS, Bonten MJ, Safdari K, et al. Epidemiology, management, and risk-adjusted  
387 mortality of ICU-acquired enterococcal bacteremia. *Clin Infect Dis* 2015; **61**:  
388 1413-20.
- 389 7. Kramer TS, Remschmidt C, Werner S, et al. The importance of adjusting for

- 1  
2  
3  
4 390 Enterococcus species when assessing the burden of vancomycin resistance: a cohort  
5  
6  
7 391 study including over 1000 cases of enterococcal bloodstream infections. *Antimicrob*  
8  
9  
10 392 *Resist Infect Control* 2018; **7**: 133.
- 11  
12  
13 393 8. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of  
14  
15  
16 394 new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis.  
17  
18  
19 395 *Lancet Infect Dis* 2018; **18**: 318-27.
- 20  
21  
22 396 9. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan.  
23  
24  
25 397 *London J Prim Care (Abingdon)* 2010; **3**: 115-9.
- 26  
27  
28 398 10. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in  
29  
30  
31 399 Ontario. *N Engl J Med* 2007; **357**: 1393-402.
- 32  
33  
34 400 11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with  
35  
36  
37 401 ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-9.
- 38  
39  
40 402 12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively  
41  
42  
43 403 drug-resistant and pandrug-resistant bacteria: an international expert proposal for  
44  
45  
46 404 interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**:  
47  
48  
49 405 268-81.
- 50  
51  
52 406 13. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill  
53  
54  
55 407 patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;  
56  
57  
58 408 **271**: 1598-601.
- 59  
60

- 1  
2  
3  
4 409 14. Laupland KB, Zygun DA, Davies HD, et al. Population-based assessment of intensive  
5  
6  
7 410 care unit-acquired bloodstream infections in adults: incidence, risk factors, and  
8  
9  
10 411 associated mortality rate. *Crit Care Med* 2002; **30**: 2462-7.
- 11  
12  
13 412 15. Barnett AG, Page K, Campbell M, et al. The increased risks of death and extra lengths  
14  
15  
16 413 of hospital and ICU stay from hospital-acquired bloodstream infections: a  
17  
18  
19 414 case-control study. *BMJ Open* 2013; **3**: e003587.
- 20  
21  
22 415 16. Marra AR, Camargo LF, Pignatari AC, et al. Nosocomial bloodstream infections in  
23  
24  
25 416 Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide  
26  
27  
28 417 surveillance study. *J Clin Microbiol* 2011; **49**: 1866-71.
- 29  
30  
31 418 17. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in  
32  
33  
34 419 patients with *Acinetobacter baumannii* infection: systematic review and  
35  
36  
37 420 meta-analysis. *Clin Microbiol Infect* 2014; **20**: 416-23.
- 38  
39  
40 421 18. Schwab F, Geffers C, Behnke M, et al. ICU mortality following ICU-acquired  
41  
42  
43 422 primary bloodstream infections according to the type of pathogen: a prospective  
44  
45  
46 423 cohort study in 937 Germany ICUs (2006-2015). *PloS One* 2018; **13**: e0194210.
- 47  
48  
49 424 19. Caballero-Granado FJ, Becerril B, Cuberos L, et al. Attributable mortality rate and  
50  
51  
52 425 duration of hospital stay associated with enterococcal bacteremia. *Clin Infect Dis*  
53  
54  
55 426 2001; **32**: 587-94.
- 56  
57  
58 427 20. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically  
59  
60

- 1  
2  
3  
4 428 ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis*  
5  
6  
7 429 2005; **41**: 1591-8.  
8  
9  
10 430 21. Tseng SH, Lee CM, Lin TY, et al. Combating antimicrobial resistance: antimicrobial  
11  
12  
13 431 stewardship program in Taiwan. *J Microbiol Immunol Infect* 2012; **45**: 79-89.  
14  
15  
16 432 22. Howard D, Cordell R, McGowan JE, Jr., et al. Measuring the economic costs of  
17  
18  
19 433 antimicrobial resistance in hospital settings: summary of the Centers for Disease  
20  
21  
22 434 Control and Prevention-Emory Workshop. *Clin Infect Dis* 2001; **33**: 1573-8.  
23  
24  
25 435 23. Mauldin PD, Salgado CD, Hansen IS, et al. Attributable hospital cost and length of  
26  
27  
28 436 stay associated with health care-associated infections caused by antibiotic-resistant  
29  
30  
31 437 gram-negative bacteria. *Antimicrob Agents Chemother* 2010; **54**: 109-15.  
32  
33  
34 438 24. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia  
35  
36  
37 439 in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin*  
38  
39  
40 440 *Infect Dis* 2009; **48**: 1695-703.  
41  
42  
43 441 25. Dimopoulos G, Ntziora F, Rachiotis G, et al. *Candida albicans* versus non-*albicans*  
44  
45  
46 442 intensive care unit-acquired bloodstream infections: differences in risk factors and  
47  
48  
49 443 outcome. *Anesth Analg* 2008; **106**: 523-9.  
50  
51  
52 444 26. Moran C, Grussemyer CA, Spalding JR, et al. Comparison of costs, length of stay,  
53  
54  
55 445 and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream  
56  
57  
58 446 infections. *Am J Infect Control* 2010; **38**: 78-80.  
59  
60

- 1  
2  
3  
4 447 27. Gong X, Luan T, Wu X, et al. Invasive candidiasis in intensive care units in China:  
5  
6  
7 448 risk factors and prognoses of *Candida albicans* and non-*albicans* *Candida* infections.  
8  
9  
10 449 *Am J Infect Control* 2016; **44**: e59-63.  
11  
12  
13 450 28. Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia  
14  
15  
16 451 in 3648 patients: data from the prospective antifungal therapy (PATH Alliance®)  
17  
18  
19 452 registry, 2004-2008. *Diagn Microbiol Infect Dis* 2012; **74**: 323-31.  
20  
21  
22 453 29. Barchiesi F, Orsetti E, Gesuita R, et al.; Candidemia Study Group. Epidemiology,  
23  
24  
25 454 clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy  
26  
27  
28 455 from 2010 to 2014. *Infection* 2016; **44**: 205-13.  
29  
30  
31 456 30. Nelson RE, Samore MH, Jones M, et al. Reducing time-dependent bias in estimates of  
32  
33  
34 457 the attributable cost of health care-associated Methicillin-resistant *Staphylococcus*  
35  
36  
37 458 *aureus* infections: a comparison of three estimation strategies. *Med Care* 2015; **53**:  
38  
39  
40 459 827-34.  
41  
42  
43 460 31. Kuo SC, Shih SM, Hsieh LY, et al. Antibiotic restriction policy paradoxically  
44  
45  
46 461 increased private drug consumptions outside Taiwan's National Health Insurance. *J*  
47  
48  
49 462 *Antimicrob Chemother* 2017; **72**: 1544-5.  
50  
51  
52 463 32. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative  
53  
54  
55 464 data. *JAMA* 2012; **307**: 1433-5.  
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466 **Table 1. Characteristics of the intensive care unit patients with bloodstream infections**  
 467 **and the matched comparison cohort.**

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (63.03%)	17,861 (62.74%)	0.006
Age, years, mean (SD)	65.12 (21.62)	65.08 (20.60)	0.002
Length of stay before index date/ pseudo-index date, days, mean (SD)	15.69 (12.14)	15.29 (11.96)	0.033

## Monthly income, USD

Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001

## Urbanization level

1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002

## Hospital level

Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007

## Charlson Comorbidity Index

score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019

## Comorbidities

Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005
Myocardial infarction	525 (3.69%)	1,124 (3.95%)	0.014
Heart failure	2,532 (17.79%)	5,173 (18.17%)	0.01



Peripheral vascular disease	742 (5.21%)	1,509 (5.3%)	0.004
Liver disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Chronic kidney disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Dyslipidemia	2,766 (19.43%)	5,683 (19.96%)	0.013
Cancer	2,753 (19.34%)	5,635 (19.79%)	0.011
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (4.86%)	0.074
Use of inotropic agents	11,398 (80.08%)	22,858 (80.29%)	0.005
Use of steroid	9 (0.06%)	20 (0.07%)	0.003
Use of ventilator	12,493 (87.77%)	25,075 (88.08%)	0.01
Use of ventilator (>3 days)	11,668 (81.97%)	23,458 (82.4%)	0.011
Emergent renal replacement therapy	2615 (18.37%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

468 Abbreviations: BSI = bloodstream infection; SD = standard deviation.

469 **Table 2. Clinical and economic outcomes among patients with bloodstream infections and the matched comparison cohort.**

Outcomes	Full cohort			Matched cohort		
	ICU patients	Comparison	<i>P</i> -value	ICU patients	Comparison	<i>P</i> -value
	with BSI	cohort		with BSI	cohort	
No. of patients	17,834	713,518		14,234	28,468	
Clinical outcomes						
In-hospital mortality, n (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.2%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.37%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.48%)	9,189 (32.28%)	<0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 30)	10 (4, 21)	< 0.0001

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	(IQR)					
Cost of hospitalization (USD) <sup>a</sup> , median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,246)	(6,289, 16,932)	

470 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

471 <sup>a</sup>The costs are standardized and presented as the values in 2017.

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472 **Table 3. Clinical outcomes for the various pathogen groups.**

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
<i>Acinetobacter baumannii</i> (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
<i>Pseudomonas aeruginosa</i> (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae <sup>b</sup> (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
<i>Staphylococcus aureus</i> (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
<i>Enterococcus species</i> <sup>c</sup> (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
<i>Candida albicans</i> (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non- <i>albicans Candida</i> <sup>d</sup> (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

473 Abbreviations: MDR = multiple drug resistance.

474 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this  
475 analysis.

476 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*,  
477 *Enterobacter aerogenes*, and *Serratia marcescens*.

478 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other

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479 *Enterococcus species.*

480 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida*

481 *glabrata.*

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484 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,342 (5,500, 7,184)
<i>Acinetobacter baumannii</i>	9.4 (7.65, 11.14)	6,767 (5,823, 7,632)
<i>Pseudomonas aeruginosa</i>	10.01 (7.83, 12.19)	6,781 (5,609, 7,913)
Enterobacteriaceae <sup>b</sup>	15.05 (13.33, 16.76)	7,414 (6,881, 8,007)
<i>Staphylococcus aureus</i>	14.72 (12.63, 16.81)	5,241 (4,528, 5,894)
<i>Enterococcus species</i> <sup>c</sup>	10.66 (7.85, 13.48)	7,219 (6,305, 8,132)
<i>Candida albicans</i>	11.37 (8.82, 13.92)	8,688 (7,512, 9,864)

Non- <i>albicans Candida</i> <sup>d</sup>	15.13 (11.77, 18.49)	11,446 (10,025, 12,927)
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485 Abbreviations: MDR = multiple drug resistance.

486 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this analysis.

487 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Serratia marcescens*.

488 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

489 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

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4 493 **FIGURE LEGENDS**  
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7 494 **Figure 1. Flow diagram of the study design.**  
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16 497 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National

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19 498 Health Insurance Research Database.  
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4 **505 SUPPLEMENTARY FILES:**  
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7 **506** Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before  
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10 **507** enrollment and the number of patients infected after matching.  
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13 **508** Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched  
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16 **509** comparison cohort.  
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19 **510** Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.  
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22 **511** Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the  
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25 **512** discharge.  
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28 **513** Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.  
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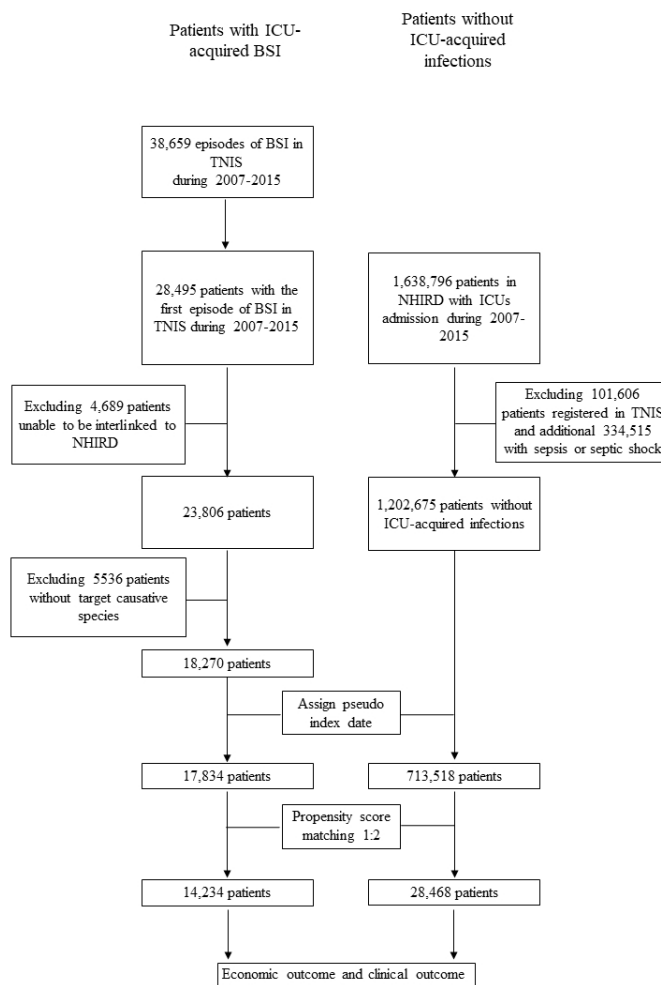


Figure 1. Flow diagram of the study design.

60x108mm (300 x 300 DPI)

1 **Supplementary Table 1. The number of episodes of intensive care unit-acquired**  
 2 **bloodstream infections caused by common pathogens before enrollment and the number**  
 3 **of patients infected after matching.**

	No. of BSI episodes before enrollment <sup>a</sup>	No. of patients after matching <sup>b</sup>
<i>Acinetobacter baumannii</i>	5,214	1,761
<i>Staphylococcus aureus</i>	4,382	1,721
<i>Klebsiella pneumoniae</i>	3,965	1,357
<i>Pseudomonas aeruginosa</i>	2,619	853
<i>Candida albicans</i>	2,554	951
<i>Escherichia coli</i>	2,287	843
<i>Enterobacter cloacae</i>	1,982	746
<i>Enterococcus faecium</i>	1,950	647
<i>Stenotrophomonas maltophilia</i>	1,599	454
<i>Enterococcus faecalis</i>	1,427	419
<i>Serratia marcescens</i>	1,239	439
<i>Candida tropicalis</i>	890	329
<i>Burkholderia cepacia</i>	808	251
Other <i>Enterococcus species</i> <sup>c</sup>	688	211
<i>Elizabethkingia meningoseptica</i>	659	173
<i>Chryseobacterium indologenes</i>	553	152
<i>Candida parapsilosis</i>	534	177
<i>Candida glabrata</i>	461	197
<i>Enterobacter aerogenes</i>	419	163

4 Abbreviations: BSI= bloodstream infection.

5 <sup>a</sup>The number of episodes of bloodstream infections with known pathogens was 38,659.

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3 6 Coagulase-negative staphylococci was excluded from analyses due to possibility of  
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5 7 contamination. One episode may have multiple pathogens. There were 30,697 episodes of  
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7 8 bloodstream infections caused by the pathogens listed above.

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9 <sup>b</sup>The number of patients enrolled case was 14,234 (Table 1) but only patients with  
10  
11 10 bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it  
12  
13 11 was 11,844. There were 2,390 patients with bloodstream infections caused by multiple  
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15 12 pathogens.

