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院內感染相關額外死亡與長期罹病：以金黃色葡萄球菌與鮑氏不動桿菌為例

Excess Mortality and Long-term Morbidity from Healthcare-associated Infections: Using *Staphylococcus aureus* and *Acinetobacter baumannii* as Examples

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論文中文題目

院內感染相關額外死亡與長期罹病：以金黃色葡萄球菌與鮑氏不動桿菌為例

論文英文題目

Excess Mortality and Long-term Morbidity from Healthcare-associated Infections: Using *Staphylococcus aureus* and *Acinetobacter baumannii* as Examples

本論文係蘇秋霞君（學號 D96842001）在國立臺灣大學流行病學與預防醫學研究所完成之博士學位論文，於民國 102 年 7 月 31 日承下列考試委員審查通過及口試及格，特此證明。

口試委員：方啓泰 張上淳 （簽名）

（指導教授）

誌謝

本論文得以完成，首先要感謝指導老師方啟泰博士的悉心指導，論文由一開始的初步構想、形成雛形、研訂計畫書、資料分析、結果解釋和論文撰寫，這段漫長的研究期間，雖然經常會發生卡關，但是一路上有老師的敦敦教誨和加油鼓勵，遇到的困難也迎刃而解。同時也感謝共同指導老師張上淳博士，是您帶領我進入院內感染監視流行病學的領域，研究的過程中不時地指導我正確的方向，您的修養氣度和學識涵養，使我在學習過程中獲益良多。

本論文的完成感謝疾病管制署感染管制及生物安全組的簡麗蓉科長大力協助，因為有妳的指導及體諒，使得我的研究得以應用數個大型資料庫，架構出研究世代，順利完成院內感染疾病負擔的估計，也使得本論文能夠更完整而嚴謹。

博士班修業的日子，研究室裡與同學的共同生活點滴，學術上的討論、言不及義的八卦、一起準備資格考和口試的革命情感、以及約定要一起畢業的決心.....，感謝同學的共同勉勵，因為有妳們的陪伴，讓我在徬徨無措時，不會感到孤單；讓我在失去學習目標時，能夠借助你們的力量，重新找回初衷。

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中文摘要

背景：院內感染 (Healthcare-associated infection) 是住院病人常見的併發症，其中金黃色葡萄球菌 (*Staphylococcus aureus*) 是重要的致病菌，但過去研究欠缺對於感染金黃色葡萄球菌後，是否增加長期額外死亡或罹病風險的評估。另外，對碳青黴烯類抗生素產生抗藥性的鮑氏不動桿菌 (carbapenem-resistant *Acinetobacter baumannii*) 於近年來越來越常見，但是碳青黴烯類抗生素抗藥性是否會增加死亡風險或罹病風險，過去研究則未有定論。本研究以金黃色葡萄球菌和鮑氏不動桿菌為例，探討院內感染是否增加長期死亡或罹病風險。於金黃色葡萄球菌院內感染研究中，研究目的為評估相較於未感染的對照病人，金黃色葡萄球菌院內感染長期是否增加死亡風險或罹病風險；於鮑氏不動桿菌院內感染研究中，研究目的為評估相較對碳青黴烯類抗生素具感受性鮑氏不動桿菌感染病例，碳青黴烯類抗生素抗藥性是否會增加感染鮑氏不動桿菌個案的長期死亡風險或罹病風險。

方法：本研究以參與台灣院內感染監視系統 (Taiwan Nosocomial Infection Surveillance, TNIS) 通報的醫院為研究對象，採回溯性族群基礎的配對世代研究法，以 1:2 的比例選取與院內感染個案相同配對條件的非院內感染個案，配對條件包括醫院、性別、年齡、就醫科別、潛在疾病及院內感染前住院日數。在院內感染金黃色葡萄球菌研究中，總共納入 3070 名金黃色葡萄球菌院內感染個案，及 6140 名配對的非院內感染個案。在院內感染鮑氏不動桿菌研究中，總共納入 2213 名鮑氏不動桿菌院內感染個案，及 4426 名配對的非院內感染個案。主要研究測量為 1 年額外死亡率、新發慢性呼吸器依賴及新發末期腎病透析依賴的風險。

結果：在院內感染金黃色葡萄球菌研究中，我們發現住院病人院內感染金黃色葡萄球菌的 1 年死亡率較配對的非院內感染病人額外增加 20.2%的死亡風險 (*P*<0.001)。新發慢性呼吸器依賴及末期腎病透析依賴的風險則分別額外增加 7.3%和 2.6% (*P*s<0.001)。每件金黃色葡萄球菌院內感染平均可延長住院天數 12 天，增加醫療費用 5978 美元 (*P*s<0.001)。在院內感染鮑氏不動桿菌研究中，我們發現住院病人感染碳青黴烯類抗生素抗藥性鮑氏不動桿菌的 1 年死亡率，較感染對碳青黴烯類抗生素具感受性鮑氏不動桿菌 (carbapenem-susceptible *A. baumannii*) 的病人額外增加 11.8% (*P*<0.001)。碳青黴烯類抗生素抗藥性會增加新發慢性呼吸器依賴的風險為 5.2% (*P*s<0.001)；每件碳青黴烯類抗生素抗藥性平均可增加感染鮑氏不動桿菌住院病人的醫療費用 2511 美元 (*P*s<0.001)。

結論：不論是院內感染金黃色葡萄球菌或鮑氏不動桿菌都有顯著的長期負面效應，包括額外死亡率和增加罹病率；而且院內感染抗藥性鮑氏不動桿菌也較非抗藥性鮑氏不動桿菌導致較高的死亡和罹病發生。本研究建議未來推動相關感染管制計畫和抗生素管理措施的成效評估時，應一併將院內感染及抗藥性所引起的長期死亡及罹病一併納入防治成本效性分析。

關鍵詞：院內感染、金黃色葡萄球菌、鮑氏不動桿菌、抗藥性、死亡率、慢性呼吸器依賴、末期腎病透析依賴

Abstract

Background: Healthcare-associated infection (HAI) is one of the most common complications affecting hospitalized patients. *Staphylococcus aureus* is a leading cause of HAIs, but the impact of *S. aureus* HAIs on the long-term survival and functional status of hospitalized patients remain unknown. Beside, carbapenem-resistant *Acinetobactor baumannii* (CRAB) has emerged as a major cause of HAIs, but the impact of carbapenem resistance on the long-term outcomes in patients with *A. baumannii* HAIs has not yet been well studied. This study aimed to examine whether HAIs increase the risks for long-term mortality and disability, using *S. aureus* and *A. baumannii* as examples. In the *S. aureus* HAI study, we aimed to examine whether *S. aureus* HAIs increase the risks for long-term mortality and disability. In the *A. baumannii* HAI study, we aimed to examine whether carbapenem resistance increase the risks for long-term mortality and disability after *A. baumannii* HAIs.

Methods: We conducted a retrospective population-based matched cohort study of hospitalized patients in acute care hospitals which participated in Taiwan Nosocomial

Infection Surveillance (TNIS). We individually matched patients with HAIs to inpatients without HAIs at a 1:2 ratio by age, gender, hospital, specialty, underlying diseases, and the length of stay before onset of the HAI. In the *S. aureus* HAIs study, we included 3070 inpatients with *S. aureus* HAIs and 6140 matched uninfected inpatients. In the *A. baumannii* HAIs study, 2213 inpatients with *A. baumannii* HAIs and 4426 matched uninfected inpatients were included. Main outcome measures are one-year excess risks for mortality, new-onset chronic ventilator dependence, and new-onset dialysis-dependent end-stage renal disease.