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17 13 <sup>c</sup>*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis*.  
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15 **Supplementary Table 2. Propensity score model results of probability of bloodstream**  
 16 **infections among intensive care unit patients and matched comparison cohort.**

Parameter	Estimate	Odds ratios	95% Confidence interval		P-value
			Lower	Upper	
			Age, years	-0.0014	
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

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2						
3	Dependent	--	1.000	--	--	--
4						
5	<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
6						
7	657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
8						
9	>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
10						
11						
12	Urbanization level					
13						
14	1 (urban)		1.000			
15						
16	2	0.0093	1.0094	0.9516	1.0706	0.7560
17						
18	3	-0.0006	0.9994	0.9293	1.0748	0.9872
19						
20	4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
21						
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23						
24	Hospital level					
25						
26	Level I (Medical center)	--	1.000	--	--	--
27						
28	Level II (Regional					
29	hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
30						
31	Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
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35	Charlson Comorbidity Index					
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37	score					
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39	0	--	1.000	--	--	--
40						
41	1	0.1421	1.1527	1.0681	1.2439	0.0003
42						
43	2	0.2932	1.3407	1.2390	1.4508	<0.0001
44						
45	≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
46						
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49	Comorbidities					
50						
51	Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
52						
53	Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
54						
55	Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
56						
57	Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292
58						
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Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

18 **Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and**  
 19 **antimicrobial agents used to define drug resistance.**

Pathogens	Antimicrobial categories	Antimicrobial agents	
<i>Acinetobacter baumannii</i> <sup>a</sup>	Aminoglycosides	Gentamicin	
		Tobramycin	
		Amikacin	
		Netilmicin	
	Carbapenems	Imipenem	
		Meropenem	
		Doripenem	
	Fluoroquinolones	Ciprofloxacin	
		Levofloxacin	
		Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid	
		Extended-spectrum cephalosporins	Cefotaxime
			Cefepime
			Cefpirome
<i>Pseudomonas aeruginosa</i> <sup>a</sup>	Aminoglycosides	Ceftazidime	
		Ceftriaxone	
		Gentamicin	
		Tobramycin	
	Carbapenems	Amikacin	
		Meropenem	



		Doripenem
		Ciprofloxacin
	Fluoroquinolones	Levofloxacin
		Piperacillin-tazobactam
	Antipseudomonal penicillins + $\beta$ -lactamase inhibitors	Ticarcillin-clavulanic acid
		Cefepime
	Antipseudomonal cephalosporins	Cefpirome
		Ceftazidime
		Gentamicin
		Tobramycin
	Aminoglycosides	Amikacin
		Netilmicin
		Imipenem
		Meropenem
	Carbapenems	Doripenem
		Ertapenem
		Ciprofloxacin
		Levofloxacin
		Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
		Cefotaxime
		Cefepime
	Extended-spectrum cephalosporins	Cefpirome
		Ceftazidime
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33	<i>Enterobacteriaceae</i> <sup>a</sup>	
34	( <i>Escherichia coli</i> ,	
35	<i>Klebsiella pneumoniae</i> ,	
36	<i>Enterobacter cloacae</i>	
37	<i>Enterobacter</i>	
38	<i>aerogenes</i> , or <i>Serratia</i>	
39	<i>marcescens</i> )	
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		Ceftriaxone
	Glycopeptides	Vancomycin
<i>Staphylococcus aureus</i> <sup>b</sup>	$\beta$ -lactamase-resistant penicillins	Oxacillin
<i>Enterococcus faecium</i> ,		
<i>Enterococcus faecalis</i> ,	Glycopeptides	Vancomycin
or other <i>Enterococcus</i>		
<i>species</i> <sup>b</sup>		

<sup>a</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories.

<sup>b</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent.

23 **Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to**  
 24 **the discharge.<sup>a</sup>**

			25
	<b>Excess costs or length of</b>		
<b>Clinical outcomes</b>	<b>hospitalization</b>		<b>P-value</b>
	<b>(95% Confidence interval)<sup>b</sup></b>		
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	< 0.0001	26
Cost of hospitalization, USD	8,871 (8,475, 9,268)	< 0.0001	27
			28
			29
			30
			31

32 <sup>a</sup>A total of 7,939 of patients with intensive care unit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

33 <sup>b</sup>Adjusted imbalanced variables in Table 1.

34

35 **Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.**

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9-year excessive hospitalization or healthcare cost		
Pathogen groups	Length of hospitalization after the index date	Cost of hospitalization (USD) <sup>b, c</sup>
(Numbers of patients) <sup>a</sup>	(days) <sup>b</sup>	
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
<i>Acinetobacter baumannii</i> (5,214)	66,374	40,003,372
<i>Pseudomonas aeruginosa</i> (2,619)	33,340	20,093,754
<i>Enterobacteriaceae</i> <sup>d</sup> (9,486)	120,757	72,779,438
<i>Staphylococcus aureus</i> (4,382)	55,783	33,620,019
<i>Enterococcus species</i> <sup>e</sup> (4,045)	51,493	31,034,454
<i>Candida albicans</i> (2,554)	32,512	19,595,054
<i>Non-albicans Candida</i> <sup>f</sup> (1,872)	23,831	14,362,546

37 Abbreviations: MDR= multiple drug resistance.

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3 38 <sup>a</sup>The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The  
4  
5 39 inclusion and exclusion criteria in the method section were not applied in this Table (see Figure 1).  
6

7  
8 40 <sup>b</sup>The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s)  
9  
10 41 and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was  
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12 42 difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average  
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14 43 hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was  
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17 44 that in matched control group.

18  
19 45  $Ave_{Hospitalization}$  per case = [(sum of hospitalization length)/the number of patients].

20  
21 46 Excessive  $Ave_{Hospitalization}$  per person = ( $Ave_{Hospitalization}$  in bloodstream infection group) - ( $Ave_{Hospitalization}$  in comparison group).

22  
23 47 Total excessive hospitalization length over 9 years = (excessive  $Ave_{Hospitalization}$  per person) × (total number of episodes over 9 years)

24  
25 48 The 9-year excessive healthcare cost was calculated similarly.

26  
27 49 <sup>c</sup>The costs are standardized and presented the values in 2017.

28  
29 50 <sup>d</sup>*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa*, and *Serratia*  
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32 51 *marcescens*.

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34 52 <sup>e</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

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36 53 <sup>f</sup>*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.  
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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	#1 and #3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(b) For matched studies, give matching criteria and number of exposed and unexposed	#9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	#9-12
		(b) Describe any methods used to examine subgroups and interactions	#9-12
		(c) Explain how missing data were addressed	#19
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	#12
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#14
		(b) Give reasons for non-participation at each stage	#14
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#14
		(b) Indicate number of participants with missing data for each variable of interest	#19
		(c) Summarise follow-up time (eg, average and total amount)	#14-15
Outcome data	15*	Report numbers of outcome events or summary measures over time	#14-15
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#14-15
		(b) Report category boundaries when continuous variables were categorized	#14-15
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#15
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	#16
<b>Limitations</b>			#18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	#16-19
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#22-23

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan: A nationwide population-based retrospective cohort study

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3 **Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections**  
4 **in Taiwan: A nationwide population-based retrospective cohort study**

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4 35 **ABSTRACT**

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7 36 **Objectives:** To estimate the clinical and economic impact of intensive care unit-acquired  
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10 37 bloodstream infections in Taiwan.

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13 38 **Design:** Retrospective cohort study.

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16 39 **Setting:** Nationwide Taiwanese population in the National Health Insurance Research  
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19 40 Database and the Taiwan Nosocomial Infections Surveillance (2007-2015) dataset.

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22 41 **Participants:** The first episodes of intensive care unit-acquired bloodstream infections in  
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25 42 patients  $\geq 20$  years of age in the datasets. Propensity score-matching (1:2) of demographic  
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28 43 data, comorbidities, and disease severity was performed to select a comparison cohort from a  
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31 44 pool of intensive care unit patients without intensive care unit-acquired infections from the  
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34 45 same datasets.

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37 46 **Primary and secondary outcome measures:** The 14-day mortality rate, length of  
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40 47 hospitalization, and healthcare cost.

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43 48 **Results:** After matching, the in-hospital mortality of 14,234 patients with intensive care  
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46 49 unit-acquired bloodstream infections was 44.23%, compared to 33.48% for 28,468 intensive  
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49 50 care unit patients without bloodstream infections. The 14-day mortality rate was also higher  
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53 51 in the bloodstream infections cohort (4,323, 30.37% vs. 6,766 deaths, 23.77%, respectively;  $p$   
54  
55 52  $< 0.001$ ). Furthermore, the patients with intensive care unit-acquired bloodstream infections  
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58 53 had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] vs. 10  
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4 54 days [IQR 4–21], respectively;  $p < 0.001$ ) and a higher healthcare cost (16,038 US dollars  
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7 55 [IQR 9,667–25,946] vs. 10,372 US dollars [IQR 6,289–16,932], respectively;  $p < 0.001$ ). The  
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10 56 excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars,  
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13 57 respectively. Similar results were observed in subgroup analyses of various World Health  
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16 58 Organization's priority pathogens and *Candida* spp.

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19 59 **Conclusions:** Intensive care unit-acquired bloodstream infections in critically ill patients  
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21  
22 60 were associated with increased mortality, longer hospital stays, and higher healthcare costs.  
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31 63 **Keywords:** bloodstream infection; healthcare costs; hospital stay; intensive care unit;  
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34 64 mortality.  
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4 **66 STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 8 67 1. A large number of patients obtained from Nationwide Taiwanese population from two  
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10 68 datasets in Taiwan were included.  
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13 69 2. Propensity score-matching was performed to select a comparison cohort.  
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16 70 3. The 14-day and 28-day mortality rate, length of hospitalization, and healthcare cost were  
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18 71 analyzed.  
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22 72 4. Subgroup analyses of several drug-resistant pathogens were conducted.  
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25 73 5. The retrospective design may include some unmeasurable bias.  
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## 74 BACKGROUND

75 Critically ill patients in intensive care units (ICUs) are vulnerable to various infections,  
76 and these can lead to increased morbidity, mortality, and healthcare costs. Bloodstream  
77 infections (BSIs) are one of the most common infections acquired by ICU patients. It was  
78 reported that BSIs affected approximately 7 % of patients admitted to ICUs.[1] Previous  
79 studies have shown that ICU-acquired BSIs resulted in attributable mortality of 24.8%,[2]  
80 extended hospital stays by 13.5 days[3] and the cost of treatment was approximately 12,321  
81 US dollars per case. Moreover, despite advances in medical care and the development of new  
82 therapies, the outcome of BSIs in critically ill patients is adversely affected by a greater  
83 number of vulnerable hosts and the emergence of drug-resistant pathogens.

84 Discrepancies regarding the impact of pathogens on mortality have been reported.  
85 However, worse clinical outcome and higher economic burden have been reported for  
86 patients with BSI caused by resistant pathogens.[1, 4] For example, BSIs involving  
87 third-generation cephalosporin-resistant *Enterobacteriaceae* have been shown to significantly  
88 increase mortality risk compared to BSIs involving susceptible strains.[4] Moreover,  
89 candidemia has been associated with a 4-fold increase in mortality, while *Staphylococcus*  
90 *aureus* BSIs doubled the risk of mortality.[1] Meanwhile, the clinical impact of *Enterococci*  
91 remains a controversial topic.[5-7] Therefore, it is important not only to describe the clinical  
92 and economic impact of infections, but also to decipher the impact of individual pathogens.

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4 93 Due to the limited number of cases and the complex clinical characteristics of critically ill  
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7 94 patients, previous studies have reported either clinical or economic outcomes, have focused  
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10 95 on several species of pathogens, or have assessed only a limited number of pathogens. In the  
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13 96 present study, a health insurance database and a nationwide surveillance system for  
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16 97 healthcare-associated infections were used to estimate the clinical and economic  
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19 98 consequences of ICU-acquired BSIs caused by different pathogens in a large number of  
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22 99 patients in Taiwan. In addition, the impact of individual pathogens, especially  
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25 100 antibiotic-resistant bacteria on the World Health Organization (WHO) priority list,[8] were  
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28 101 investigated.  
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4 **102 METHODS**

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7 **103 Data sources**

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10 104 Two datasets, the National Health Insurance Research Database (NHIRD) and the  
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13 105 Taiwan Nosocomial Infection Surveillance (TNIS) dataset, were used in this study.  
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16 106 Demographic data, diagnoses (according to the International Classification of Diseases, 9th  
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19 107 Revision, Clinical Modification [ICD-9-CM]), procedures, and medications for patients  
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22 108 enrolled in Taiwan's national insurance system have been collected in the NHIRD since  
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25 109 1995.[9] In 2007, the TNIS was launched by the Taiwan Centers for Disease Control to  
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28 110 evaluate the epidemiologic trend of healthcare-associated infections in the ICUs in Taiwan.  
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31 111 The latter is a web-based surveillance system which collects clinical information of patients  
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34 112 with healthcare-associated infections from the ICUs of participating hospitals. This  
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37 113 information includes demographic data, infection foci, causative pathogens, and antimicrobial  
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40 114 susceptibility results. Participation in TNIS is essential for the hospital accreditation in  
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43 115 Taiwan.

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46 116 Both datasets were deposited in a database maintained by the Health and Welfare Data  
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49 117 Science Center, Ministry of Health and Welfare. Individual personal identification numbers  
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52 118 were encrypted so that data from the NHIRD and TNIS datasets could be interlinked. The  
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55 119 institutional review board of the National Health Research Institutes approved this study  
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58 120 (EC1051207-R4).  
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4 1217 122 **Study population, data collection, and propensity-score matching**

10 123 This retrospective cohort study enrolled adult patients who underwent ICU  
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13 124 hospitalization between 2007 and 2015 in Taiwan. From the entries in the TNIS database, we  
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16 125 identified all of the patients whose first episode of an ICU-acquired BSI occurred during the  
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19 126 study period. Coagulase-negative *Staphylococci* are often identified in the ICUs but a certain  
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22 127 proportion is associated with contamination; therefore, these cases were not included in our  
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25 128 analysis. We included species that constituted > 1 % of known bloodstream pathogens  
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28 129 (Supplementary Table 1), which constituted 79.4% of all ICU-acquired BSI episodes. The  
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31 130 index date for each case was defined as the date on which a positive blood culture result was  
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34 131 obtained. The encrypted personal identification numbers of included patients were interlinked  
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37 132 with NHIRD to retrieve their demographic data, comorbidities, procedures, and medications.

40 133 For comparison, we identified ICU patients who did not have ICU-acquired infections  
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43 134 registered in TNIS database. In addition, patients with a discharge diagnosis of sepsis  
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46 135 (ICD-9-CM: 038.X, 995.91), severe sepsis (ICD-9-CM: 995.92), or septic shock (ICD-9-CM:  
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49 136 785.52) in the comparison cohort, but not in the BSI group, were also excluded. The pool of  
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52 137 comparison patients was created for selection of those with the same admission date as any  
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55 138 patient with ICU-acquired BSI. Because the comparison patients did not have index date of  
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58 139 acquisition of infection, they were assigned “pseudo-index dates” during hospitalization,

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4 140 which was selected from the index date of patients with the same day of hospitalization in the  
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7 141 BSI group. Baseline variables and those associated with ICU-acquired BSIs were first  
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10 142 selected. Propensity scores were then calculated for the likelihood of ICU-acquired BSIs by  
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13 143 multivariate logistic regression analysis. Variables were removed from the multivariable  
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16 144 model in a stepwise fashion. We used 1:2 greedy matching [10] within a caliper width equal  
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19 145 to 0.1 of the standard deviation of the logit of the propensity score. (Supplementary Table 2).  
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22 146 Patient data from January 2005 were used to ensure that individuals were followed for at least  
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25 147 two years prior to their selection for this study in order to confirm comorbidities[11] and for  
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28 148 matching purposes. The variables with missing values included monthly income and  
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31 149 urbanization level. Missing values were treated as a separate category by itself. The low rate  
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34 150 of missing data (Table 1) may not have a great impact on our study.  
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## 38 39 40 152 **Patient and Public Involvement**

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43 153 Patients and the public were not directly involved in the planning of this study.  
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## 47 48 49 155 **Outcome measurements**

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52 156 Clinical outcomes included in-hospital, 14-day, and 28-day mortality rate after the index  
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55 157 date/pseudo-index date. Economic outcomes included hospitalization length after the index  
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58 158 date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined  
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4 159 as the duration of hospital stay after the index date/pseudo-index date. The overall cost of  
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7 160 hospitalization was calculated. The costs were standardized and presented in values from  
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10 161 2017.

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### 16 163 **Subgroup analysis**

19 164 To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different  
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22 165 pathogens, we performed analyses on patients infected with single pathogen. For example,  
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25 166 the impact of WHO priority bacteria and *Candida* were examined separately, as was the  
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28 167 impact of drug resistance in these bacteria. We included patients whose first episode of an  
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31 168 ICU-acquired BSI were caused by bacteria on the WHO priority list or *Candida*. Therefore,  
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34 169 the clinical and economic outcomes of patients with *Acinetobacter baumannii*, *Pseudomonas*  
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37 170 *aeruginosa*, common *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*,  
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40 171 *Enterobacter* species, and *Serratia marcescens*), *S. aureus*, *Enterococcus* species, *Candida*  
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43 172 *albicans*, and non-*albicans Candida* (*Candida tropicalis*, *Candida parapsilosis*, and *Candida*  
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46 173 *glabrata*) were determined.

49 174 The definition of multiple drug resistance (MDR) of WHO priority bacteria according to  
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52 175 the European Centre for Disease Prevention and Control (ECDC) was modified[12]  
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55 176 (Supplementary Table 3). In this study, non-susceptibility to at least one agent in at least  
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58 177 three antimicrobial categories in Gram-negative bacteria was defined as MDR. Oxacillin- and  
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4 178 vancomycin-non-susceptible *S. aureus* and vancomycin-non-susceptible *Enterococcus*

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7 179 species were considered MDR Gram-positive bacteria.

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### 11 12 13 181 **Sensitivity analysis**

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16 182 To avoid competing risk between mortality and length of hospitalization/healthcare cost,

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19 183 we included patients who survived to discharge. For these patients, length of hospitalization

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22 184 after the index date/pseudo-index date and hospitalization costs were determined.

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### 26 27 28 186 **Statistical analysis**

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31 187 Descriptive statistics were used to examine baseline demographic and clinical

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34 188 characteristics of the ICU patients included in this study. To account for potential

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37 189 confounding biases among the study cohort, propensity score matching analysis was

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40 190 performed. Propensity scores were calculated with multivariate logistic regression.

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43 191 Standardized differences between the two groups with differences less than 0.1 were

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46 192 confirmed in order to assess baseline characteristics. The Mann-Whitney U test was used to

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49 193 evaluate economic outcomes and the Chi-squared test was used to evaluate mortality rate.

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52 194 Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of

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55 195 mortality in patients with BSI and the comparison cohort, while a generalized linear model

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58 196 was used to calculate  $\beta$  values to estimate excess costs and length of hospitalization.

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4 197 Variables with a  $p$ -value  $< 0.05$  were eligible for inclusion in the model.  $P$ -values less than  
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7 198 0.05 were considered statistically significant. All analyses were performed by using SAS  
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10 199 statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA).  
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## 201 RESULTS

202 Among 38,659 episodes of ICU-acquired BSIs registered in TNIS during the 9-year  
203 study period, 28,495 patients were identified to have their first episode of a BSI. The NHIRD  
204 included 1,638,796 patients who underwent ICU hospitalization (Figure 1). After excluding  
205 patients whose data could not be interlinked with NHIRD or who did not have target  
206 pathogens, 14,234 patients with ICU-acquired BSIs were successfully matched to 28,468  
207 ICU patients without ICU-acquired infections (1:2). The demographic and clinical  
208 characteristics of the patients with BSI and comparison cohort are presented in Table 1. The  
209 groups had standardized differences that were  $< 10\%$  for all of the continuous and  
210 dichotomous categorical variables which were examined.

211 Table 2 lists the clinical and economic outcomes of the ICU patients with BSIs and the  
212 comparison cohort. The ICU patients with BSIs suffered a higher in-hospital mortality rate  
213 (44.23% vs. 33.48%, respectively;  $p < 0.001$ ), a higher 14-day mortality rate (30.37% vs.  
214 23.77%, respectively;  $p < 0.001$ ), and a higher 28-day mortality (39.48% vs. 32.28%,  
215 respectively;  $p < 0.001$ ). Logistic regression analyses showed that the OR of in-hospital  
216 mortality for the ICU patients with BSIs was 1.67 (95% confidence interval [CI], 1.59–1.75;  
217  $p < 0.001$ ), and it was 1.42 (95% CI, 1.35–1.49;  $p < 0.001$ ) for 14-day mortality and 1.41  
218 (95% CI, 1.34–1.47;  $p < 0.001$ ) for 28-day mortality. These significant associations were also  
219 observed in the subgroup analyses performed (Table 3).

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4 220 The ICU patients with BSIs had a longer length of hospitalization after the index date  
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7 221 (18 vs. 10 days, respectively;  $p < 0.001$ ). Moreover, on average, their hospital stay was  
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10 222 extended by 12.69 days (95% CI, 11.92–13.47;  $p < 0.001$ ). The subgroup analyses performed  
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13 223 (Table 4) showed that all of the causative pathogens shared a similar trend. Compared with  
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16 224 the patients without ICU-acquired infections, the duration of hospitalization after the index  
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19 225 date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp.  
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22 226 was longer. In addition, hospitalization costs of the ICU patients with BSIs were higher  
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25 227 (16,038 vs. 10,372, respectively;  $p < 0.001$ ) (Table 2), with the excess cost being 7,669 US  
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28 228 dollars per patient (95% CI, 7,380–7,958;  $p < 0.001$ ). Table 4 presents the higher costs  
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31 229 associated with each of the various causative pathogen.

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34 230 For the ICU patients with BSIs who survived to discharge, their length of hospitalization  
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37 231 and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively,  
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40 232 (Supplementary Table 4) compared to the survivors without ICU-acquired infections.  
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## 233 DISCUSSION

234 This study demonstrated that ICU patients with BSIs in Taiwan had significantly worse  
235 clinical outcomes and higher economic burden than ICU patients without ICU-acquired  
236 infections from the same population. For example, the patients with BSI exhibited 1.67-,  
237 1.42-, and 1.41-fold increases in in-hospital, 14-day, and 28-day mortality rates, respectively.  
238 Per case, the patients with BSI had an excess hospital stay of 12.69 days and cost of 7,669 US  
239 dollars. Furthermore, a similar clinical and economic impact was observed among all of the  
240 causative pathogens examined.

241 BSIs have been associated with higher mortality and morbidity, contingent on the  
242 causative pathogen involved.[1,3,13-16] For example, worse clinical outcomes have been  
243 reported for patients with BSIs caused by *A. baumannii*,[16,17] *P. aeruginosa*,[15,16] *S.*  
244 *aureus*,[1,4,15,16] *Enterobacteriaceae*,[4,16] and *Candida* spp.[1,16,18] In contrast,  
245 controversial results have been obtained regarding the mortality of patients affected by  
246 enterococcal bacteremia. While some authors have argued that *Enterococcus* spp. represents  
247 a low virulence pathogen[1] and is not associated with increased mortality unless in the  
248 presence of endocarditis,[19] other authors have reported contrasting results.[5,6,16,18] In  
249 the present study, significantly higher mortality was observed for patients with enterococcal  
250 bacteremia, and this may be due to vulnerability of the hosts examined, increased resistance,  
251 and a larger study population.

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4 252 The high healthcare burden of BSIs reported in previous literature[3,13,20] and in the  
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7 253 present study underscores the importance of preventing ICU-acquired BSIs by infection  
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10 254 control measurements. Furthermore, the results of these studies help to assess cost  
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13 255 effectiveness of infection control measurements in the process of policy-making. For example,  
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16 256 patients with ICU-acquired BSIs during the 9-year period cost Taiwan an estimated 297  
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19 257 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate  
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22 258 of infection by 10%[21] would translate into a savings of 30 million US dollars and 49,213  
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25 259 patient-days saved.

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28 260 Drug resistance has been found to be correlated with higher medical costs due to the  
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31 261 need for second-line antimicrobials for treatment, as well as additional diagnostic and  
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34 262 treatment tools.[22, 23] In the present study, the costs for MDR bacteria included extra 84  
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37 263 million US dollars and 140,043 days over nine years (Supplementary Table 5). However, cost  
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40 264 differences between susceptible and resistant strains were not determined in the present study.  
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43 265 Drug-susceptible strains were not included as controls due to differences in testing methods,  
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46 266 drugs, and breakpoints for these strains which could lead to mis-assignments of drug-resistant  
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49 267 pathogens as susceptible pathogens.

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52 268 Candidemia poses a great threat to ICU patients due to its excessive medical  
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55 269 burdens,[16,18,20] and *C. albicans* is the most common pathogen. However, in some  
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58 270 countries, the prevalence of non-*albicans* *Candida* exceeds that of *C. albicans*.[24] For those  
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4 271 infected with non-*albicans Candida*, higher rates of mortality,[24,25] longer hospitalization  
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7 272 stays, and increased hospital costs have been described;[25-27] although other studies have  
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10 273 reported contradicting findings.[28,29] These discrepancies may be due to host factors and  
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13 274 differences in the virulence and resistance patterns[24] of non-*albicans Candida*. In the  
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16 275 present study, the crude 14-day and in-hospital mortality rates of 951 patients infected with *C.*  
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19 276 *albicans* were 37.96% and 55.94%, respectively. In comparison, among 703 patients infected  
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22 277 with non-*albicans Candida*, these rates were 34.99% and 53.06%, respectively. While the  
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25 278 hospital costs and length of stay were higher in the non-*albicans Candida* group compared to  
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28 279 the *C. albicans* group, the 95% CI overlapped for the two groups (Table 4). These data  
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31 280 suggested that the clinical and economic outcomes of these two groups did not greatly differ.  
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34 281 However, the present study was not designed to specifically compare the outcomes of those  
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37 282 infected with *C. albicans* versus non-*albicans Candida*. Therefore, additional studies with a  
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40 283 larger number of patients, adjustment for host factors, and consideration of antifungal drugs,  
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43 284 incubation time, and treatment duration are needed to clarify the impact of each *Candida*  
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46 285 species.

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49 286 The large number of patients examined in this study and the use of propensity score  
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52 287 matching represent two major strengths of the present study. These aspects also allowed the  
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55 288 impact of each pathogen group to be discerned. However, there were also several limitations  
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58 289 associated with the present study which merit discussion. First, the exact cost after the index  
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4 290 date could not be retrieved from the NHIRD. Therefore, the high total cost shown in this  
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7 291 study may be due to costs incurred prior to the onset of a BSI. It is possible that matching of  
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10 292 the duration before the index date and comorbidity may have reduced overestimations of  
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13 293 healthcare costs due to time-dependent bias.[30] Second, confounding factors associated with  
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16 294 clinical impact, such as APACHE II or Pitt Bacteremia scores, were not included in this study.  
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19 295 Instead, other clinical risk factors (Charlson Comorbidity Index score, number of organ  
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22 296 failures, use of inotropic agents, and receipt of invasive procedures) were incorporated in our  
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25 297 model. Third, our study is inherently limited by its retrospective design, which includes a  
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28 298 dependence on the accuracy of the ICD codes used and unmeasurable bias.[31,32] Fourth, the  
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31 299 prolonged hospitalization may have been due to a change in patient management in response  
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34 300 to a BSI, rather than increased morbidity due to a BSI.[15] In addition, the number of  
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37 301 participating hospitals varied during study period and therefore was considered in propensity  
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40 302 score matching. Finally, the collection of personal identification numbers is not mandatory in  
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43 303 TNIS, which resulted in failure of interlink. However, their impact on the outcome was  
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46 304 unknown.

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## 306 **CONCLUSIONS**

307 ICU-acquired BSIs have a negative clinical and economic impact on affected patients  
308 regardless of the causative pathogens involved. Awareness of these negative affects is

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309 important for promoting infection control measurements and for policy-making.

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4 **311 LIST OF ABBREVIATIONS**  
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7 312 BSI = bloodstream infection;  
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10 313 CI = confidence interval;  
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13 314 ECDC = European Centre for Disease Prevention and Control;  
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16 315 ICD-9-CM = international classification of diseases, 9th revision, clinical modification;  
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19 316 ICU = intensive care unit;  
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22 317 IQR = interquartile range;  
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25 318 MDR = multiple drug resistance;  
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28 319 NHIRD = National Health Insurance Research Database;  
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31 320 OR = odds ratio;  
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34 321 TNIS = Taiwan Nosocomial Infection Surveillance;  
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37 322 WHO = World Health Organization;  
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4 **324 DECLARATIONS**

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7 **325 Ethics approval and consent to participate**

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10 326 The institutional review board of the National Health Research Institutes approved this study  
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13 327 (EC1051207-R4).  
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19 **329 Consent for publication**

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22 330 Not applicable.  
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28 **332 Availability of data and materials**

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31 333 The data that support the findings of this study are available from Ministry of Health and  
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34 334 Welfare, Taiwan but restrictions apply to the availability of these data, which were used  
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36  
37 335 under license for the current study, and so are not publicly available. Data are however  
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40 336 available from the authors upon reasonable request and with permission of Ministry of Health  
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43 337 and Welfare, Taiwan.  
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52 340 The authors declare that they have no competing interests.  
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19 348

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31 352 Formal analysis: SMS, YTC

34 353 Funding acquisition: YCW, SCK

37 354 Investigation: YCW, SCK

40 355 Methodology: YTC, CAH, SCK

43 356 Project administration: YCW, CAH, SCK

46 357 Resources: YTC, CAH, SCK

49 358 Software: SMS, YTC

52 359 Supervision: SMS, YTC

55 360 Validation: CAH, SCK

58 361 Visualization: YCW, SMS



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363 Writing—review & editing: YCW, CAH, SCK

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370 **REFERENCES**

- 371 1. Prowle JR, Echeverri JE, Ligabo EV, et al. Acquired bloodstream infection in the  
372 intensive care unit: incidence and attributable mortality. *Crit Care* 2011; **15**: R100.
- 373 2. Garrouste-Orgeas M, Timsit JF, Tafflet M, et al. Excess risk of death from intensive  
374 care unit-acquired nosocomial bloodstream infections: a re-appraisal. *Clin Infect Dis*  
375 2006; **42**: 1118-26.
- 376 3. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired  
377 bloodstream infections. *J Hosp Infect* 2006; **63**: 124-32.
- 378 4. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of  
379 bloodstream infections caused by antimicrobial-susceptible and non-susceptible  
380 Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011:  
381 a multicentre retrospective cohort study. *Euro Surveill* 2016; **21**: pii=30319.
- 382 5. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to  
383 nosocomial enterococcal bacteremia: a controlled study. *Am J Infect Control* 1989;  
384 **17**: 323-9.
- 385 6. Ong DS, Bonten MJ, Safdari K, et al. Epidemiology, management, and risk-adjusted  
386 mortality of ICU-acquired enterococcal bacteremia. *Clin Infect Dis* 2015; **61**:  
387 1413-20.
- 388 7. Kramer TS, Remschmidt C, Werner S, et al. The importance of adjusting for

- 1  
2  
3  
4 389 Enterococcus species when assessing the burden of vancomycin resistance: a cohort  
5  
6  
7 390 study including over 1000 cases of enterococcal bloodstream infections. *Antimicrob*  
8  
9  
10 391 *Resist Infect Control* 2018; **7**: 133.
- 11  
12  
13 392 8. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of  
14  
15  
16 393 new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis.  
17  
18  
19 394 *Lancet Infect Dis* 2018; **18**: 318-27.
- 20  
21  
22 395 9. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan.  
23  
24  
25 396 *London J Prim Care (Abingdon)* 2010; **3**: 115-9.
- 26  
27  
28 397 10. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in  
29  
30  
31 398 Ontario. *N Engl J Med* 2007; **357**: 1393-402.
- 32  
33  
34 399 11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with  
35  
36  
37 400 ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-9.
- 38  
39  
40 401 12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively  
41  
42  
43 402 drug-resistant and pandrug-resistant bacteria: an international expert proposal for  
44  
45  
46 403 interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**:  
47  
48  
49 404 268-81.
- 50  
51  
52 405 13. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill  
53  
54  
55 406 patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;  
56  
57  
58 407 **271**: 1598-601.
- 59  
60