Results: For the *S. aureus* HAI study, patients with *S. aureus* HAIs had an excess one-year mortality of 20.2% compared with matched uninfected inpatients (P<0.001). The excess risk for new-onset chronic ventilator dependence and dialysis-dependent end-stage renal disease was 7.3% and 2.6%, respectively (Ps<0.001). *S. aureus* HAIs were also associated with an excess hospital stay of 12 days and an extra cost of US $5978 ($P$s<0.001). For the *A. baumannii* HAI study, carbapenem resistance was associated with an increased excess one-year mortality of 11.8% in CRAB patients compared with carbapenem-susceptible *A. baumannii* (CSAB) patients (P <0.001). The excess risk of carbapenem resistance for

new-onset chronic ventilator dependence was 5.2% (P <0.001). Carbapenem resistance was also associated with an extra cost of US $2511 ($P$ <0.001).

Conclusion: Both *S. aureus* HAIs and *A. baumannii* HAIs have substantial negative effect on the long-term outcome of hospitalized patients in terms of both mortality and disability. Furthermore, carbapenem resistance in patients with *A. baumannii* HAIs further increased the risk for adverse long-term outcomes. The negative impact on the long-term outcome should be taken into consideration in future cost-effectiveness studies of the control and prevention interventions for *S. aureus* HAIs and *A. baumannii* HAIs.

Keywords: healthcare-associated infection, *Staphylococcus aureus*, *Acinetobacter baumannii*, carbapenem resistance, mortality, chronic ventilator dependence, dialysis-dependent end-stage renal disease

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Chapter 1: Introduction

1.1 Healthcare-Associated Infections

Healthcare-associated infections (HAIs) (also known as nosocomial infections) are those infections that occur during the process of healthcare. It does not include the infections present or incubating at the time of admission [1]. HAI is one of the major complications affecting hospitalized patients [2]. The World Health Organization estimated roughly 5-10% of patients admitted to acute care hospitals acquired one or more HAIs in developed country [3]. Although HAIs have a significant impact on patients' health, it was still not recognized as a public health issue. The main reason is that HAI is usually considered as a quality-control issue in the hospital management. As a result, few researches have investigated the burden of HAI using rigorous epidemiologic approach, and limited data are available to understand the impact of HAIs on public health.

1.2 Taiwan Nosocomial Infection Surveillance System

To monitor the occurrence of HAIs in hospitals, Taiwan Centers for Diseases Control established the Taiwan Nosocomial Infection Surveillance (TNIS) system in 2007 and invited all hospitals to participate. The purposes of the TNIS were to help participating hospitals to develop their own surveillance systems for HAIs and to provide timely recognition of infection control problems. TNIS adopts voluntary reporting, and each hospital may provide their data either through web-based entry or convey their data electronically through interchange platform. The web-based report mechanism allow the hospital infection control nurse enters the HAI data on the TNIS website directly, and mainly serves for the hospitals which lack HAI surveillance system of their own. The other mechanism, conveying surveillance data electronically through interchange platform, serves for the hospitals which had built their own HAI surveillance system. Through this mechanism, surveillance data could be routinely transferred from hospital information systems to the TNIS system automatically [4].

1.3 *Staphylococcus aureus* Infections

Staphylococcus aureus is a leading cause of healthcare-associated infections (HAIs)

[5,6]. *S. aureus* infections can cause severe sepsis complicated by acute renal failure and respiratory failure requiring intensive care [7,8]. *S. aureus* bacteremia is associated with an in-hospital mortality of as high as 15–60% [9], especially in critically ill patients [10-12]. Bacteremia of methicillin-resistant *S. aureus* (MRSA) [13-17] has a higher attributable mortality than that of methicillin-susceptible *S. aureus* (MSSA) [6,18]. Thus, *S. aureus* HAIs can have substantial impacts on the patient's survival and well-being.

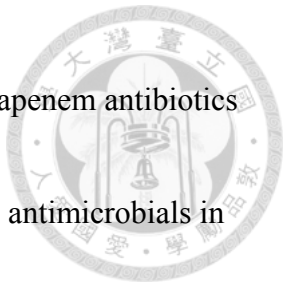
The negative effects of *S. aureus* HAIs on the outcomes of hospitalized patients have not yet been well studied. The existing literature includes only six small studies, which reported an increased risk for short-term mortality by 2.2–7.3 folds in patients with *S. aureus* HAIs compared to inpatients without HAIs [19-24]. Table 1 is the summary table of the six studies shows in. Most studies focused on surgical site infection (sample size: 18–286 cases) [19-21] or bloodstream infection (sample size: 19 cases) [22]; only one study examined all-type *S. aureus* HAIs (sample size: 27 cases) [23]. None of the studies have investigated the impact of *S. aureus* HAIs on mortality beyond 90 days [25]. The functional status of survivors has not been studied, either. The acute respiratory or renal failure occurring during sepsis may be irreversible and

thus result in long-term ventilator or dialysis dependence, causing huge financial burdens.

The TNIS data show that *S. aureus* is one of the leading causative pathogens of HAIs in Taiwan [4]. MRSA accounts for up to 79% and 81% of all *S. aureus* isolates at regional hospitals and medical centers, respectively [4]. To understand the impact of *S. aureus* HAIs on the long-term outcomes of hospitalized patients, we conducted a nationwide population-based matched cohort study of inpatients at 114 hospitals participating in the TNIS.

1.4 *Acinetobacter baumannii* Infections

Acinetobacter baumannii is a significant pathogen which causes healthcare-associated infections (HAIs) and is frequently responsible for outbreaks in hospitals [26,27]. This species is ubiquitous in nature and can survive for prolonged periods on healthcare environment [28,29]. *A. baumannii* mainly causes pneumonia, bloodstream infections, urinary tract infection, or surgical site infections. Moreover, patients with *A. baumannii* infections had an excess mortality ranging from 7.8% in general patients to 43% in



critically ill patients compared with uninfected patients [30,31]. Carbapenem antibiotics (e.g. imipenem and meropenem) were traditionally the most effective antimicrobials in the treatment of *A. baumannii* infections [32]. However, increasing carbapenem resistance leaves few therapeutic options. A study reported that ineffective empirical antimicrobial therapy was associated with a higher risk of mortality [33]. Carbapenem-resistant *A. baumannii* (CRAB) has become common worldwide [34]. *A. baumannii* HAIs could have substantial impacts on the patient's outcome but the influence of carbapenem resistance in terms of the negative effects of carbapenem resistance in *A. baumannii* HAI on the outcomes of patients have not yet been well studied.

The existing literature includes only four small matched cohort study, which reported an increased risk for short-term mortality by 1.4–6.9 folds in patients with CRAB HAIs compared to matched patients with Carbapenem-susceptible *A. baumannii* (CSAB) HAIs [33,35-37]. Table 2 is the summary table of the four studies. Of the four studies, two studies focused on bloodstream infections (sample size: 40–46 matched-pairs) [33,35] and the other two studies examined all-type *A. baumannii* HAIs

(sample size: 42–91 matched-pairs) [36,37]. However, the impact on mortality may depend on the site of infections [38] and none of the study has examined the different infection types in the same time. Also, none of these studies have investigated the impact of carbapenem resistance on long-term mortality. The functional status of survivors has not been studied, either. The acute respiratory or renal failure occurring during sepsis may be irreversible and thus result in long-term ventilator or dialysis dependence, causing huge financial burdens.