- 1  
2  
3  
4 408 14. Laupland KB, Zygun DA, Davies HD, et al. Population-based assessment of intensive  
5  
6  
7 409 care unit-acquired bloodstream infections in adults: incidence, risk factors, and  
8  
9  
10 410 associated mortality rate. *Crit Care Med* 2002; **30**: 2462-7.  
11  
12  
13 411 15. Barnett AG, Page K, Campbell M, et al. The increased risks of death and extra lengths  
14  
15  
16 412 of hospital and ICU stay from hospital-acquired bloodstream infections: a  
17  
18  
19 413 case-control study. *BMJ Open* 2013; **3**: e003587.  
20  
21  
22 414 16. Marra AR, Camargo LF, Pignatari AC, et al. Nosocomial bloodstream infections in  
23  
24  
25 415 Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide  
26  
27  
28 416 surveillance study. *J Clin Microbiol* 2011; **49**: 1866-71.  
29  
30  
31 417 17. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in  
32  
33  
34 418 patients with *Acinetobacter baumannii* infection: systematic review and  
35  
36  
37 419 meta-analysis. *Clin Microbiol Infect* 2014; **20**: 416-23.  
38  
39  
40 420 18. Schwab F, Geffers C, Behnke M, et al. ICU mortality following ICU-acquired  
41  
42  
43 421 primary bloodstream infections according to the type of pathogen: a prospective  
44  
45  
46 422 cohort study in 937 Germany ICUs (2006-2015). *PloS One* 2018; **13**: e0194210.  
47  
48  
49 423 19. Caballero-Granado FJ, Becerril B, Cuberos L, et al. Attributable mortality rate and  
50  
51  
52 424 duration of hospital stay associated with enterococcal bacteremia. *Clin Infect Dis*  
53  
54  
55 425 2001; **32**: 587-94.  
56  
57  
58 426 20. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically  
59  
60

- 1  
2  
3  
4 427 ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis*  
5  
6  
7 428 2005; **41**: 1591-8.  
8  
9  
10 429 21. Tseng SH, Lee CM, Lin TY, et al. Combating antimicrobial resistance: antimicrobial  
11  
12  
13 430 stewardship program in Taiwan. *J Microbiol Immunol Infect* 2012; **45**: 79-89.  
14  
15  
16 431 22. Howard D, Cordell R, McGowan JE, Jr., et al. Measuring the economic costs of  
17  
18  
19 432 antimicrobial resistance in hospital settings: summary of the Centers for Disease  
20  
21  
22 433 Control and Prevention-Emory Workshop. *Clin Infect Dis* 2001; **33**: 1573-8.  
23  
24  
25 434 23. Mauldin PD, Salgado CD, Hansen IS, et al. Attributable hospital cost and length of  
26  
27  
28 435 stay associated with health care-associated infections caused by antibiotic-resistant  
29  
30  
31 436 gram-negative bacteria. *Antimicrob Agents Chemother* 2010; **54**: 109-15.  
32  
33  
34 437 24. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia  
35  
36  
37 438 in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin*  
38  
39  
40 439 *Infect Dis* 2009; **48**: 1695-703.  
41  
42  
43 440 25. Dimopoulos G, Ntziora F, Rachiotis G, et al. *Candida albicans* versus non-*albicans*  
44  
45  
46 441 intensive care unit-acquired bloodstream infections: differences in risk factors and  
47  
48  
49 442 outcome. *Anesth Analg* 2008; **106**: 523-9.  
50  
51  
52 443 26. Moran C, Grussemeier CA, Spalding JR, et al. Comparison of costs, length of stay,  
53  
54  
55 444 and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream  
56  
57  
58 445 infections. *Am J Infect Control* 2010; **38**: 78-80.  
59  
60

- 1  
2  
3  
4 446 27. Gong X, Luan T, Wu X, et al. Invasive candidiasis in intensive care units in China:  
5  
6  
7 447 risk factors and prognoses of *Candida albicans* and non-*albicans* *Candida* infections.  
8  
9  
10 448 *Am J Infect Control* 2016; **44**: e59-63.  
11  
12  
13 449 28. Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia  
14  
15  
16 450 in 3648 patients: data from the prospective antifungal therapy (PATH Alliance®)  
17  
18  
19 451 registry, 2004-2008. *Diagn Microbiol Infect Dis* 2012; **74**: 323-31.  
20  
21  
22 452 29. Barchiesi F, Orsetti E, Gesuita R, et al.; Candidemia Study Group. Epidemiology,  
23  
24  
25 453 clinical characteristics, and outcome of candidemia in a tertiary referral center in Italy  
26  
27  
28 454 from 2010 to 2014. *Infection* 2016; **44**: 205-13.  
29  
30  
31 455 30. Nelson RE, Samore MH, Jones M, et al. Reducing time-dependent bias in estimates of  
32  
33  
34 456 the attributable cost of health care-associated Methicillin-resistant *Staphylococcus*  
35  
36  
37 457 *aureus* infections: a comparison of three estimation strategies. *Med Care* 2015; **53**:  
38  
39  
40 458 827-34.  
41  
42  
43 459 31. Kuo SC, Shih SM, Hsieh LY, et al. Antibiotic restriction policy paradoxically  
44  
45  
46 460 increased private drug consumptions outside Taiwan's National Health Insurance. *J*  
47  
48  
49 461 *Antimicrob Chemother* 2017; **72**: 1544-5.  
50  
51  
52 462 32. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative  
53  
54  
55 463 data. *JAMA* 2012; **307**: 1433-5.  
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465 **Table 1. Characteristics of the intensive care unit patients with bloodstream infections**  
 466 **and the matched comparison cohort.**

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (63.03%)	17,861 (62.74%)	0.006
Age, years, mean (SD)	65.12 (21.62)	65.08 (20.60)	0.002
Length of stay before index date/ pseudo-index date, days, mean (SD)	15.69 (12.14)	15.29 (11.96)	0.033

## Monthly income, USD

Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001
Unknown	14 (0.1%)	33 (0.12%)	0.005

## Urbanization level

1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002
Unknown	11 (0.08%)	21 (0.07%)	0.001

## Hospital level

Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007

## Charlson Comorbidity Index

score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019

## Comorbidities

Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005



Myocardial infarction	525 (3.69%)	1,124 (3.95%)	0.014
Heart failure	2,532 (17.79%)	5,173 (18.17%)	0.01
Peripheral vascular disease	742 (5.21%)	1,509 (5.3%)	0.004
Liver disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Chronic kidney disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Dyslipidemia	2,766 (19.43%)	5,683 (19.96%)	0.013
Cancer	2,753 (19.34%)	5,635 (19.79%)	0.011
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (4.86%)	0.074
Use of inotropic agents	11,398 (80.08%)	22,858 (80.29%)	0.005
Use of steroid	9 (0.06%)	20 (0.07%)	0.003
Use of ventilator	12,493 (87.77%)	25,075 (88.08%)	0.01
Use of ventilator (>3 days)	11,668 (81.97%)	23,458 (82.4%)	0.011
Emergent renal replacement therapy	2615 (18.37%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

467 Abbreviations: BSI = bloodstream infection; SD = standard deviation.

468

469 **Table 2. Clinical and economic outcomes among patients with bloodstream infections and the matched comparison cohort.**

Outcomes	Full cohort			Matched cohort		
	ICU patients	Comparison	<i>P</i> -value	ICU patients	Comparison	<i>P</i> -value
	with BSI	cohort		with BSI	cohort	
No. of patients	17,834	713,518		14,234	28,468	
Clinical outcomes						
In-hospital mortality, n (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.2%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.3%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.4%)	9,189 (32.28%)	<0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 30)	10 (4, 21)	< 0.0001

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	(IQR)						
Cost of hospitalization (USD) <sup>a</sup> , median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001	
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,246)	(6,289, 16,932)		

470 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

471 <sup>a</sup>The costs are standardized and presented as the values in 2017.

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472 **Table 3. Clinical outcomes for the various pathogen groups.**

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
<i>Acinetobacter baumannii</i> (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
<i>Pseudomonas aeruginosa</i> (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae <sup>b</sup> (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
<i>Staphylococcus aureus</i> (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
<i>Enterococcus species</i> <sup>c</sup> (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
<i>Candida albicans</i> (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non- <i>albicans Candida</i> <sup>d</sup> (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

473 Abbreviations: MDR = multiple drug resistance.

474 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this  
475 analysis.

476 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*,  
477 *Enterobacter aerogenes*, and *Serratia marcescens*.

478 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other

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479 *Enterococcus species.*

480 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida*

481 *glabrata.*

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484 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,342 (5,500, 7,184)
<i>Acinetobacter baumannii</i>	9.4 (7.65, 11.14)	6,767 (5,823, 7,632)
<i>Pseudomonas aeruginosa</i>	10.01 (7.83, 12.19)	6,791 (5,609, 7,913)
Enterobacteriaceae <sup>b</sup>	15.05 (13.33, 16.76)	7,414 (6,881, 8,007)
<i>Staphylococcus aureus</i>	14.72 (12.63, 16.81)	5,241 (4,528, 5,894)
<i>Enterococcus species</i> <sup>c</sup>	10.66 (7.85, 13.48)	7,219 (6,305, 8,132)
<i>Candida albicans</i>	11.37 (8.82, 13.92)	8,698 (7,512, 9,864)

Non- <i>albicans Candida</i> <sup>d</sup>	15.13 (11.77, 18.49)	11,446 (10,025, 12,927)
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485 Abbreviations: MDR = multiple drug resistance.

486 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this analysis.

487 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Serratia marcescens*.

488 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

489 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

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4 493 **FIGURE LEGENDS**  
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7 494 **Figure 1. Flow diagram of the study design.**  
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16 497 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National

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19 498 Health Insurance Research Database.  
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505 **SUPPLEMENTARY FILES:**

506 Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before  
507 enrollment and the number of patients infected after matching.

508 Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched  
509 comparison cohort.

510 Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

511 Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the  
512 discharge.

513 Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.

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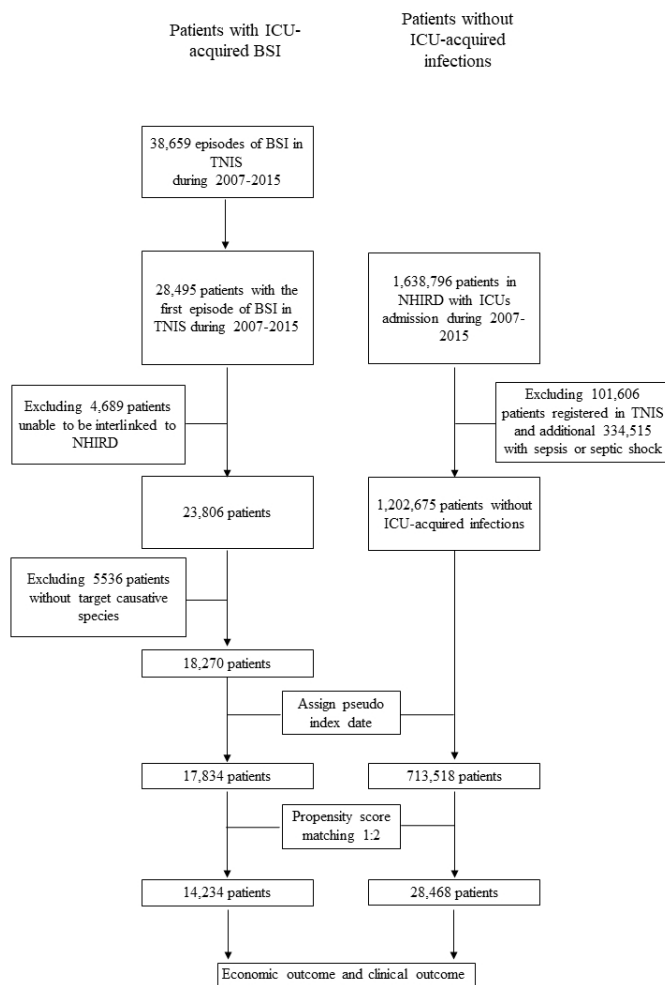


Figure 1. Flow diagram of the study design.

60x108mm (300 x 300 DPI)

1 **Supplementary Table 1. The number of episodes of intensive care unit-acquired**  
 2 **bloodstream infections caused by common pathogens before enrollment and the number**  
 3 **of patients infected after matching.**

	No. of BSI episodes before enrollment <sup>a</sup>	No. of patients after matching <sup>b</sup>
<i>Acinetobacter baumannii</i>	5,214	1,761
<i>Staphylococcus aureus</i>	4,382	1,721
<i>Klebsiella pneumoniae</i>	3,965	1,357
<i>Pseudomonas aeruginosa</i>	2,619	853
<i>Candida albicans</i>	2,554	951
<i>Escherichia coli</i>	2,287	843
<i>Enterobacter cloacae</i>	1,982	746
<i>Enterococcus faecium</i>	1,950	647
<i>Stenotrophomonas maltophilia</i>	1,599	454
<i>Enterococcus faecalis</i>	1,427	419
<i>Serratia marcescens</i>	1,239	439
<i>Candida tropicalis</i>	890	329
<i>Burkholderia cepacia</i>	808	251
Other <i>Enterococcus species</i> <sup>c</sup>	688	211
<i>Elizabethkingia meningoseptica</i>	659	173
<i>Chryseobacterium indologenes</i>	553	152
<i>Candida parapsilosis</i>	534	177
<i>Candida glabrata</i>	461	197
<i>Enterobacter aerogenes</i>	419	163

4 Abbreviations: BSI= bloodstream infection.

5 <sup>a</sup>The number of episodes of bloodstream infections with known pathogens was 38,659.

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3 6 Coagulase-negative staphylococci was excluded from analyses due to possibility of  
4  
5 7 contamination. One episode may have multiple pathogens. There were 30,697 episodes of  
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7 8 bloodstream infections caused by the pathogens listed above.

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9 9 <sup>b</sup>The number of patients enrolled case was 14,234 (Table 1) but only patients with  
10  
11 10 bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it  
12  
13 11 was 11,844. There were 2,390 patients with bloodstream infections caused by multiple  
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15 12 pathogens.

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17 13 <sup>c</sup>*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis*.  
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15 **Supplementary Table 2. Propensity score model results of probability of bloodstream**  
 16 **infections among intensive care unit patients and matched comparison cohort.**

Parameter	Estimate	Odds ratios	95% Confidence interval		P-value
			Lower	Upper	
			Age, years	-0.0014	
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

1						
2						
3	Dependent	--	1.000	--	--	--
4						
5	<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
6						
7	657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
8						
9	>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
10						
11						
12	Urbanization level					
13						
14	1 (urban)		1.000			
15						
16	2	0.0093	1.0094	0.9516	1.0706	0.7560
17						
18	3	-0.0006	0.9994	0.9293	1.0748	0.9872
19						
20	4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
21						
22						
23						
24	Hospital level					
25						
26	Level I (Medical center)	--	1.000	--	--	--
27						
28	Level II (Regional					
29	hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
30						
31	Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
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35	Charlson Comorbidity Index					
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37	score					
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39	0	--	1.000	--	--	--
40						
41	1	0.1421	1.1527	1.0681	1.2439	0.0003
42						
43	2	0.2932	1.3407	1.2390	1.4508	<0.0001
44						
45	≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
46						
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49	Comorbidities					
50						
51	Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
52						
53	Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
54						
55	Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
56						
57	Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292
58						
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Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

18 **Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and**  
 19 **antimicrobial agents used to define drug resistance.**

Pathogens	Antimicrobial categories	Antimicrobial agents	
<i>Acinetobacter baumannii</i> <sup>a</sup>	Aminoglycosides	Gentamicin	
		Tobramycin	
		Amikacin	
		Netilmicin	
	Carbapenems	Imipenem	
		Meropenem	
		Doripenem	
	Fluoroquinolones	Ciprofloxacin	
		Levofloxacin	
		Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid	
		Extended-spectrum cephalosporins	Cefotaxime
			Cefepime
			Cefpirome
<i>Pseudomonas aeruginosa</i> <sup>a</sup>	Aminoglycosides	Ceftazidime	
		Ceftriaxone	
		Gentamicin	
		Tobramycin	
	Carbapenems	Amikacin	
		Meropenem	



		Doripenem
		Ciprofloxacin
	Fluoroquinolones	Levofloxacin
		Piperacillin-tazobactam
	Antipseudomonal penicillins + $\beta$ -lactamase inhibitors	Ticarcillin-clavulanic acid
		Cefepime
	Antipseudomonal cephalosporins	Cefpirome
		Ceftazidime
		Gentamicin
		Tobramycin
	Aminoglycosides	Amikacin
		Netilmicin
		Imipenem
		Meropenem
	Carbapenems	Doripenem
		Ertapenem
		Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + $\beta$ -lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
		Cefotaxime
		Cefepime
	Extended-spectrum cephalosporins	Cefpirome
		Ceftazidime
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33	<i>Enterobacteriaceae</i> <sup>a</sup>	
34	( <i>Escherichia coli</i> ,	
35	<i>Klebsiella pneumoniae</i> ,	
36	<i>Enterobacter cloacae</i>	
37	<i>Enterobacter</i>	
38	<i>aerogenes</i> , or <i>Serratia</i>	
39	<i>marcescens</i> )	
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		Ceftriaxone
	Glycopeptides	Vancomycin
<i>Staphylococcus aureus</i> <sup>b</sup>	$\beta$ -lactamase-resistant penicillins	Oxacillin
<i>Enterococcus faecium</i> ,		
<i>Enterococcus faecalis</i> ,	Glycopeptides	Vancomycin
or other <i>Enterococcus</i>		
<i>species</i> <sup>b</sup>		

<sup>a</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories.

<sup>b</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent.

23 **Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to**  
 24 **the discharge.<sup>a</sup>**

		25
<b>Clinical outcomes</b>	<b>Excess costs or length of hospitalization (95% Confidence interval)<sup>b</sup></b>	<b>P-value</b>
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	26 27 28 < 0.0001 <sub>29</sub>
Cost of hospitalization, USD	8,871 (8,475, 9,268)	30 31 < 0.0001

32 <sup>a</sup>A total of 7,939 of patients with intensive care unit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

33 <sup>b</sup>Adjusted imbalanced variables in Table 1.

34

35 **Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.**

36

9-year excessive hospitalization or healthcare cost		
Pathogen groups	Length of hospitalization after the index date	Cost of hospitalization (USD) <sup>b, c</sup>
(Numbers of patients) <sup>a</sup>	(days) <sup>b</sup>	
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
<i>Acinetobacter baumannii</i> (5,214)	66,374	40,003,372
<i>Pseudomonas aeruginosa</i> (2,619)	33,340	20,093,754
<i>Enterobacteriaceae</i> <sup>d</sup> (9,486)	120,757	72,779,438
<i>Staphylococcus aureus</i> (4,382)	55,783	33,620,019
<i>Enterococcus species</i> <sup>e</sup> (4,045)	51,493	31,034,454
<i>Candida albicans</i> (2,554)	32,512	19,595,054
<i>Non-albicans Candida</i> <sup>f</sup> (1,872)	23,831	14,362,546

37 Abbreviations: MDR= multiple drug resistance.

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3 38 <sup>a</sup>The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The  
4  
5 39 inclusion and exclusion criteria in the method section were not applied in this Table (see Figure 1).  
6

7  
8 40 <sup>b</sup>The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s)  
9  
10 41 and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was  
11  
12 42 difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average  
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14 43 hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was  
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17 44 that in matched control group.

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19 45  $Ave_{Hospitalization}$  per case = [(sum of hospitalization length)/the number of patients].

20  
21 46 Excessive  $Ave_{Hospitalization}$  per person = ( $Ave_{Hospitalization}$  in bloodstream infection group) - ( $Ave_{Hospitalization}$  in comparison group).

22  
23 47 Total excessive hospitalization length over 9 years = (excessive  $Ave_{Hospitalization}$  per person) × (total number of episodes over 9 years)

24  
25 48 The 9-year excessive healthcare cost was calculated similarly.

26  
27 49 <sup>c</sup>The costs are standardized and presented the values in 2017.

28  
29 50 <sup>d</sup>*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa*, and *Serratia*  
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31  
32 51 *marcescens*.

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34 52 <sup>e</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

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36 53 <sup>f</sup>*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.  
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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	#1 and #3-4
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(b) For matched studies, give matching criteria and number of exposed and unexposed	#9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	#9-12
		(b) Describe any methods used to examine subgroups and interactions	#9-12
		(c) Explain how missing data were addressed	#10
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	#12
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#14
		(b) Give reasons for non-participation at each stage	#14
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#14 and #30-32
		(b) Indicate number of participants with missing data for each variable of interest	#19 and #31
		(c) Summarise follow-up time (eg, average and total amount)	#14-15
Outcome data	15*	Report numbers of outcome events or summary measures over time	#14-15
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#14-15
		(b) Report category boundaries when continuous variables were categorized	#14-15
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#15
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	#16
<b>Limitations</b>			#18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	#16-20
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#22-23

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections in Taiwan: A nationwide population-based retrospective cohort study

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4 **1 Article category: Original research**  
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10 **3 Clinical and Economic Impact of Intensive Care Unit-Acquired Bloodstream Infections**  
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13 **4 in Taiwan: A nationwide population-based retrospective cohort study**  
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33 **Text: 2742 words**

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4 35 **ABSTRACT**

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7 36 **Objectives:** To estimate the clinical and economic impact of intensive care unit-acquired  
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10 37 bloodstream infections in Taiwan.

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13 38 **Design:** Retrospective cohort study.

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16 39 **Setting:** Nationwide Taiwanese population in the National Health Insurance Research  
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19 40 Database and the Taiwan Nosocomial Infections Surveillance (2007-2015) dataset.

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22 41 **Participants:** The first episodes of intensive care unit-acquired bloodstream infections in  
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25 42 patients  $\geq 20$  years of age in the datasets. Propensity score-matching (1:2) of demographic  
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28 43 data, comorbidities, and disease severity was performed to select a comparison cohort from a  
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31 44 pool of intensive care unit patients without intensive care unit-acquired infections from the  
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34 45 same datasets.

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37 46 **Primary and secondary outcome measures:** The 14-day mortality rate, length of  
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40 47 hospitalization, and healthcare cost.

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43 48 **Results:** After matching, the in-hospital mortality of 14,234 patients with intensive care  
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46 49 unit-acquired bloodstream infections was 44.23%, compared to 33.48% for 28,468 intensive  
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49 50 care unit patients without bloodstream infections. The 14-day mortality rate was also higher  
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53 51 in the bloodstream infections cohort (4,323, 30.37% vs. 6,766 deaths, 23.77%, respectively;  $p$   
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55 52  $< 0.001$ ). Furthermore, the patients with intensive care unit-acquired bloodstream infections  
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58 53 had a prolonged length of hospitalization after their index date (18 days[IQR 7–39] vs. 10  
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4 54 days [IQR 4–21], respectively;  $p < 0.001$ ) and a higher healthcare cost (16,038 US dollars  
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7 55 [IQR 9,667–25,946] vs. 10,372 US dollars [IQR 6,289–16,932], respectively;  $p < 0.001$ ). The  
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10 56 excessive hospital stay and healthcare cost per case were 12.69 days and 7,669 US dollars,  
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12  
13 57 respectively. Similar results were observed in subgroup analyses of various World Health  
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16 58 Organization’s priority pathogens and *Candida* spp.

19 59 **Conclusions:** Intensive care unit-acquired bloodstream infections in critically ill patients  
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22 60 were associated with increased mortality, longer hospital stays, and higher healthcare costs.  
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31 63 **Keywords:** bloodstream infection; healthcare costs; hospital stay; intensive care unit;  
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34 64 mortality.  
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4 **66 STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 8 67 1. A large number of patients obtained from Nationwide Taiwanese population from two  
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10 68 datasets in Taiwan were included.  
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13 69 2. Propensity score-matching was performed to select a comparison cohort.  
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16 70 3. The 14-day and 28-day mortality rate, length of hospitalization, and healthcare cost were  
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18 71 analyzed.  
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22 72 4. Subgroup analyses of several drug-resistant pathogens were conducted.  
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26 73 5. The retrospective design may include some unmeasurable bias.  
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## 74 BACKGROUND

75 Critically ill patients in intensive care units (ICUs) are vulnerable to various infections,  
76 and these can lead to increased morbidity, mortality, and healthcare costs. Bloodstream  
77 infections (BSIs) are one of the most common infections acquired by ICU patients. It was  
78 reported that BSIs affected approximately 7 % of patients admitted to ICUs.[1] Previous  
79 studies have shown that ICU-acquired BSIs resulted in attributable mortality of 24.8%,[2]  
80 extended hospital stays by 13.5 days[3] and the cost of treatment was approximately 12,321  
81 US dollars per case. Moreover, despite advances in medical care and the development of new  
82 therapies, the outcome of BSIs in critically ill patients is adversely affected by a greater  
83 number of vulnerable hosts and the emergence of drug-resistant pathogens.

84 Discrepancies regarding the impact of pathogens on mortality have been reported.  
85 However, worse clinical outcome and higher economic burden have been reported for  
86 patients with BSI caused by resistant pathogens.[1, 4] For example, BSIs involving  
87 third-generation cephalosporin-resistant *Enterobacteriaceae* have been shown to significantly  
88 increase mortality risk compared to BSIs involving susceptible strains.[4] Moreover,  
89 candidemia has been associated with a 4-fold increase in mortality, while *Staphylococcus*  
90 *aureus* BSIs doubled the risk of mortality.[1] Meanwhile, the clinical impact of *Enterococci*  
91 remains a controversial topic.[5-7] Therefore, it is important not only to describe the clinical  
92 and economic impact of infections, but also to decipher the impact of individual pathogens.

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4 93 Due to the limited number of cases and the complex clinical characteristics of critically ill  
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7 94 patients, previous studies have reported either clinical or economic outcomes, have focused  
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10 95 on several species of pathogens, or have assessed only a limited number of pathogens. In the  
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13 96 present study, a health insurance database and a nationwide surveillance system for  
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16 97 healthcare-associated infections were used to estimate the clinical and economic  
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19 98 consequences of ICU-acquired BSIs caused by different pathogens in a large number of  
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22 99 patients in Taiwan. In addition, the impact of individual pathogens, especially  
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25 100 antibiotic-resistant bacteria on the World Health Organization (WHO) priority list,[8] were  
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28 101 investigated.



## 102 **METHODS**

### 103 **Data sources**

104 Two datasets, the National Health Insurance Research Database (NHIRD) and the  
105 Taiwan Nosocomial Infection Surveillance (TNIS) dataset, were used in this study.  
106 Demographic data, diagnoses (according to the International Classification of Diseases, 9th  
107 Revision, Clinical Modification [ICD-9-CM]), procedures, and medications for patients  
108 enrolled in Taiwan's national insurance system have been collected in the NHIRD since  
109 1995.[9] In 2007, the TNIS was launched by the Taiwan Centers for Disease Control to  
110 evaluate the epidemiologic trend of healthcare-associated infections in the ICUs in Taiwan.  
111 The latter is a web-based surveillance system which collects clinical information of patients  
112 with healthcare-associated infections from the ICUs of participating hospitals. This  
113 information includes demographic data, infection foci, causative pathogens, and antimicrobial  
114 susceptibility results. Participation in TNIS is essential for the hospital accreditation in  
115 Taiwan.

116 Both datasets were deposited in a database maintained by the Health and Welfare Data  
117 Science Center, Ministry of Health and Welfare. Individual personal identification numbers  
118 were encrypted so that data from the NHIRD and TNIS datasets could be interlinked. The  
119 institutional review board of the National Health Research Institutes approved this study  
120 (EC1051207-R4).

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4 1217 122 **Study population, data collection, and propensity-score matching**

10 123 This retrospective cohort study enrolled adult patients who underwent ICU  
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13 124 hospitalization between 2007 and 2015 in Taiwan. From the entries in the TNIS database, we  
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16 125 identified all of the patients whose first episode of an ICU-acquired BSI occurred during the  
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19 126 study period. Coagulase-negative *Staphylococci* are often identified in the ICUs but a certain  
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22 127 proportion is associated with contamination; therefore, these cases were not included in our  
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25 128 analysis. We included species that constituted > 1 % of known bloodstream pathogens  
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28 129 (Supplementary Table 1), which constituted 79.4% of all ICU-acquired BSI episodes. The  
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31 130 index date for each case was defined as the date on which a positive blood culture result was  
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34 131 obtained. The encrypted personal identification numbers of included patients were interlinked  
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37 132 with NHIRD to retrieve their demographic data, comorbidities, procedures, and medications.

40 133 For comparison, we identified ICU patients who did not have ICU-acquired infections  
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43 134 registered in TNIS database. In addition, patients with a discharge diagnosis of sepsis  
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46 135 (ICD-9-CM: 038.X, 995.91), severe sepsis (ICD-9-CM: 995.92), or septic shock (ICD-9-CM:  
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49 136 785.52) in the comparison cohort, but not in the BSI group, were also excluded. The pool of  
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52 137 comparison patients was created for selection of those with the same admission date as any  
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55 138 patient with ICU-acquired BSI. Because the comparison patients did not have index date of  
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58 139 acquisition of infection, they were assigned “pseudo-index dates” during hospitalization,  
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4 140 which was selected from the index date of patients with the same day of hospitalization in the  
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7 141 BSI group. Baseline variables and those associated with ICU-acquired BSIs were first  
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10 142 selected. Propensity scores were then calculated for the likelihood of ICU-acquired BSIs by  
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13 143 multivariate logistic regression analysis. Variables were removed from the multivariable  
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16 144 model in a stepwise fashion. We used 1:2 greedy matching [10] within a caliper width equal  
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19 145 to 0.1 of the standard deviation of the logit of the propensity score. (Supplementary Table 2).  
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22 146 Patient data from January 2005 were used to ensure that individuals were followed for at least  
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25 147 two years prior to their selection for this study in order to confirm comorbidities [11] and for  
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28 148 matching purposes. The determination of comorbidities and organ dysfunction by ICD-9-CM  
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31 149 codes were in accordance with the previous studies [11-13]. The variables with missing  
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34 150 values included monthly income and urbanization level. Missing values were treated as a  
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37 151 separate category by itself. The low rate of missing data (Table 1) may not have a great  
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40 152 impact on our study.

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#### 44 45 46 154 **Patient and Public Involvement**

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49 155 Patients and the public were not directly involved in the planning of this study.

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#### 53 54 55 157 **Outcome measurements**

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58 158 Clinical outcomes included in-hospital, 14-day, and 28-day mortality rate after the index  
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4 159 date/pseudo-index date. Economic outcomes included hospitalization length after the index  
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7 160 date/pseudo-index date and cost of overall hospitalization. Hospitalization length was defined  
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10 161 as the duration of hospital stay after the index date/pseudo-index date. The overall cost of  
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13 162 hospitalization was calculated. The costs were standardized and presented in values from  
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### 20 21 22 165 **Subgroup analysis**

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25 166 To evaluate the clinical and economic impact of ICU-acquired BSIs caused by different  
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28 167 pathogens, we performed analyses on patients infected with single pathogen. For example,  
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31 168 the impact of WHO priority bacteria and *Candida* were examined separately, as was the  
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34 169 impact of drug resistance in these bacteria. We included patients whose first episode of an  
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37 170 ICU-acquired BSI were caused by bacteria on the WHO priority list or *Candida*. Therefore,  
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40 171 the clinical and economic outcomes of patients with *Acinetobacter baumannii*, *Pseudomonas*  
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43 172 *aeruginosa*, common *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*,  
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46 173 *Enterobacter* species, and *Serratia marcescens*), *S. aureus*, *Enterococcus* species, *Candida*  
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49 174 *albicans*, and non-*albicans Candida* (*Candida tropicalis*, *Candida parapsilosis*, and *Candida*  
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52 175 *glabrata*) were determined.