The TNIS data show that *A. baumannii* was the 2nd most frequently isolated microorganism from HAIs in 2008, representing 11% of all causal microorganisms [4]. The prevalence of CRAB among all *A. baumannii* HAIs was dramatically increased from 14.1% in 2003 to 46.3% in 2008. In the same time, the incidence rates of CRAB HAIs increased from 0.06 to 0.12 per 1000 patient days [39,40]. To understand the impact of carbapenem resistance on the long-term outcomes after patients with *A. baumannii* HAIs, we conducted a nationwide population-based matched cohort study of inpatients at acute care hospitals participating in the TNIS. The methodology has been previously successfully used in evaluate the impact of healthcare-associated

Staphylococcus aureus infections on patients' long-term outcome [41].

Chapter 2: Methods

2.1 Study Design

We conducted a retrospective population-based matched cohort study comparing outcomes between hospitalized patients with *S. aureus*/*A. baumannii* HAIs and patients without HAIs, matched by age, gender, hospital, specialty, underlying diseases, and the length of stay before onset of the *S. aureus*/*A. baumannii* HAI.

2.2 Objectives

The specific aims for the *S. aureus*/*A. baumannii* HAI study were showed in Figure 1. The long-term outcomes were one-year excess risks for mortality, new-onset chronic ventilator dependence, and new-onset dialysis-dependent end-stage renal disease. The short-term outcomes were prolonged hospital stay and extra hospital costs during the hospitalization.

2.3 Data Sources

The framework of study was showed in Figure 2. Data on exposure group in term of *S. aureus*/*A. baumannii* HAIs were derived from the TNIS. Data on non-exposure group in term of uninfected patient was derived from the National Health Insurance (NHI). Data on the short-term outcomes including hospital stay and costs was from NHI. The long-term mortality and disability was from National Death Registry and Catastrophic Illness Registry, respectively.

2.4 Short-term vs. Long-term Impact of HAIs

In the present study, the one-year outcomes were analyzed to assess whether HAIs increase the risks of short-term mortality/morbidities and/or long-term mortality/ morbidities. The short-term and long-term impacts of HAIs are explained using survival curves diagrams shown in Figure 3. For an HAI with only short-term impact, there is an excess mortality/morbidities in HAI patient compared with uninfected patients within month, but no difference existed in the mortality/morbidities rates between the two groups at the end of one-year follow up. On the other hand, for a HAI with long-term impact, the mortality/morbidity rate is different permanently.

2.5 Ethical Statement

To protect the privacy of the patients, the personal identification numbers were encrypted before database linking. The *S. aureus* HAI study protocol (no. TwCDCIRB990008) was reviewed and approved a priori by the institutional review board (IRB) of Taiwan Centers for Diseases Control (Taipei, Taiwan). The IRB approved the exemption of informed consent because all personal information had been anonymized.

2.6 Settings

Taiwan Centers for Diseases Control established the TNIS and invited all hospitals to voluntarily participate. For *S. aureus* HAI study, 114 out of the total 495 hospitals in Taiwan had ever notified *S. aureus* HAIs cases. The 114 hospitals included 8 medical centers, 43 regional hospitals, and 63 local hospitals (with a median bed capacity of 1318, 581, and 182, respectively), which had a total of 3307878 hospitalizations covered by the NHI during the study period from 2006 through 2008. For *A. baumannii*

HAI study, 96 out of the total 495 hospitals in Taiwan had ever notified *A. baumannii* HAIs cases to TNIS. The 96 hospitals included 8 medical centers, 40 regional hospitals, and 48 local hospitals (with a median bed capacity of 1284, 582, and 236, respectively), which had a total of 3177017 hospitalizations covered by the NHI during the study period from 2006 through 2008.

2.7 HAI Surveillance and Notification

In all participating hospitals, infection control nurses routinely review all hospitalizations for all types of HAIs (including bloodstream infection, pneumonia, surgical site infection, urinary tract infection, and other types of HAIs) using the US Centers for Disease Control and Prevention (CDC) (Atlanta, GA, USA) surveillance definitions [42]. The identified HAI cases were notified to the TNIS. The reported data included the patient's age, gender, HAI onset date, site of infection, and microbiological results (e.g. organisms isolated from blood, urine, respiratory tract, surgical sites, and other non-sterile sites, as well as antimicrobial susceptibility). The onset date was the date when the first clinical symptom(s)/sign(s) occurred or the earliest positive culture

was sampled, as specified for the type of HAI by the CDC definition.

2.8 Patients with *S. aureus*/*A. baumannii* HAIs

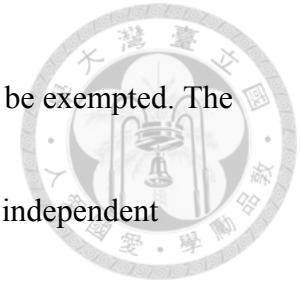
We included all notified *S. aureus*/*A. baumammii* HAIs cases that occurred at least 48 hours after admission in 2006–2008 for linkage with the NHI dataset. If a patient had multiple episodes of HAIs during hospitalization, only the first episode and its first isolate were considered in this study. Cases with the HAI occurring within 48 hours of the admission or beyond the hospitalization period were excluded, because we used the length of stay before onset of the *S. aureus*/*A. baumammii* HAI as one of the matching variables to identify a suitable matched uninfected inpatient [12,18].

2.9 Matched Inpatients without HAIs

Each *S. aureus/A. baumannii* HAI case was individually matched at a 1:2 ratio to inpatients without HAIs that were hospitalized during the same study period. The matching was based on age (within a 5-year difference), gender, as well as the same hospital, primary specialty/subspecialty, and indicators of underlying disease

severity—including the length of stay before onset of the *S. aureus*/*A. baumammii* HAI [12,18] and the presence and type of seven classes of severe illnesses at admission (i.e. cancer, dialysis-dependent end stage renal disease, liver cirrhosis with complications, chronic ventilator dependence, major trauma, generalized autoimmune syndrome, and spinal injury/myeleterosis). If there were more than two candidate uninfected inpatients, we chose the two that had the closest admission dates to that of the *S. aureus/A. baumannii* HAI case. If no suitable match was found, we reduced the matching requirement of primary specialty/subspecialty to just primary specialty. If a suitable match still could not be identified, we considered the matching process to have failed.

We used the NHI database to obtain patient data for individual matching and validation of comparability. The NHI in Taiwan has a coverage rate of 99% due to universal health insurance [43]. The NHI claims data recorded five major diagnoses (i.e. one primary diagnosis and up to four secondary diagnoses) for the patient, which were reported by the hospital based on the ICD–9–CM coding system. We ascertained the presence and type of severe illnesses using the Catastrophic Illness Registry, which is a subset of the NHI database (and thus has the same coverage rate). There are 30 major



categories of catastrophic illnesses for which patient copayment can be exempted. The certification, which is strictly regulated by the NHI bureau, requires independent evaluation by two specialist physicians to confirm both the diagnosis and irreversibility of the illness [44].

2.10 Validation of Comparability

To validate comparability between the *S. aureus/A.baumannii* HAI cases and matched uninfected inpatients on baseline characteristics before onset of *S. aureus/A.baumannii* HAIs, we examined the between-group difference on clinical variables unrelated to HAIs (i.e. the presence of ischemic heart disease, congestive heart failure, stroke, diabetes, hypertension, elective surgical procedures, and medications for treating cardiovascular and/or neoplastic disorders).

2.11 Ascertainment of Outcomes

We derived the data on survival status and date of death using the National Death Registry (from Department of Health, Taiwan), which contains all the death certificates

of Taiwanese citizens. The data on new-onset chronic ventilator dependence and dialysis-dependent end-stage renal disease were ascertained using the Catastrophic Illness Registry. To ensure a 100% one-year follow-up rate, data of both registries were updated to the end of year 2009. We used the date of Catastrophic Illness Certificate application as the onset date of chronic ventilator dependence and dialysis-dependent end-stage renal disease. To distinguish old events that were already present at admission from new-onset events that occurred after the index date, we defined the index date for *S. aureus/A.baumannii* HAI patients as the onset date of the *S. aureus/A.baumannii* HAI; that for uninfected patients was the admission date plus the length of stay before onset of the *S. aureus*/*A. baumammii* HAI of the matched case (Figure 4). We used three linkage variables (encrypted personal ID, encrypted hospital ID, and admission date) to link the anonymized patient data between different datasets.