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55 176 The definition of multiple drug resistance (MDR) of WHO priority bacteria according to  
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58 177 the European Centre for Disease Prevention and Control (ECDC) was modified [14]  
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4 178 (Supplementary Table 3). In this study, non-susceptibility to at least one agent in at least  
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7 179 three antimicrobial categories in Gram-negative bacteria was defined as MDR. Oxacillin- and  
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10 180 vancomycin-non-susceptible *S. aureus* and vancomycin-non-susceptible *Enterococcus*  
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13 181 species were considered MDR Gram-positive bacteria.  
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### 19 183 **Sensitivity analysis**

22 184 To avoid competing risk between mortality and length of hospitalization/healthcare cost,  
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25 185 we included patients who survived to discharge. For these patients, length of hospitalization  
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28 186 after the index date/pseudo-index date and hospitalization costs were determined.  
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### 34 188 **Statistical analysis**

37 189 Descriptive statistics were used to examine baseline demographic and clinical  
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40 190 characteristics of the ICU patients included in this study. To account for potential  
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43 191 confounding biases among the study cohort, propensity score matching analysis was  
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46 192 performed. Propensity scores were calculated with multivariate logistic regression.  
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49 193 Standardized differences between the two groups with differences less than 0.1 were  
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52 194 confirmed in order to assess baseline characteristics. The Mann-Whitney U test was used to  
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55 195 evaluate economic outcomes and the Chi-squared test was used to evaluate mortality rate.  
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58 196 Conditional logistic regression was used to calculate odds ratios (ORs) to evaluate risk of  
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4 197 mortality in patients with BSI and the comparison cohort, while a generalized linear model  
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7 198 was used to calculate  $\beta$  values to estimate excess costs and length of hospitalization.  
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10 199 Variables with a  $p$ -value  $< 0.05$  were eligible for inclusion in the model.  $P$ -values less than  
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13 200 0.05 were considered statistically significant. All analyses were performed by using SAS  
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16 201 statistical software (version 9.4, SAS Institute Inc., Cary, NC, USA).  
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## 203 RESULTS

204 Among 38,659 episodes of ICU-acquired BSIs registered in TNIS during the 9-year  
205 study period, 28,495 patients were identified to have their first episode of a BSI. The NHIRD  
206 included 1,638,796 patients who underwent ICU hospitalization (Figure 1). After excluding  
207 patients whose data could not be interlinked with NHIRD or who did not have target  
208 pathogens, 14,234 patients with ICU-acquired BSIs were successfully matched to 28,468  
209 ICU patients without ICU-acquired infections (1:2). The demographic and clinical  
210 characteristics of the patients with BSI and comparison cohort are presented in Table 1. The  
211 groups had standardized differences that were  $< 10\%$  for all of the continuous and  
212 dichotomous categorical variables which were examined.

213 Table 2 lists the clinical and economic outcomes of the ICU patients with BSIs and the  
214 comparison cohort. The ICU patients with BSIs suffered a higher in-hospital mortality rate  
215 (44.23% vs. 33.48%, respectively;  $p < 0.001$ ), a higher 14-day mortality rate (30.37% vs.  
216 23.77%, respectively;  $p < 0.001$ ), and a higher 28-day mortality (39.48% vs. 32.28%,  
217 respectively;  $p < 0.001$ ). Logistic regression analyses showed that the OR of in-hospital  
218 mortality for the ICU patients with BSIs was 1.67 (95% confidence interval [CI], 1.59–1.75;  
219  $p < 0.001$ ), and it was 1.42 (95% CI, 1.35–1.49;  $p < 0.001$ ) for 14-day mortality and 1.41  
220 (95% CI, 1.34–1.47;  $p < 0.001$ ) for 28-day mortality. These significant associations were also  
221 observed in the subgroup analyses performed (Table 3).

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4 222 The ICU patients with BSIs had a longer length of hospitalization after the index date  
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7 223 (18 vs. 10 days, respectively;  $p < 0.001$ ). Moreover, on average, their hospital stay was  
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10 224 extended by 12.69 days (95% CI, 11.92–13.47;  $p < 0.001$ ). The subgroup analyses performed  
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13 225 (Table 4) showed that all of the causative pathogens shared a similar trend. Compared with  
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16 226 the patients without ICU-acquired infections, the duration of hospitalization after the index  
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19 227 date for those with BSIs caused by MDR bacteria, WHO priority bacteria, or *Candida* spp.  
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22 228 was longer. In addition, hospitalization costs of the ICU patients with BSIs were higher  
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25 229 (16,038 vs. 10,372, respectively;  $p < 0.001$ ) (Table 2), with the excess cost being 7,669 US  
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28 230 dollars per patient (95% CI, 7,380–7,958;  $p < 0.001$ ). Table 4 presents the higher costs  
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31 231 associated with each of the various causative pathogen.

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34 232 For the ICU patients with BSIs who survived to discharge, their length of hospitalization  
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37 233 and healthcare costs were increased by 19.59 days and 8,871 US dollars, respectively,  
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40 234 (Supplementary Table 4) compared to the survivors without ICU-acquired infections.  
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## 235 DISCUSSION

236 This study demonstrated that ICU patients with BSIs in Taiwan had significantly worse  
237 clinical outcomes and higher economic burden than ICU patients without ICU-acquired  
238 infections from the same population. For example, the patients with BSI exhibited 1.67-,  
239 1.42-, and 1.41-fold increases in in-hospital, 14-day, and 28-day mortality rates, respectively.  
240 Per case, the patients with BSI had an excess hospital stay of 12.69 days and cost of 7,669 US  
241 dollars. Furthermore, a similar clinical and economic impact was observed among all of the  
242 causative pathogens examined.

243 BSIs have been associated with higher mortality and morbidity, contingent on the  
244 causative pathogen involved. [1, 3, 15-18] For example, worse clinical outcomes have been  
245 reported for patients with BSIs caused by *A. baumannii*, [18, 19] *P. aeruginosa*, [17, 18] *S.*  
246 *aureus*, [1, 4, 17, 18] *Enterobacteriaceae*, [4, 18] and *Candida* spp. [1, 18, 20] In contrast,  
247 controversial results have been obtained regarding the mortality of patients affected by  
248 enterococcal bacteremia. While some authors have argued that *Enterococcus* spp. represents  
249 a low virulence pathogen [1] and is not associated with increased mortality unless in the  
250 presence of endocarditis, [21] other authors have reported contrasting results. [5, 6, 18, 20] In  
251 the present study, significantly higher mortality was observed for patients with enterococcal  
252 bacteremia, and this may be due to vulnerability of the hosts examined, increased resistance,  
253 and a larger study population.

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4 254 The high healthcare burden of BSIs reported in previous literature [3, 15, 22] and in the  
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7 255 present study underscores the importance of preventing ICU-acquired BSIs by infection  
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10 256 control measurements. Furthermore, the results of these studies help to assess cost  
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13 257 effectiveness of infection control measurements in the process of policy-making. For example,  
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16 258 patients with ICU-acquired BSIs during the 9-year period cost Taiwan an estimated 297  
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19 259 million US dollars and 492,129 days (supplementary Table 5). A policy that reduced the rate  
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22 260 of infection by 10% [23] would translate into a savings of 30 million US dollars and 49,213  
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25 261 patient-days saved.

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28 262 Drug resistance has been found to be correlated with higher medical costs due to the  
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31 263 need for second-line antimicrobials for treatment, as well as additional diagnostic and  
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34 264 treatment tools. [24, 25] In the present study, the costs for MDR bacteria included extra 84  
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37 265 million US dollars and 140,043 days over nine years (Supplementary Table 5). However, cost  
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40 266 differences between susceptible and resistant strains were not determined in the present study.  
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43 267 Drug-susceptible strains were not included as controls due to differences in testing methods,  
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46 268 drugs, and breakpoints for these strains which could lead to mis-assignments of drug-resistant  
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49 269 pathogens as susceptible pathogens.

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52 270 Candidemia poses a great threat to ICU patients due to its excessive medical burdens,  
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55 271 [18, 20, 22] and *C. albicans* is the most common pathogen. However, in some countries, the  
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58 272 prevalence of non-*albicans* *Candida* exceeds that of *C. albicans*. [26] For those infected with  
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4 273 non-*albicans Candida*, higher rates of mortality,[26, 27] longer hospitalization stays, and  
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7 274 increased hospital costs have been described;[27-29] although other studies have reported  
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10 275 contradicting findings.[30, 31] These discrepancies may be due to host factors and  
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13 276 differences in the virulence and resistance patterns [26] of non-*albicans Candida*. In the  
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16 277 present study, the crude 14-day and in-hospital mortality rates of 951 patients infected with *C.*  
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19 278 *albicans* were 37.96% and 55.94%, respectively. In comparison, among 703 patients infected  
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22 279 with non-*albicans Candida*, these rates were 34.99% and 53.06%, respectively. While the  
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25 280 hospital costs and length of stay were higher in the non-*albicans Candida* group compared to  
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28 281 the *C. albicans* group, the 95% CI overlapped for the two groups (Table 4). These data  
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31 282 suggested that the clinical and economic outcomes of these two groups did not greatly differ.  
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34 283 However, the present study was not designed to specifically compare the outcomes of those  
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37 284 infected with *C. albicans* versus non-*albicans Candida*. Therefore, additional studies with a  
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40 285 larger number of patients, adjustment for host factors, and consideration of antifungal drugs,  
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43 286 incubation time, and treatment duration are needed to clarify the impact of each *Candida*  
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49 288 The large number of patients examined in this study and the use of propensity score  
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52 289 matching represent two major strengths of the present study. These aspects also allowed the  
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55 290 impact of each pathogen group to be discerned. However, there were also several limitations  
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58 291 associated with the present study which merit discussion. First, the exact cost after the index  
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4 292 date could not be retrieved from the NHIRD. Therefore, the high total cost shown in this  
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7 293 study may be due to costs incurred prior to the onset of a BSI. It is possible that matching of  
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10 294 the duration before the index date and comorbidity may have reduced overestimations of  
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13 295 healthcare costs due to time-dependent bias.[32] Second, confounding factors associated with  
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16 296 clinical impact, such as APACHE II or Pitt Bacteremia scores, were not included in this study.  
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19 297 Instead, other clinical risk factors (Charlson Comorbidity Index score, number of organ  
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22 298 failures, use of inotropic agents, and receipt of invasive procedures) were incorporated in our  
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25 299 model. Third, our study is inherently limited by its retrospective design, which includes a  
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28 300 dependence on the accuracy of the ICD codes used and unmeasurable bias.[33, 34] Fourth,  
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31 301 the prolonged hospitalization may have been due to a change in patient management in  
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34 302 response to a BSI, rather than increased morbidity due to a BSI.[17] Fifth, the number of  
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37 303 participating hospitals varied during study period and therefore was considered in propensity  
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40 304 score matching. Finally, the collection of personal identification numbers is not mandatory in  
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43 305 TNIS, which resulted in failure of interlink. However, their impact on the outcome was  
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46 306 unknown. In addition, the administrative data are inherently subjected to coding errors and  
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49 307 changes in coding practices.[34]

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## 53 54 55 309 **CONCLUSIONS**

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58 310 ICU-acquired BSIs have a negative clinical and economic impact on affected patients  
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311 regardless of the causative pathogens involved. Awareness of these negative affects is

312 important for promoting infection control measurements and for policy-making.

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4 **314 LIST OF ABBREVIATIONS**  
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6  
7 315 BSI = bloodstream infection;  
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10 316 CI = confidence interval;  
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13 317 ECDC = European Centre for Disease Prevention and Control;  
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16 318 ICD-9-CM = international classification of diseases, 9th revision, clinical modification;  
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19 319 ICU = intensive care unit;  
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22 320 IQR = interquartile range;  
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25 321 MDR = multiple drug resistance;  
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28 322 NHIRD = National Health Insurance Research Database;  
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31 323 OR = odds ratio;  
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34 324 TNIS = Taiwan Nosocomial Infection Surveillance;  
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37 325 WHO = World Health Organization;  
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4 **327 DECLARATIONS**

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7 **328 Ethics approval and consent to participate**

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10 329 The institutional review board of the National Health Research Institutes approved this study  
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13 330 (EC1051207-R4).

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19 **332 Consent for publication**

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22 333 Not applicable.

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28 **335 Availability of data and materials**

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31 336 The data that support the findings of this study are available from Ministry of Health and

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34 337 Welfare, Taiwan but restrictions apply to the availability of these data, which were used

35  
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37 338 under license for the current study, and so are not publicly available. Data are however

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40 339 available from the authors upon reasonable request and with permission of Ministry of Health

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43 340 and Welfare, Taiwan.

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52 343 The authors declare that they have no competing interests.

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19 351

22 352 **Author contributions**

25 353 Conceptualization: CAH, SCK

28 354 Data curation: YTC, CAH, SCK

31 355 Formal analysis: SMS, YTC

34 356 Funding acquisition: YCW, SCK

37 357 Investigation: YCW, SCK

40 358 Methodology: YTC, CAH, SCK

43 359 Project administration: YCW, CAH, SCK

46 360 Resources: YTC, CAH, SCK

49 361 Software: SMS, YTC

52 362 Supervision: SMS, YTC

55 363 Validation: CAH, SCK

58 364 Visualization: YCW, SMS



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366 Writing—review & editing: YCW, CAH, SCK

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## 373 REFERENCES

- 374 1. Prowle JR, Echeverri JE, Ligabo EV, et al. Acquired bloodstream infection in the  
375 intensive care unit: incidence and attributable mortality. *Crit Care* 2011; **15**: R100.
- 376 2. Garrouste-Orgeas M, Timsit JF, Tafflet M, et al. Excess risk of death from intensive  
377 care unit-acquired nosocomial bloodstream infections: a re-appraisal. *Clin Infect Dis*  
378 2006; **42**: 1118-26.
- 379 3. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired  
380 bloodstream infections. *J Hosp Infect* 2006; **63**: 124-32.
- 381 4. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of  
382 bloodstream infections caused by antimicrobial-susceptible and non-susceptible  
383 Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011:  
384 a multicentre retrospective cohort study. *Euro Surveill* 2016; **21**: pii=30319.
- 385 5. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to  
386 nosocomial enterococcal bacteremia: a controlled study. *Am J Infect Control* 1989;  
387 **17**: 323-9.
- 388 6. Ong DS, Bonten MJ, Safdari K, et al. Epidemiology, management, and risk-adjusted  
389 mortality of icu-acquired enterococcal bacteremia. *Clin Infect Dis* 2015; **61**: 1413-20.
- 390 7. Kramer TS, Remschmidt C, Werner S, et al. The importance of adjusting for  
391 enterococcus species when assessing the burden of vancomycin resistance: a cohort  
392 study including over 1000 cases of enterococcal bloodstream infections. *Antimicrob*  
393 *Resist Infect Control* 2018; **7**: 133.
- 394 8. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of  
395 new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis.  
396 *Lancet Infect Dis* 2018; **18**: 318-27.
- 397 9. Wu TY, Majeed A, Kuo KN. An overview of the healthcare system in Taiwan.  
398 *London J Prim Care (Abingdon)* 2010; **3**: 115-9.
- 399 10. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in  
400 Ontario. *N Engl J Med* 2007; **357**: 1393-402.
- 401 11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with  
402 ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-9.
- 403 12. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining  
404 comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; **43**:  
405 1130-9.
- 406 13. Shen HN, Lu CL, Li CY. Effect of diabetes on severity and hospital mortality in  
407 patients with acute pancreatitis: a national population-based study. *Diabetes Care*  
408 2012; **35**: 1061-6.
- 409 14. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively

- 1  
2  
3  
4 410 drug-resistant and pandrug-resistant bacteria: an international expert proposal for  
5 411 interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**:  
6 412 268-81.
- 8 413 15. Pittet D, Tarara D, Wenzel RP. Nosocomial Bloodstream Infection in Critically III  
9 414 Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality. *JAMA* 1994;  
10 415 **271**: 1598-601.
- 12 416 16. Laupland KB, Zygun DA, Davies HD, et al. Population-based assessment of intensive  
13 417 care unit-acquired bloodstream infections in adults: Incidence, risk factors, and  
14 418 associated mortality rate. *Crit Care Med* 2002; **30**: 2462-7.
- 17 419 17. Barnett AG, Page K, Campbell M, et al. The increased risks of death and extra lengths  
18 420 of hospital and ICU stay from hospital-acquired bloodstream infections: a  
19 421 case-control study. *BMJ Open* 2013; **3**: e003587.
- 21 422 18. Marra AR, Camargo LF, Pignatari AC, et al. Nosocomial bloodstream infections in  
22 423 Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide  
23 424 surveillance study. *J Clin Microbiol* 2011; **49**: 1866-71.
- 26 425 19. Lemos EV, de la Hoz FP, Einarson TR, et al. Carbapenem resistance and mortality in  
27 426 patients with *Acinetobacter baumannii* infection: systematic review and  
28 427 meta-analysis. *Clin Microbiol Infect* 2014; **20**: 416-23.
- 30 428 20. Schwab F, Geffers C, Behnke M, et al. ICU mortality following ICU-acquired  
31 429 primary bloodstream infections according to the type of pathogen: A prospective  
32 430 cohort study in 937 Germany ICUs (2006-2015). *PloS One* 2018; **13**: e0194210.
- 35 431 21. Caballero-Granado FJ, Becerril B, Cuberos L, et al. Attributable mortality rate and  
36 432 duration of hospital stay associated with enterococcal bacteremia. *Clin Infect Dis*  
37 433 2001; **32**: 587-94.
- 39 434 22. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically  
40 435 ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis*  
41 436 2005; **41**: 1591-8.
- 44 437 23. Tseng SH, Lee CM, Lin TY, et al. Combating antimicrobial resistance: Antimicrobial  
45 438 stewardship program in Taiwan. *J Microbiol Immunol Infect* 2012; **45**: 79-89.
- 47 439 24. Howard D, Cordell R, McGowan JE, Jr., et al. Measuring the economic costs of  
48 440 antimicrobial resistance in hospital settings: summary of the Centers for Disease  
49 441 Control and Prevention-Emory Workshop. *Clin Infect Dis* 2001; **33**: 1573-8.
- 51 442 25. Mauldin PD, Salgado CD, Hansen IS, et al. Attributable hospital cost and length of  
52 443 stay associated with health care-associated infections caused by antibiotic-resistant  
53 444 gram-negative bacteria. *Antimicrob Agents Chemother* 2010; **54**: 109-15.
- 56 445 26. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and Outcomes of Candidemia  
57 446 in 2019 Patients: Data from the Prospective Antifungal Therapy Alliance Registry.  
58 447 *Clin Infect Dis* 2009; **48**: 1695-703.
- 59  
60

- 1  
2  
3 448 27. Dimopoulos G, Ntziora F, Rachiotis G, et al. *Candida albicans* versus non-*albicans*  
4 449 intensive care unit-acquired bloodstream infections: differences in risk factors and  
5 450 outcome. *Anesth Analg* 2008; **106**: 523-9.  
6  
7  
8 451 28. Moran C, Grussemeyer CA, Spalding JR, et al. Comparison of costs, length of stay,  
9 452 and mortality associated with *Candida glabrata* and *Candida albicans* bloodstream  
10 453 infections. *Am J Infect Control* 2010; **38**: 78-80.  
11  
12 454 29. Gong X, Luan T, Wu X, et al. Invasive candidiasis in intensive care units in China:  
13 455 Risk factors and prognoses of *Candida albicans* and non-*albicans* *Candida* infections.  
14 456 *Am J Infect Control* 2016; **44**: e59-63.  
15  
16 457 30. Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia  
17 458 in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance(R))  
18 459 registry, 2004-2008. *Diagn Microbiol Infect Dis* 2012; **74**: 323-31.  
19  
20 460 31. Barchiesi F, Orsetti E, Gesuita R, et al. Epidemiology, clinical characteristics, and  
21 461 outcome of candidemia in a tertiary referral center in Italy from 2010 to 2014.  
22 462 *Infection* 2016; **44**: 205-13.  
23  
24 463 32. Nelson RE, Samore MH, Jones M, et al. Reducing Time-dependent Bias in Estimates  
25 464 of the Attributable Cost of Health Care-associated Methicillin-resistant  
26 465 *Staphylococcus aureus* Infections: A Comparison of Three Estimation Strategies. *Med*  
27 466 *Care* 2015; **53**: 827-34.  
28  
29 467 33. Kuo SC, Shih SM, Hsieh LY, et al. Antibiotic restriction policy paradoxically  
30 468 increased private drug consumptions outside Taiwan's National Health Insurance. *J*  
31 469 *Antimicrob Chemother* 2017; **72**: 1544-5.  
32  
33 470 34. Sarrazin MSV, Rosenthal GE. Finding pure and simple truths with administrative  
34 471 data. *JAMA* 2012; **307**: 1433-5.  
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473 **Table 1. Characteristics of the intensive care unit patients with bloodstream infections**  
 474 **and the matched comparison cohort.**

Characteristics	Patients with BSI, n (%)	Comparison cohort, n (%)	Standardized difference
No. of patients	14,234	28,468	
Year of Index Date			
2007	1,244 (8.74%)	3,474 (12.2%)	0.113
2008	1,608 (11.3%)	3,101 (10.89%)	0.013
2009	1,714 (12.04%)	2,923 (10.27%)	0.056
2010	1,745 (12.26%)	3,119 (10.96%)	0.041
2011	1,947 (13.68%)	3,107 (10.91%)	0.084
2012	1,727 (12.13%)	3,119 (10.96%)	0.037
2013	1,496 (10.51%)	2,985 (10.49%)	0.001
2014	1,371 (9.63%)	3,226 (11.33%)	0.056
2015	1,382 (9.71%)	3,414 (11.99%)	0.073
Season of In-date			
Mar-May	3,564 (25.04%)	7,207 (25.32%)	0.006
Jun-Aug	3,577 (25.13%)	7,224 (25.38%)	0.006
Sep-Nov	3,519 (24.72%)	6,964 (24.46%)	0.006
Dec-Feb	3,574 (25.11%)	7,073 (24.85%)	0.006
Males	8,971 (63.03%)	17,861 (62.74%)	0.006
Age, years, mean (SD)	65.12 (21.62)	65.08 (20.60)	0.002
Length of stay before index date/ pseudo-index date, days, mean (SD)	15.69 (12.14)	15.29 (11.96)	0.033

## Monthly income, USD

Dependent	2,416 (16.97%)	4,813 (16.91%)	0.002
< 657.33	4,740 (33.3%)	9,575 (33.63%)	0.007
657.33–1504.60	6,324 (44.43%)	12,563 (44.13%)	0.006
> 1504.60	740 (5.2%)	1,484 (5.21%)	0.001
Unknown	14 (0.1%)	33 (0.12%)	0.005

## Urbanization level

1 (urban)	3,639 (25.57%)	7,293 (25.62%)	0.001
2	3,968 (27.88%)	7,920 (27.82%)	0.001
3	2,227 (15.65%)	4,432 (15.57%)	0.002
4 (rural)	4,389 (30.83%)	8,802 (30.92%)	0.002
Unknown	11 (0.08%)	21 (0.07%)	0.001

## Hospital level

Medical center	7,168 (50.36%)	14,393 (50.56%)	0.004
Regional hospital	6,125 (43.03%)	12,242 (43%)	0.001
Local hospital	940 (6.6%)	1,833 (6.44%)	0.007

## Charlson Comorbidity Index

score, mean (SD)	3.085 (2.80)	3.105 (2.95)	0.007
0	2,950 (20.73%)	6,411 (22.52%)	0.044
1	1,930 (13.56%)	3,928 (13.8%)	0.007
2	2,283 (16.04%)	4,251 (14.93%)	0.031
≥ 3	7,071 (49.68%)	13,878 (48.75%)	0.019

## Comorbidities

Diabetes mellitus	4,840 (34%)	9,642 (33.87%)	0.003
Cerebrovascular disease	3,552 (24.95%)	7,048 (24.76%)	0.005

Myocardial infarction	525 (3.69%)	1,124 (3.95%)	0.014
Heart failure	2,532 (17.79%)	5,173 (18.17%)	0.01
Peripheral vascular disease	742 (5.21%)	1,509 (5.3%)	0.004
Liver disease	2,740 (19.25%)	5,393 (18.94%)	0.008
Chronic kidney disease	3,864 (27.15%)	7,982 (28.04%)	0.02
Dyslipidemia	2,766 (19.43%)	5,683 (19.96%)	0.013
Cancer	2,753 (19.34%)	5,635 (19.79%)	0.011
Number of dysfunctional organs, mean (SD)	1.015 (0.809)	1.02 (0.855)	0.005
0	4,035 (28.35%)	8,549 (30.03%)	0.037
1	6,445 (45.28%)	12,293 (43.18%)	0.042
2	3,273 (22.99%)	6,243 (21.93%)	0.026
≥ 3	481 (3.38%)	1,383 (4.86%)	0.074
Use of inotropic agents	11,398 (80.08%)	22,858 (80.29%)	0.005
Use of steroid	9 (0.06%)	20 (0.07%)	0.003
Use of ventilator	12,493 (87.77%)	25,075 (88.08%)	0.01
Use of ventilator (>3 days)	11,668 (81.97%)	23,458 (82.4%)	0.011
Emergent renal replacement therapy	2615 (18.37%)	5,370 (18.86%)	0.013
Propensity score (SD)	0.128 (0.109)	0.127 (0.109)	0.004

475 Abbreviations: BSI = bloodstream infection; SD = standard deviation.

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477 **Table 2. Clinical and economic outcomes among patients with bloodstream infections and the matched comparison cohort.**

Outcomes	Full cohort			Matched cohort		
	ICU patients	Comparison	<i>P</i> -value	ICU patients	Comparison	<i>P</i> -value
	with BSI	cohort		with BSI	cohort	
No. of patients	17,834	713,518		14,234	28,468	
Clinical outcomes						
In-hospital mortality, n (%)	8,639 (48.44)	65,282 (9.15)	< 0.0001	6,295 (44.2%)	9,532 (33.48%)	< 0.0001
14-day mortality, n (%)	5,693 (31.92)	54,998 (7.71)	< 0.0001	4,323 (30.37%)	6,766 (23.77%)	< 0.0001
28-day mortality, n (%)	7,469 (42.01)	73,552 (10.31)	< 0.0001	5,619 (39.48%)	9,189 (32.28%)	< 0.0001
Economic outcomes						
Length of hospitalization after the index date/pseudo-index date, days, median	18 (6, 40)	6 (3, 13)	< 0.0001	18 (7, 30)	10 (4, 21)	< 0.0001



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	(IQR)					
Cost of hospitalization (USD) <sup>a</sup> , median	18,457	4,971	< 0.0001	16,038	10,372	< 0.0001
(IQR)	(10,938, 30,778)	(2,770, 8,598)		(9,667, 25,246)	(6,289, 16,932)	

478 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; IQR= interquartile range.

479 <sup>a</sup>The costs are standardized and presented as the values in 2017.

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480 **Table 3. Clinical outcomes for the various pathogen groups.**

Pathogen groups (Number of patients)	Odds ratio (95% Confidence interval)		
	In-hospital mortality	14-days mortality	28-days mortality
MDR Gram-negative bacteria (2,232)	2.12 (1.89, 2.38)	1.77 (1.57, 1.99)	1.79 (1.6, 2)
MDR Gram-positive bacteria (1,429)	1.84 (1.59, 2.12)	1.52 (1.31, 1.76)	1.5 (1.3, 1.72)
<i>Acinetobacter baumannii</i> (1,761)	1.67 (1.47, 1.91)	1.45 (1.26, 1.66)	1.45 (1.27, 1.66)
<i>Pseudomonas aeruginosa</i> (853)	1.69 (1.41, 2.03)	1.73 (1.42, 2.1)	1.47 (1.23, 1.77)
Enterobacteriaceae <sup>b</sup> (3,548)	1.59 (1.45, 1.75)	1.28 (1.16, 1.41)	1.31 (1.19, 1.43)
<i>Staphylococcus aureus</i> (1,721)	1.63 (1.42, 1.87)	1.24 (1.07, 1.44)	1.31 (1.15, 1.51)
<i>Enterococcus species</i> <sup>c</sup> (1,277)	1.87 (1.6, 2.18)	1.69 (1.44, 1.99)	1.6 (1.37, 1.85)
<i>Candida albicans</i> (951)	2.04 (1.71, 2.43)	1.61 (1.35, 1.91)	1.68 (1.42, 1.98)
Non- <i>albicans Candida</i> <sup>d</sup> (703)	1.97 (1.61, 2.41)	1.58 (1.29, 1.95)	1.61 (1.32, 1.95)

481 Abbreviations: MDR = multiple drug resistance.

482 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this  
483 analysis.

484 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*,  
485 *Enterobacter aerogenes*, and *Serratia marcescens*.

486 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other

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487 *Enterococcus species.*

488 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida*

489 *glabrata.*

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492 **Table 4. Economic outcomes for the various pathogen groups.**

Pathogen groups	Excess costs or length of hospitalization (95% Confidence interval)	
	Length of hospitalization after the index date (days)	Cost of hospitalization (USD)
MDR Gram-negative bacteria	10.41 (8.55, 12.27)	7,563 (6,725, 8,401)
MDR Gram-positive bacteria	13.82 (11.38, 16.27)	6,342 (5,500, 7,184)
<i>Acinetobacter baumannii</i>	9.4 (7.65, 11.14)	6,767 (5,823, 7,632)
<i>Pseudomonas aeruginosa</i>	10.01 (7.83, 12.19)	6,791 (5,609, 7,913)
Enterobacteriaceae <sup>b</sup>	15.05 (13.33, 16.76)	7,414 (6,881, 8,007)
<i>Staphylococcus aureus</i>	14.72 (12.63, 16.81)	5,241 (4,528, 5,894)
<i>Enterococcus species</i> <sup>c</sup>	10.66 (7.85, 13.48)	7,219 (6,305, 8,132)
<i>Candida albicans</i>	11.37 (8.82, 13.92)	8,698 (7,512, 9,864)

Non- <i>albicans Candida</i> <sup>d</sup>	15.13 (11.77, 18.49)	11,446 (10,025, 12,927)
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493 Abbreviations: MDR = multiple drug resistance.

494 <sup>a</sup>Only patients with bloodstream infections involving a single pathogen were included in this analysis.

495 <sup>b</sup>Enterobacteriaceae included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Serratia marcescens*.

496 <sup>c</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

497 <sup>d</sup>Non-*albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

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4 501 **FIGURE LEGENDS**  
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7 502 **Figure 1. Flow diagram of the study design.**  
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16 505 Abbreviations: ICU = intensive care unit; BSI = bloodstream infection; TNIS = Taiwan Nosocomial Infections Surveillance; NHIRD = National

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4 **513 SUPPLEMENTARY FILES:**  
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7 514 Supplementary Table 1. The number of episodes of intensive care unit-acquired bloodstream infections caused by common pathogens before  
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10 515 enrollment and the number of patients infected after matching.

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13 516 Supplementary Table 2. Propensity score model results of probability of bloodstream infections among intensive care unit patients and matched  
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16 517 comparison cohort.

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19 518 Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and antimicrobial agents used to define drug resistance.

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22 519 Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to the  
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28 521 Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.  
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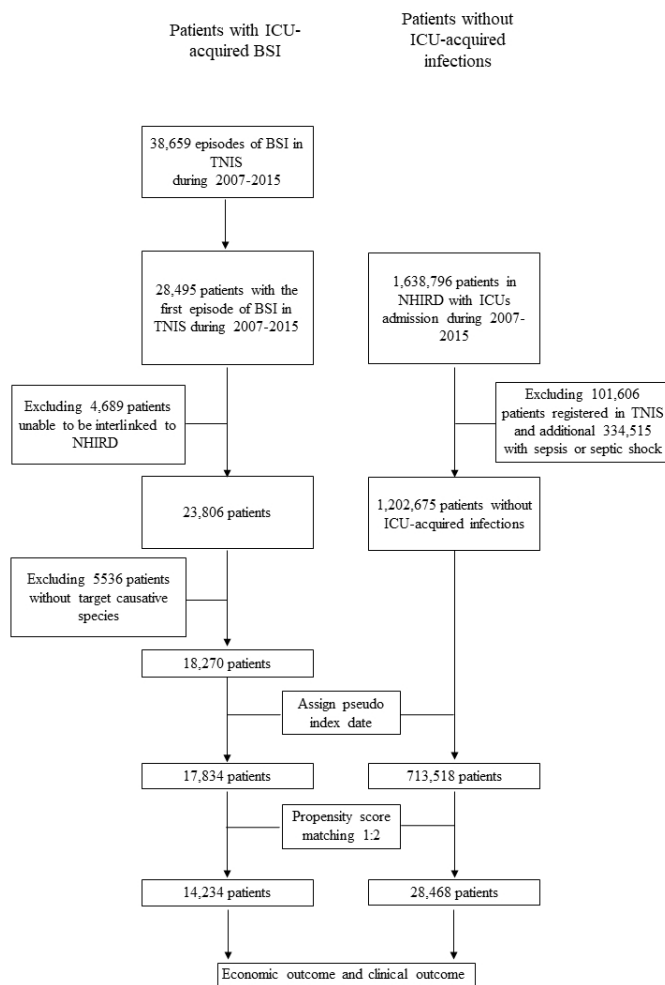


Figure 1. Flow diagram of the study design.

60x108mm (300 x 300 DPI)



1 **Supplementary Table 1. The number of episodes of intensive care unit-acquired**  
 2 **bloodstream infections caused by common pathogens before enrollment and the number**  
 3 **of patients infected after matching.**

	No. of BSI episodes before enrollment <sup>a</sup>	No. of patients after matching <sup>b</sup>
<i>Acinetobacter baumannii</i>	5,214	1,761
<i>Staphylococcus aureus</i>	4,382	1,721
<i>Klebsiella pneumoniae</i>	3,965	1,357
<i>Pseudomonas aeruginosa</i>	2,619	853
<i>Candida albicans</i>	2,554	951
<i>Escherichia coli</i>	2,287	843
<i>Enterobacter cloacae</i>	1,982	746
<i>Enterococcus faecium</i>	1,950	647
<i>Stenotrophomonas maltophilia</i>	1,599	454
<i>Enterococcus faecalis</i>	1,427	419
<i>Serratia marcescens</i>	1,239	439
<i>Candida tropicalis</i>	890	329
<i>Burkholderia cepacia</i>	808	251
Other <i>Enterococcus</i> species <sup>c</sup>	688	211
<i>Elizabethkingia meningoseptica</i>	659	173
<i>Chryseobacterium indologenes</i>	553	152
<i>Candida parapsilosis</i>	534	177
<i>Candida glabrata</i>	461	197
<i>Enterobacter aerogenes</i>	419	163

4 Abbreviations: BSI= bloodstream infection.

5 <sup>a</sup>The number of episodes of bloodstream infections with known pathogens was 38,659.

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3 6 Coagulase-negative staphylococci was excluded from analyses due to possibility of  
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5 7 contamination. One episode may have multiple pathogens. There were 30,697 episodes of  
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7 8 bloodstream infections caused by the pathogens listed above.

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9 <sup>b</sup>The number of patients enrolled case was 14,234 (Table 1) but only patients with  
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11 10 bloodstream infections caused by a single pathogen was counted here (Table 3 and 4) and it  
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13 11 was 11,844. There were 2,390 patients with bloodstream infections caused by multiple  
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15 12 pathogens.

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17 13 <sup>c</sup>*Enterococcus species* other than *Enterococcus faecium* and *Enterococcus faecalis*.  
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15 **Supplementary Table 2. Propensity score model results of probability of bloodstream**  
 16 **infections among intensive care unit patients and matched comparison cohort.**

Parameter	Estimate	Odds ratios	95% Confidence interval		P-value
			Lower	Upper	
			Age, years	-0.0014	
Length of stay before index date/pseudo-index date, days	0.0063	1.0063	0.9909	1.0219	0.4243
Year of index date					
2007	--	1.000	--	--	--
2008	0.2803	1.3235	1.2105	1.4470	<0.0001
2009	0.4057	1.5003	1.3709	1.6419	<0.0001
2010	0.3662	1.4423	1.3146	1.5824	<0.0001
2011	0.4363	1.5470	1.4019	1.7072	<0.0001
2012	0.3246	1.3835	1.2457	1.5364	<0.0001
2013	0.2361	1.2663	1.1312	1.4174	<0.0001
2014	0.0780	1.0811	0.9590	1.2188	0.2021
2015	0.0354	1.0360	0.9128	1.1759	0.5838
Season of Indate					
Mar-May	--	1.000	--	--	--
Jun-Aug	0.0198	1.0200	0.9534	1.0912	0.5659
Sep-Nov	0.0404	1.0412	0.9787	1.1077	0.2008
Dec-Feb	0.0401	1.0409	0.9816	1.1038	0.1806
Male	0.0111	1.0112	0.9662	1.0583	0.6326
Monthly income, USD					

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3	Dependent	--	1.000	--	--	--
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5	<657.33	0.0518	1.0532	0.9824	1.1291	0.1444
6						
7	657.33–1504.60	0.0699	1.0724	0.9985	1.1518	0.0550
8						
9	>1504.60	0.0984	1.1034	0.9871	1.2334	0.0835
10						
11						
12	Urbanization level					
13						
14	1 (urban)		1.000			
15						
16	2	0.0093	1.0094	0.9516	1.0706	0.7560
17						
18	3	-0.0006	0.9994	0.9293	1.0748	0.9872
19						
20	4 (rural)	-0.0163	0.9838	0.9291	1.0417	0.5753
21						
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23						
24	Hospital level					
25						
26	Level I (Medical center)	--	1.000	--	--	--
27						
28	Level II (Regional					
29	hospital)	-0.0068	0.9932	0.9364	1.0534	0.8200
30						
31	Level III (Local hospital)	-0.0439	0.9570	0.7894	1.1603	0.6548
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35	Charlson Comorbidity Index					
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37	score					
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39	0	--	1.000	--	--	--
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41	1	0.1421	1.1527	1.0681	1.2439	0.0003
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43	2	0.2932	1.3407	1.2390	1.4508	<0.0001
44						
45	≥ 3	0.3456	1.4129	1.2880	1.5498	<0.0001
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49	Comorbidities					
50						
51	Diabetes mellitus	0.0050	1.0051	0.9521	1.0610	0.8553
52						
53	Cerebrovascular disease	-0.0419	0.9589	0.8833	1.0410	0.3166
54						
55	Myocardial infarction	-0.0702	0.9322	0.7377	1.1779	0.5564
56						
57	Heart failure	-0.0607	0.9411	0.8525	1.0389	0.2292
58						
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Peripheral vascular disease	-0.0299	0.9706	0.8779	1.0731	0.5601
Liver disease	-0.0437	0.9572	0.8832	1.0375	0.2877
Chronic kidney disease	-0.1133	0.8929	0.8179	0.9748	0.0114
Dyslipidemia	-0.0425	0.9584	0.8916	1.0302	0.2490
Cancer	-0.1626	0.8499	0.7934	0.9105	<0.0001
Number of dysfunctional organs					
0	--	1.000	--	--	--
1	0.1450	1.1561	0.9750	1.3707	0.0951
2	0.2044	1.2268	0.8853	1.6999	0.2195
≥ 3	-0.2233	0.7999	0.4839	1.3222	0.3839
Use of inotropic agents	0.0551	1.0567	0.7982	1.3989	0.7001
Use of steroid	-0.0091	0.9909	0.4451	2.2061	0.9822
Use of ventilator	-0.0226	0.9776	0.8350	1.1446	0.7786
Use of ventilator (>3 days)	0.0279	1.0283	0.6260	1.6891	0.9122
Emergent renal replacement therapy	0.0024	1.0024	0.8515	1.1801	0.9770

17

18 **Supplementary Table 3. WHO priority pathogens, antimicrobial categories, and**  
 19 **antimicrobial agents used to define drug resistance.**

Pathogens	Antimicrobial categories	Antimicrobial agents	
<i>Acinetobacter baumannii</i> <sup>a</sup>	Aminoglycosides	Gentamicin	
		Tobramycin	
		Amikacin	
		Netilmicin	
	Carbapenems	Imipenem	
		Meropenem	
		Doripenem	
	Fluoroquinolones	Ciprofloxacin	
		Levofloxacin	
		Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid	
		Extended-spectrum cephalosporins	Cefotaxime
			Cefepime
	Cefpirome		
<i>Pseudomonas aeruginosa</i> <sup>a</sup>	Aminoglycosides	Ceftazidime	
		Ceftriaxone	
		Gentamicin	
		Tobramycin	
	Carbapenems	Amikacin	
		Netilmicin	
		Imipenem	
		Meropenem	

		Doripenem
		Ciprofloxacin
	Fluoroquinolones	Levofloxacin
		Piperacillin-tazobactam
	Antipseudomonal penicillins + $\beta$ -lactamase inhibitors	Ticarcillin-clavulanic acid
		Cefepime
	Antipseudomonal cephalosporins	Cefpirome
		Ceftazidime
		Gentamicin
		Tobramycin
	Aminoglycosides	Amikacin
		Netilmicin
		Imipenem
		Meropenem
	Carbapenems	Doripenem
		Ertapenem
		Ciprofloxacin
		Levofloxacin
	Antipseudomonal penicillins + $\beta$ -lactamase inhibitors	Piperacillin-tazobactam
		Ticarcillin-clavulanic acid
		Cefotaxime
		Cefepime
	Extended-spectrum cephalosporins	Cefpirome
		Ceftazidime
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33	<i>Enterobacteriaceae</i> <sup>a</sup>	
34	( <i>Escherichia coli</i> ,	
35	<i>Klebsiella pneumoniae</i> ,	
36	<i>Enterobacter cloacae</i>	
37	<i>Enterobacter</i>	
38	<i>aerogenes</i> , or <i>Serratia</i>	
39	<i>marcescens</i> )	
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		Ceftriaxone
	Glycopeptides	Vancomycin
<i>Staphylococcus aureus</i> <sup>b</sup>	$\beta$ -lactamase-resistant penicillins	Oxacillin
<i>Enterococcus faecium</i> ,		
<i>Enterococcus faecalis</i> ,	Glycopeptides	Vancomycin
or other <i>Enterococcus</i>		
<i>species</i> <sup>b</sup>		

<sup>a</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories.

<sup>b</sup>Drug resistance was defined as being non-susceptible to  $\geq 1$  agent.



23 **Supplementary Table 4. The economic outcomes among patients with bloodstream infections and comparison cohort who survived to**  
 24 **the discharge.<sup>a</sup>**

		25
<b>Clinical outcomes</b>	<b>Excess costs or length of hospitalization (95% Confidence interval)<sup>b</sup></b>	<b>P-value</b>
Length of hospitalization after the index date/pseudo-index date, days	19.59 (18.67, 20.51)	26 27 28 < 0.0001 <sub>29</sub>
Cost of hospitalization, USD	8,871 (8,475, 9,268)	30 31 < 0.0001

32 <sup>a</sup>A total of 7,939 of patients with intensive care unit-acquired bloodstream infections and 18,936 comparators survived to the discharge.

33 <sup>b</sup>Adjusted imbalanced variables in Table 1.

34

35 **Supplementary Table 5. Estimated 9-year excessive hospitalization or healthcare cost in all patients with bloodstream infections.**

36

9-year excessive hospitalization or healthcare cost		
Pathogen groups	Length of hospitalization after the index date	Cost of hospitalization (USD) <sup>b, c</sup>
(Numbers of patients) <sup>a</sup>	(days) <sup>b</sup>	
All pathogens (38,659)	492,129	296,603,446
MDR Gram-negative bacteria (6,825)	86,882	52,363,448
MDR Gram-positive bacteria (4,176)	53,160	32,039,525
<i>Acinetobacter baumannii</i> (5,214)	66,374	40,003,372
<i>Pseudomonas aeruginosa</i> (2,619)	33,340	20,093,754
<i>Enterobacteriaceae</i> <sup>d</sup> (9,486)	120,757	72,779,438
<i>Staphylococcus aureus</i> (4,382)	55,783	33,620,019
<i>Enterococcus species</i> <sup>e</sup> (4,045)	51,493	31,034,454
<i>Candida albicans</i> (2,554)	32,512	19,595,054
<i>Non-albicans Candida</i> <sup>f</sup> (1,872)	23,831	14,362,546

37 Abbreviations: MDR= multiple drug resistance.

<sup>a</sup>The number of all episodes of intensive care unit-acquired bloodstream infections caused by designated pathogens during 2007-2015. The inclusion and exclusion criteria in the method section were not applied in this Table (see Figure 1).

<sup>b</sup>The 9-year excessive hospitalization was calculated by multiplying the number of episodes during 9-year infected by the designated pathogen(s) and the average excessive hospitalization per case with the designated pathogen(s). The average excessive hospitalization per case was difference of average hospitalization duration between the case with the designated pathogen(s) and their matched comparison. The average hospitalization duration in bloodstream infection group was the sum of total hospitalization duration divided by the number of case and so was that in matched control group.

$Ave_{Hospitalization} \text{ per case} = [(\text{sum of hospitalization length}) / \text{the number of patients}]$ .

$\text{Excessive } Ave_{Hospitalization} \text{ per person} = (Ave_{Hospitalization} \text{ in bloodstream infection group}) - (Ave_{Hospitalization} \text{ in comparison group})$ .

$\text{Total excessive hospitalization length over 9 years} = (\text{excessive } Ave_{Hospitalization} \text{ per person}) \times (\text{total number of episodes over 9 years})$

The 9-year excessive healthcare cost was calculated similarly.

<sup>c</sup>The costs are standardized and presented the values in 2017.

<sup>d</sup>*Enterobacteriaceae* included *Escherichia coli*, *Klebsiella pneumoniaea*, *Enterobacter cloacae*, *Enterobacter aerogenesa*, and *Serratia marcescens*.

<sup>e</sup>*Enterococcus species* included *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus species*.

<sup>f</sup>*Non-albicans Candida* included *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	#1 and #3-4
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#6-7
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	#8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	#9
		(b) For matched studies, give matching criteria and number of exposed and unexposed	#9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9-10
Bias	9	Describe any efforts to address potential sources of bias	#9-10
Study size	10	Explain how the study size was arrived at	#8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	#9-12
		(b) Describe any methods used to examine subgroups and interactions	#9-12
		(c) Explain how missing data were addressed	#10
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	#12
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#14
		(b) Give reasons for non-participation at each stage	#14
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#14 and #30-32
		(b) Indicate number of participants with missing data for each variable of interest	#19 and #31
		(c) Summarise follow-up time (eg, average and total amount)	#14-15
Outcome data	15*	Report numbers of outcome events or summary measures over time	#14-15
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#14-15
		(b) Report category boundaries when continuous variables were categorized	#14-15
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	#14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	#15
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	#16
<b>Limitations</b>			#18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#16-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	#16-20
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	#22-23

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).