The data of hospital costs were obtained from the NHI dataset, which recorded the total cost (including diagnosis, laboratory, drug, ward, therapeutic-procedure, and special-material fees) for the entire hospitalization period of each patient.

2.12 Statistical Analysis

We compared the main outcomes between the *S. aureus/A.baumannii* HAI group and the uninfected group using multivariate conditional logistic regression stratified by matched pairs, with adjustment for the effects of diabetes mellitus and hypertension. We compared the length of hospital stay and the hospital cost between two groups using the random effect model.

To estimate the excess mortality and long-term disability attributable to carbapenem resistance in *A. baumannii* HAIs, we first estimated the excess risk from patients with CRAB HAIs compared with matched uninfected patients, as well as the excess risk from patients with CSAB HAIs compared with matched uninfected patients. The impact of carbapenem resistance was estimated by subtracting the excess risk, length of stay, and hospital cost of CRAB group from that of CSAB. The difference of excess risk, length of stay, and hospital cost was compared using the Student's *t* test. We further adjust for the effects of ischemic heart disease (ISH), diabetes mellitus (DM), and hypertension (HT) using multivariate conditional logistic regression and random effect model as below:

$$Y \sim \beta_1(\text{AB HAIs}) + \beta_2(\text{AB HAIs})*(\text{carbapenem resistance}) + \beta_3(\text{ISH}) + \beta_4(\text{DM}) + \beta_5(\text{HT})$$

The statistical significance of impact of carbapenem resistance was evaluated by the regression coefficient β_2 of the interaction term. All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance of P values was interpreted with Bonferroni's correction for multiple comparisons.

Chapter 3: Results

3.1 *S. aureus* HAI study

3.1.1 Characteristics of Study Subjects

The 114 hospitals reported a total of 47729 HAI cases during 2006–2008. Linking between the TNIS and the NHI dataset failed for 6587 cases (13.8%) due to inconsistency in one or more of the three linkage variables. Among the remaining 41142 HAI cases, the isolated pathogen was *S. aureus* for 4027 cases. Of them, 3563 cases met the inclusion criteria and 3070 cases were successfully matched to 6140 inpatients without HAIs (successful matching rate 86.2% [3070/3563]) (Figure 5). Compared to *S. aureus* HAI cases with successful matching, the *S. aureus* HAI cases with unsuccessful matching (n=493) had a longer average length of stay before onset of the *S. aureus* HAI (95 vs. 20 days) and were more likely to have a severe illness at admission (14.0% vs. 3.7% for dialysis-dependent end-stage renal disease; 21.1% vs. 2.0% for chronic ventilator dependence) (all *P*s <0.001).

Of the 3070 *S. aureus* HAI cases, the causal *S. aureus* strains were MRSA in 2201

cases (71.7%). Patients with MRSA HAIs tended to be older (mean age: 68 vs. 62 years), had a longer average length of stay before onset of the HAI (23 vs. 13 days), and were more likely to have a severe illness at admission (4.0% vs. 2.9% for dialysis-dependent end-stage renal disease; 2.5% vs. 0.6% for chronic ventilator dependence), compared with patients with MSSA HAIs (all *P*s <0.001).

The baseline characteristics of the 3070 matched pairs are shown in Table 3. There was no statistically significant between-group difference in the matching variables and the comparability-validation variables, with the only exceptions of diabetes mellitus and hypertension. Compared with the *S. aureus* HAI group, the uninfected group had a slightly higher proportion of patients with diabetes mellitus (22.1% vs. 19.4%, *P* <0.001) and hypertension (23.2% vs. 16.8%, *P* <0.001), as well as a lower average number of diagnoses recorded in the NHI dataset (4.3 vs. 4.7, *P* <0.001).

3.1.2 Impact of *S. aureus* HAIs

Table 4 summarizes the main outcomes. *S. aureus* HAI cases had an excess in-hospital mortality, mortality within 30 days after discharge, and one-year mortality of 19.9%,

21.1%, and 20.2%, respectively (all *P*s <0.001) (Table 4). The excess one-year mortality was highest for nosocomial pneumonia (28.5%) and bloodstream infection (22.3%) (Table 5). MRSA and MSSA cases had an excess one-year mortality of 21.8% and 16.1%, respectively (Table 5 and Figure 6). *S. aureus* HAIs cases also had an excess risk for new-onset chronic ventilator dependence during hospitalization, within 30 days after discharge, and within one-year (6.8%, 7.6%, and 7.3%, respectively, all *P*s <0.001). The excess risk for new-onset dialysis-dependent end-stage renal disease during hospitalization, within 30 days after discharge, and within one-year was 1.7%, 2.3%, and 2.6%, respectively (all *P*s <0.001). After adjusting for the presence of diabetes mellitus and hypertension, the differences in outcomes between the *S. aureus* HAI group and the uninfected group remained highly statistically significant (all *P*s <0.001) (Table 4).

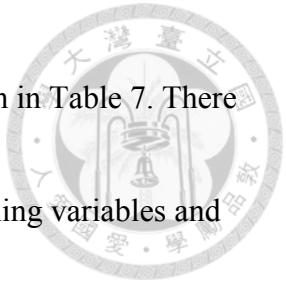
Patients with *S. aureus* HAIs had an excess hospital stay of 12 days and an extra hospital cost of $5978 compared with the matched uninfected patients (Table 6). The differences were significant in subgroup analysis by the site of infection (bloodstream, pneumonia, urinary tract, and surgical site of infection), the type of antimicrobial

resistance (MSSA and MRSA), and the presence (or absence) of severe illnesses at admission (all *P*s <0.001) (Table 6).

3.2 *A. baumannii* HAI study

3.2.1 Characteristics of Study Subjects

The 96 hospitals reported a total of 39245 HAI cases during 2006–2008. Linking between the TNIS and the NHI dataset failed for 7219 cases (18.4%) due to inconsistency in one or more of the three linkage variables. Among the remaining 32026 HAI cases, the isolated pathogen was *A. baumannii* for 2503 cases. Of them, 2396 cases met the inclusion criteria and 2213 cases were successfully matched to 4426 inpatients without HAIs (successful matching rate 92.4% [2213/2396]) (Figure 7). Compared to *A. baumannii* HAI cases with successful matching, the *A. baumannii* HAI cases with unsuccessful matching (n=183) had a longer average length of stay before onset of the *A. baumannii* HAI (32 days vs. 17 days) and were more likely to have a severe illness at admission (13.7% vs. 2.8% for dialysis-dependent end-stage renal disease; 15.3% vs. 2.3% for chronic ventilator dependence) (all *P*s <0.001).



The baseline characteristics of the 2213 matched pairs are shown in Table 7. There was no statistically significant between-group difference in the matching variables and the comparability-validation variables, with the only exceptions of ischemic heart disease, diabetes mellitus, and hypertension. Compared with the *A. baumannii* HAI group, the uninfected group had a slightly higher proportion of patients with ischemic heart disease (7.2% vs. 4.5%, P <0.001), diabetes mellitus (21.5% vs. 18.0%, P =0.001), and hypertension (23.7% vs. 13.6%, P <0.001), as well as a lower average number of diagnoses recorded in the NHI dataset (4.3 vs. 4.7, P <0.001).

3.2.2 Impact of *A. baumannii* HAIs

Table 8 summarizes the main outcomes between the *A. baumannii* HAI group and the uninfected group. *A. baumannii* HAI cases had an excess in-hospital mortality, mortality within 30 days after discharge, and one-year mortality of 21.6%, 23.2%, and 20.9%, respectively (all Ps <0.001) (Table 8). The excess one-year mortality was highest for nosocomial pneumonia (28.7%) and surgical site infections (21.3%) (Table 9). CRAB and CSAB cases had an excess one-year mortality of 27.2% and 15.4%, respectively

(Table 9 and Figure 8). *A. baumannii* HAIs cases also had an excess risk for new-onset chronic ventilator dependence during hospitalization, within 30 days after discharge, and within one-year (8.6%, 10.6%, and 10.2%, respectively, all *P*s <0.001). The excess risk for new-onset dialysis-dependent end-stage renal disease during hospitalization, within 30 days after discharge, and within one-year was 0.4%, 0.4%, and 0.2%, respectively (all *P*s >0.05). After adjusting for the presence of ischemic heart disease, diabetes mellitus, and hypertension, the differences in outcomes of mortality and new-onset chronic ventilator dependence between the *A. baumannii* HAI group and the uninfected group remained highly statistically significant (all *P*s <0.001) (Table 10).

Patients with *A. baumannii* HAIs had an excess hospital stay of 9.9 days and an extra hospital cost of $6096 compared with the matched uninfected patients (Table 10). The differences were significant in subgroup analysis by the site of infection (bloodstream, pneumonia, urinary tract, and surgical site of infection), the type of antimicrobial resistance (CSAB and CRAB), and the presence (or absence) of severe illnesses at admission (all *P*s <0.001) (Table 10).

3.2.3 Impact of Carbapenem Resistance

Of the 2213 *A. baumannii* HAI cases, the causal *A. baumannii* strains were CRAB in 1036cases (46.8%). Patients with CRAB HAIs (n=1036) tended to be older (mean age: 70 vs. 68 years), had a longer average length of stay before onset of the *A. baumannii* HAI (19 vs. 16 days), and were more likely to occur in intensive care units (55% vs. 34%), compared with patients with CSAB HAIs (n=1177) (all *P*s <0.001). These data implied the important differences in severity of underline diseases between patients with CRAB HAIs and CSAB HAIs.

Table 11 summarizes the main outcomes of carbapenem resistance in *A. baumannii* HAIs. The excess one-year mortality was 27.2% among CRAB patients compared with their matched uninfected inpatients, and 15.4% among CSAB patients compared with their matched uninfected inpatients, resulting in an attributable mortality of 11.8% (all *P*s <0.001). The excess one-year mortality of cabapenem resistance was the highest for nosocomial bloodstream (27.6%) and follows by urinary tract infections (12.4%). Carbapenem resistance had an excess risk for new-onset chronic ventilator dependence of 5.2% (*P*s <0.001) and had an extra hospital cost of $2511 (*P* <0.001) (Table 11 and

Table 12).

Chapter 4: Discussion

4.1 *S. aureus* HAI study

This study is the largest cohort study to date that has investigated the negative effects of *S. aureus* HAIs on the outcomes of hospitalized patients. Using national databases, we included 3070 inpatients with *S. aureus* HAIs and 6140 matched uninfected inpatients. Our results show that *S. aureus* HAIs significantly increased the risks for long-term mortality and disabilities including new-onset chronic ventilator dependence and new-onset dialysis-dependent end-stage renal disease, with an excess one-year risk of 20.2%, 7.3%, and 2.6%, respectively (all *P*s<0.001). *S. aureus* HAIs were also associated with an excess hospital stay of 12 days and an extra hospital cost of $5978 (*P*s<0.001).

In addition to a large sample size, our study has the advantage of enhancing comparability by individually matching the *S. aureus* HAI cases to uninfected inpatients on potential confounding factors including age, gender, hospital, primary specialty/subspecialty, and underlying disease severity. Analysis of the validation

variables did show a lack of difference in most baseline characteristics (e.g. the frequency of cardiovascular diseases, elective surgery, and antineoplastic agent use), with the exception of a slightly higher proportion of patients with diabetes mellitus and hypertension in the uninfected group. The most likely explanation for the difference is that diabetes mellitus and hypertension were more likely to be recorded among the five major diagnoses of the patient in the NHI database for the uninfected group that had a lower average number of diagnoses. Even if the result reflects a genuine difference in these two comorbidities, the higher proportions of patients with diabetes mellitus and hypertension (which may adversely affect the outcomes) in the uninfected group would have caused an underestimation for the negative impact of *S. aureus* HAIs and thus the actual excess risks would have been higher than the observed values.

Our findings on the excess mortality, prolonged hospital stay, and extra hospital costs associated with *S. aureus* HAIs are consistent with the existing literature [19-24]. Previous studies, which involved smaller numbers of patients and mainly focused on surgical site infections, reported an excess 90-day crude mortality of 10.5–16.8% for patients with *S. aureus* surgical site infections [19,21,22]. Using population-based data,

our study validates the previous results and found an excess one-year mortality of 12.4%. Furthermore, our study extends the results to patients with *S. aureus* HAIs in general. We also first show that patients with *S. aureus* pneumonia and bloodstream infection suffered the highest excess one-year mortality of 28.5% and 21.3%, respectively.

In addition to an excess infection-related mortality, our study shows that *S. aureus* HAIs increase the risk for long-term disability. Severe *S. aureus* infections can cause acute organ dysfunction [45], particularly in patients with pre-existing chronic lung or renal disease(s). Blot et al. compared 85 cases of *S. aureus* bacteremia with 170 matched uninfected patients and found that the former had a significantly longer length of ventilator dependence than the latter [6]. Reach et al. composed a large study of 1575 matched pairs and found that MRSA patients were more likely to undergo mechanical ventilation than uninfected patients (excess risk: 7.5%) [46]. Our study first provides evidence on the potential irreversibility of *S. aureus* HAIs-related ventilator dependence and renal failure, showing that *S. aureus* HAIs increased the risks for new-onset chronic ventilator dependence and dialysis-dependent end-stage renal disease by 7.3% and 2.6%,

respectively, compared with patients with the same type and severity of underlying disease but without HAIs. Therefore, *S. aureus* HAIs can cause irreversible organ dysfunction and profoundly affect the patient's long-term well-being.

The excess risks for long-term mortality and disability highlight the importance to reduce occurrence of *S. aureus* HAI, which is a preventable disease. One of the main causes for the spread of MRSA within hospitals is poor hand hygiene compliance among healthcare workers [47]. Studies have found that the incidence of HAIs can be decreased by the introduction of hand hygiene programs and other measures [48]. There is growing literature supporting the beneficial effects of hand hygiene [40,49]. A systemic review of 30 intervention studies suggested that 10–70% of HAIs are probably preventable with appropriate infection control [50]. A recent randomized controlled trial proves that active surveillance and decolonization of nasal *S. aureus* carriers on admission can further reduce the incidence rate of surgical site infection [51].

Our results on the excess mortality/disability and excess hospital stay/costs indicate that a reduction in incidence of *S. aureus* HAIs can translate to improved long-term outcomes and significant cost savings, particularly when the huge financial burdens of

providing long-term ventilator and dialysis services are taken into consideration.

Our study was limited by the voluntary nature of TNIS participation and HAI case notification. The 114 hospitals in current study may not represent all hospitals in Taiwan. Nevertheless, we minimize the potential effect of self-selection bias on the estimated excess risk associated with *S. aureus* HAIs, by individually matching the *S. aureus* HAI cases to uninfected inpatients by the hospital. Because the notification of HAI cases was also voluntary, it is possible that some of the 6140 matched uninfected inpatients might indeed have HAIs, which would have caused an underestimation of *S. aureus* HAI-associated excess risks for long-term mortality and disability. Therefore, our findings represent a conservative estimate for the negative impact of *S. aureus* HAIs.

4.2 *A. baumannii* HAI study

This study is the largest cohort study to date that has investigated the negative effects of carbapenem resistance on the outcomes of patients with *A. baumannii* HAIs. Using national databases, we included 1177 CSAB and 1036 CRAB patients to

demonstrate the burden of carbapenem resistance. Our results show that carbapenem resistance in patients with *A. baumannii* HAIs increased the risks for long-term mortality of 11.8% and disability (new-onset chronic ventilator dependence) of 5.2% (all *P*s<0.001). Carbapenem resistance were also associated with extra hospital cost of $2511 (*P*s<0.001).

In addition to large sample size, our study has the advantage of enhancing comparability between CRAB and CSAB HAI patients by individually matching the *A. baumannii* HAI cases to uninfected inpatients on potential confounding factors of age, gender, hospital, primary specialty/subspecialty, and underlying disease severity. Analysis of the validation variables did show a lack of difference in most baseline characteristics (e.g. elective surgery and antineoplastic agent use), with the exception of a slightly higher proportion of patients with ischemic heart disease, diabetes mellitus, and hypertension in the uninfected group. The most likely explanation for the difference is that those diagnoses were more likely to be recorded among the five major diagnoses of the patient in the NHI database for the uninfected group that had a lower average number of diagnoses.

Our findings on the excess mortality associated with carbapenem resistance in patients with *A.baumannii* HAIs are consistent with the existing literature [33,35-37]. Previous studies, which involved smaller numbers of patients and mainly focused on bloodstream infections, reported an excess crude mortality of 4.8–30.0% for carbapenem resistance in patients with *A.baumannii* HAIs [33,35-37]. Using population-based data, our study validates the previous results and found an excess one-year mortality of 11.8%. Furthermore, our study extends the results to patients with all-type *A. baumannii* HAIs in general hospitals. We also first show that carbapenem resistance in patients with *A.baumannii* bloodstream infections and urinary tract infections suffered the highest excess one-year mortality of 27.6% and 12.4%, respectively.

In addition to an excess infection-related mortality, our study shows that carbapenem resistance in patients with *A. baumannii* HAIs increase the risk for long-term disability. Severe *A. baumannii* infections can cause acute organ dysfunction [52,53], particularly in patients with pre-existing chronic lung diseases [54]. However, to date there are no studies on the development of organ failure as a result of

carbapenem resistance *A. baumannii* HAIs. *A. baumannii* frequently causes respiratory infections in mechanically ventilated patients [55,56] and thus worsen the respiratory function after *A. baumannii* HAIs. In the present study, the most common *A. baumannii* HAIs was pneumonia, represented 38% of all *A. baumannii* HAIs. Our study first provides evidence on the potential irreversibility of CRAB HAIs-related ventilator dependence, showing that carbapenem resistance increased the risks for new-onset chronic ventilator dependence by 5.1% after *A. baumannii* HAIs. Therefore, carbapenem resistance can cause irreversible organ dysfunction and profoundly affect the patient's long-term well-being.

The excess risks for long-term mortality and disability strengthen the importance of controlling CRAB. The major risk factors of CRAB acquisition included prior exposure to antibiotics (especially carbapenems), longer hospital stay, invasive procedures, and admission to a ward with a high density of patients infected with CRAB (colonization pressure) were documented as the risk factors [57-60]. A nationwide study demonstrated a strong positive association between hospital carbapenem consumption and CRAB prevalence, and suggested that dedicated use of carbapenems would be an

important intervention to control the increase of CRAB [39]. Therefore, preventing and controlling of multidrug-resistant organisms (MDROs) are not only a national priority but also are assumed responsibility for all hospitals [61]. Successful prevention and control of MDROs needs administrative and scientific leadership, and a financial resource commitment [62]. Otherwise, the burden of antimicrobial resistance will result in increased morbidity, mortality, and costs of health care. Our results on the excess mortality/disability and excess hospital costs indicate that a reduction in incidence of CRAB can translate to improved long-term outcomes and significant cost savings, particularly when the huge financial burdens of providing long-term ventilator services are taken into consideration.

Our study was limited by the voluntary nature of TNIS participation and HAI case notification. The 96 hospitals in current study may not represent all hospitals in Taiwan. Nevertheless, we minimize the potential effect of self-selection bias on the estimated excess risk associated with carbapenem resistance, by individually matching the *A. baumannii* HAI cases to uninfected inpatients by the hospital. Because the notification of HAI cases was also voluntary, it is possible that some of the 4426 matched

uninfected inpatients might indeed have HAIs, which would have caused an underestimation of *A. baumannii* HAI-associated excess risks for long-term mortality and disability.

4.3 Comparison of *S. aureus* and *A. baumannii*

The *S. aureus* HAI study involving 3070 matched pairs show that *S. aureus* HAIs significantly increased the risks for long-term mortality and disabilities including new-onset chronic ventilator dependence and new-onset dialysis-dependent end-stage renal disease, with an excess one-year risk of 20.2%, 7.3%, and 2.6%, respectively. In the *A. baumannii* HAI study, we including 2213 matched pair show an excess one-year risk of 20.9%, 8.6%, and 0.4%, respectively. The excess risk of new-onset dialysis-dependent end-stage renal disease attribute to HAIs was found in the *S. aureus* HAI study, but the excess risk did not find in the *A. baumannii* HAI study. The most likely explanation was the different distribution in site of infection between patients with *S. aureus* HAIs and patients with *A. baumannii* HAIs, resulting in different pattern of organ dysfunction. The most common infection site in *S. aureus* HAIs was

bloodstream infections, representing 43% of all *S. aureus* HAIs. In *A. baumannii* HAIs, the most common infection type was pneumonia, representing 38% of all *A. baumannii* HAIs. *S. aureus* bacteremia can cause severe sepsis complicated by hemodynamic instability [7,8]. However, *A. baumannii* HAIs mainly cause pneumonia, particularly in patients with pre-existing chronic lung diseases. Therefore, our study found that *S. aureus* HAIs can cause irreversible renal failure and respiratory failure, but *A.baumannii* only can cause irreversible respiratory failure.

Chapter 5: Conclusion

S. aureus HAIs have substantial negative effect on the long-term outcome of hospitalized patients in terms of mortality, chronic ventilator dependence, and dialysis-dependent end-stage renal-disease. *A.baumannii* HAIs also have substantial negative effect on the long-term outcome of hospitalized patients in terms of mortality and chronic ventilator dependence. Beside, carbapenem resistance in patients with *A. baumannii* HAIs has additional negative effect on this two long-term outcomes. The negative impact on the long-term outcome of patients should be taken into consideration in future cost-effectiveness studies of the control and prevention interventions for *S. aureus* HAIs and *A. baumannii* HAIs.

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Table 1. Summary table of the impact of *S. aureus* HAIs studies

Author, year[ref]	Setting, country	Patients	Site	Organism	N	Matching/modeling	Measures	Outcome
Anderson et al., 2009 [19]	1 tertiary care center and 6 community hospitals, USA	Surgical	SSI	MRSA	659 surgical patients (150 MRSA vs 231 uninfected control or 128 MSSA)	Matching: type of operative procedure, hospital, and year of procedure Modeling: procedure at hospital, need assistance, post-operative glucose, orthopedic procedure, race, McCabe score, sex, CABG, surgical duration, and interaction term	90 days: mortality, readmission, duration of hospitalization, and hospital charges	Mortality: OR = 7.27 (↑ 11.8%) Readmission: OR = 35.0 LOS: ↑ 23 day Costs (all): ↑ 61,681
Nixon et al., 2006 [20]	1 academic medical center, UK	Surgical	SSI	MRSA	18 pairs	Matching: age, gender, American Society of Anaesthesiologists grade and residential status	Mortality, LOS, Costs (all)	Mortality: OR = 2.7 (↑ 39%) LOS: ↑ 50 day Operations: ↑ 1.6 次 Costs (all): ↑ 28,025
McGarry et al., 2004 [21]	1 tertiary-care hospital and 1 community hospital, USA	Elderly	SSI	*S. aureus*	96 *S. aureus*	Matching: surgical procedure and year Modeling: patient demographics, surgical procedure, NNIS risk index, ASA, duration of surgery, wound class, comorbid, DM, and Charlson score	90-day: Mortality (including out-of-hospital), LOS (including re-admission), cost	Mortality: OR = 5.4 (↑16.8%) LOS:↑17.2 days Costs (all):↑57014

Engemann et al., 2003 [22]	1 tertiary-care hospital and 1 community hospital, USA	General	SSI	*S. aureus*	286 SA (165 MSSA and121 MRSA)	Matching: surgical procedure and year Modeling: patient demographics, surgical procedure, NNIS risk index, ASA, duration of surgery, wound class, comorbid, DM, and Charlson score	90-day: Mortality (including out-of-hospital), LOS (including re-admission), cost	Mortality: OR = 3.4 (10.5%) LOS:↑9-day in MSSA and ↑18-days in MRSA Cost:↑23336 in MSSA and ↑62908 in MRSA
Abramson et al., 1999 [23]	1 University-based tertiary-care medical center, USA	General	BSI	*S. aureus*	19 pairs (11 MSSA and 8 MRSA)	Matching: primary diagnosis, number of secondary diagnoses, age, gender, and hospital ward	LOS, Costs (all)	LOS: ↑ 4day (MSSA) and ↑ 12 day (MRSA) Costs (all): ↑ 9,661 in MSSA and ↑ 27,083 in MRSA
Chaix et al., 1999 [24]	1000-bed ATC hospital, France	ICU	All	MRSA	27 pairs	Matching: age, severity of underlying disease classification, the simplified acute physiology score, number of organ system failures, and LOS before infection	LOS, Costs (all)	ICU Mortality: OR = 2.2 (↑ 33%) ICU LOS: ↑ 4 day Operations: ↑ 1 次 Costs (all): ↑ 13,879

Table 2. Summary table of the impact of carbapenem resistance in *A. baumannii* HAIs studies

Author, year[ref]	Setting, country	Patients	Type	N	Comparison	Matching/modeling	Measures	Outcome
Kwon et al., 2007 [33]	3 tertiary care hospitals, Korea	General	BSI	40 pairs	IRAB vs ISAB	Matching: age, Pitt bacteraemia score	30-d Mortality, LOS	↑mortality: 30% (OR=6.9)
Lee et al., 2007 [35]	1 medical center, Taiwan	General	BSI	46 pairs	MDR-AB vs MDS-AB	Matching: sex, age, severity of underlying and acute illness, and LOS before bacteremia	Sepsis-related mortality, in-hospital mortality, LOS (in-hospital and ICU), Cost (hospitalization and antibiotics)	↑Sepsis-related mortality: 21.8% (OR=4.1 sig) ↑in-hospital mortality: 8.7% (OR=1.43) ↑LOS: 13.4 ICU days, and 15.9 total days ↑Cost: 865 (antibiotics), and 3,758 (total)
Daniels et al., 2008 [36]	1 tertiary care hospitals, USA	3 SICU	All	42 pairs	MDR-AB vs non-MDR-AB	Propensity match, age, sex, type of ICU, medications, procedures, and diagnosis	28-day mortality LOS	↑mortality: NS (HR=1.4) ↑LOS before onset: 4.5 days ↑LOS after onset: NS

Sunenshine et al., 2007 [37]	2 tertiary care hospitals, USA	General	All	96	MDRAB (96) vs 1. MDSAB (91) 2.**uninfected** (89)	1. LOS before onset(±5%), similar institution 2. LOS before onset, same ward within 30 days	LOS, mortality	↑mortality (MDRAB/SAB): 8.4% **(NS)** (OR=2.6) ↑LOS (MDRAB/SAB): 6.7 d (OR=2.5)

Table 3. Baseline characteristics of 3070 matched pairs

	S. aureus HAI Patients (n=3070)	Matched Patients without HAIs (n=6140)	*P* value
Matching Variables			
Age, mean±SD/median (IQR)	67±19/72 (56–80)	67±19/72 (56–80)	–
Gender, female (%)	1051 (34.2)	2108 (34.2)	–
Type of hospital, n (%)			
Medical center	944 (30.8)	1888 (30.8)	–
Regional hospital	1610 (52.4)	3220 (52.4)	–
Local hospital	516 (16.8)	1032 (16.8)	–
Primary specialty,* n (%)			
Neurosurgery	259 (8.4)	518 (8.4)	–
Medicine	236 (7.7)	472 (7.7)	–
Surgery	170 (5.5)	345 (5.6)	–
Neurology	136 (4.4)	272 (4.4)	–
Orthopedics	116 (3.8)	232 (3.8)	–
Pediatrics	70 (2.3)	136 (2.2)	–
Plastic Surgery	61 (2.0)	122 (2.0)	–
Family Medicine	48 (1.6)	96 (1.6)	–
Severe illness, n (%)			
Cancer	520 (17.0)	1040 (17.0)	–
dialysis-dependent End-stage renal disease	114 (3.7)	228 (3.7)	–
Liver cirrhosis with complications	60 (2.0)	120 (2.0)	–
Chronic ventilator dependence	60 (2.0)	120 (2.0)	–
Generalized autoimmune syndrome	32 (0.5)	16 (0.5)	–
Spinal injury/ myeleterosis	6 (0.2)	12 (0.2)	–

Major trauma	14 (0.5)	28 (0.5)	–
Validation Variables			
Diagnosis, n (%)			
Ischemic heart disease	217 (7.1)	480 (7.8)	0.15
Congestive heart failure	226 (7.4)	444 (7.2)	0.81
Stroke	424 (13.8)	848 (13.8)	1.0
Diabetes mellitus	594 (19.4)	1354 (22.1)	0.001†
Hypertension	516 (16.8)	1427 (23.2)	<0.001†
Procedure, n (%)			
Total joint replacement	16 (0.5)	43 (0.7)	0.31
Coronary artery bypass graft	33 (1.1)	43 (0.7)	0.06
Rectoscopy	11 (0.4)	13 (0.2)	0.19
Laparoscopy	6 (0.2)	14 (0.2)	0.52
Medication, n (%)			
Statins	154 (5.0)	310 (5.0)	0.95
Streptokinase	17 (0.6)	25 (0.4)	0.33
Antigout preparations	293 (9.5)	506 (8.2)	0.04
Antineoplastic agents	159 (5.2)	387 (6.3)	0.03

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; IQR, interquartile range. *Eight out of 15 primary specialties with the most patients were listed. †Statistically significant, after Bonferroni correction (P<0.05/13=0.0038).

Table 4. Excess risks for mortality and new-onset organ failure in patients with *S. aureus* HAIs

Outcomes	Endpoint of Observation*	*S. aureus* HAI Patients	Matched Patients without HAIs	Excess Risk (%)	OR	Adjusted OR‡
Mortality	Number at risk#	3070	6140	-	-	-
	Discharge	956 (31.1)	691 (11.3)	19.9	4.5†	4.3†
	30-day after discharge	1188 (38.7)	1082 (17.6)	21.1	3.8†	3.7†
	one-year	1828 (59.5)	2416 (39.3)	20.2	3.2†	3.1†
Chronic ventilator dependence	Number at risk#	3010	6020	-	-	-
	Discharge	279 (9.3)	151 (2.5)	6.8	4.8†	4.6†
	30-day after discharge	329 (10.9)	203 (3.4)	7.6	4.2†	4.1†
	one-year	393 (13.1)	349 (5.8)	7.3	2.8†	2.7†
Dialysis-dependent end-stage renal disease	Number at risk#	2956	5912	-	-	-
	Discharge	77 (2.6)	53 (0.9)	1.7	3.5†	4.1†
	30-day after discharge	120 (4.1)	105 (1.8)	2.3	2.9†	3.6†
	one-year	153 (5.2)	153 (2.6)	2.6	2.6†	3.2†

Abbreviations: HAI, healthcare-associated infection; OR, odds ratio.

* Follow-up duration from index date to endpoint of observation.

Number at risk: the number of patients who have not yet developed the outcomes at admission.

‡ Adjusted for diabetes mellitus and hypertension.

† Statistically significant, after Bonferroni correction (all $P<0.05/18=0.0028$).

Table 5. Subgroup analysis of excess one-year mortality

Variables	*S. aureus* HAI Patients		Matched Patients without HAIs		% Difference	*P* value
	n	Event (%)	n	Event (%)		
one-year mortality, n (%)	3070	1828 (59.5)	6140	2416 (39.3)	20.2	<0.001†
By site of infection of index *S. aureus* HAI cases						
Bloodstream infection	1329	878 (66.1)	2658	1162 (43.7)	22.3	<0.001†
Pneumonia	785	540 (68.8)	1570	632 (40.3)	28.5	<0.001†
Urinary tract infection	206	111 (53.9)	412	186 (45.1)	8.7	<0.001†
Surgical site infection	310	102 (32.9)	620	127 (20.5)	12.4	<0.001†
Others	440	197 (44.8)	880	309 (35.1)	9.7	<0.001†
By antimicrobial resistance of index *S. aureus* HAI cases						
MSSA	869	419 (48.2)	1738	558 (32.1)	16.1	<0.001†
MRSA	2201	1409 (64.0)	4402	1858 (42.2)	21.8	<0.001†
By presence of severe illnesses* at admission of index *S. aureus* HAI cases						
No	2295	1255 (54.7)	4590	1491 (32.5)	22.2	<0.001†
Yes	775	573 (73.9)	1550	925 (59.7)	14.2	<0.001†

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

[*]Any of the 7 classes of severe illnesses (cancer, dialysis-dependent end stage renal disease, liver cirrhosis with complications, chronic ventilator dependence, generalized autoimmune syndrome, spinal injury/myeleterosis, and major trauma). [†] Statistically significant, after Bonferroni correction ($P<0.05/10=0.005$).

Table 6. Subgroup analysis of excess hospital stay and costs

Variables	*S. aureus* HAI Patients		Matched Patients without HAIs		Mean Difference	*P* value
	n	Mean (SD)	n	Mean (SD)		
Length of stay, mean (SD), days	3070	45 (51)	6140	33 (50)	12	<0.001†
By site of infection of index *S. aureus* HAI cases						
Bloodstream infection	1329	42 (35)	2658	33 (43)	9	<0.001†
Pneumonia	785	47 (54)	1570	30 (48)	17	<0.001†
Urinary tract infection	206	51 (64)	412	46 (63)	5	<0.001†
Surgical site infection	310	44 (36)	620	28 (28)	16	<0.001†
Others	440	50 (79)	880	38 (73)	12	<0.001†
By antimicrobial resistance of index *S. aureus* HAI cases						
MSSA	869	34 (40)	1738	23 (36)	11	<0.001†
MRSA	2201	50 (54)	4402	37 (54)	13	<0.001†
By presence of severe illnesses* at admission of index *S. aureus* HAI cases						
No	2295	46 (53)	4590	33 (49)	13	<0.001†
Yes	775	42 (45)	1550	35 (54)	7	<0.001†
Cost of hospitalization, mean (SD), in US dollars ‡	3070	12879 (13043)	6140	6900 (9006)	5979	<0.001†

By site of infection of index *S. aureus* HAI cases						
Bloodstream infection	1329	12441 (12822)	2658	7085 (9357)	5355	<0.001†
Pneumonia	785	14657 (13431)	1570	6285 (8374)	8373	<0.001†
Urinary tract infection	206	11468 (12448)	412	8477 (10351)	2991	<0.001†
Surgical site infection	310	12922 (13114)	620	6488 (6680)	6435	<0.001†
Others	440	11658 (12946)	880	6991 (9645)	4667	<0.001†
By antimicrobial resistance of index *S. aureus* HAI cases						
MSSA	869	8280 (8869)	1738	4378 (5520)	3903	<0.001†
MRSA	2201	14694 (13951)	4402	7896 (9880)	6798	<0.001†
By presence of severe illnesses* at admission of index *S. aureus* HAI cases						
No	2295	13437 (13571)	4590	6852 (8826)	6585	<0.001†
Yes	775	11225 (11181)	1550	7041 (9520)	4183	<0.001†

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

*Any of the 7 classes of severe illnesses (cancer, dialysis-dependent end stage renal disease, liver cirrhosis with complications, chronic ventilator dependence, generalized autoimmune syndrome, spinal injury/myeleterosis, and major trauma). ‡ At an exchange rate of 30 New Taiwan Dollars (NT$s) / US$. † Statistically significant, after Bonferroni correction ($P<0.05/20=0.0025$).

Table 7. Baseline characteristics of 2213 matched pairs

	A. baumannii HAI Patients (n=2213)	Matched Patients without HAIs (n=4426)	*P* value
Matching Variables			
Age, mean±SD/median (IQR)	69±17/74 (59–81)	69±17/73 (59–81)	–
Gender, female (%)	656 (29.6)	1312 (29.6)	–
Type of hospital, n (%)			
Medical center	696 (31.5)	1392 (31.5)	–
Regional hospital	1164 (52.6)	2328 (52.6)	–
Local hospital	353 (16.0)	706 (16.0)	–
Primary specialty,* n (%)			
Neurosurgery	221 (10.0)	442 (10.0)	–
medicine	200 (9.0)	400 (9.0)	–
surgery	163 (7.4)	326 (7.4)	–
Neurology	103 (4.7)	206 (4.7)	–
Orthopedics	53 (2.4)	106 (2.4)	–
Plastic Surgery	51 (2.3)	102 (2.3)	–
Family Medicine	28 (1.3)	56 (1.3)	–
Rehabilitation Medicine	27 (1.2)	54 (1.2)	–
Severe illness, n (%)			
Cancer	364 (16.4)	728 (16.4)	–
End-stage renal disease	61 (2.8)	122 (2.8)	–
Liver cirrhosis with complications	33 (1.5)	66 (1.5)	–
Chronic ventilator dependence	50 (2.3)	100 (2.3)	–

Generalized autoimmune syndrome	19 (0.9)	38 (0.9)	–
Spinal injury or myeleterosis	3 (0.1)	6 (0.1)	–
Major trauma	12 (0.5)	24 (0.5)	–
Validation Variables			
Diagnosis, n (%)			
Ischemic heart disease	100 (4.5)	318 (7.2)	<0.001†
Congestive heart failure	138 (6.2)	279 (6.3)	0.91
Stroke	349 (15.8)	609 (13.8)	0.03
Diabetes mellitus	398 (18.0)	951 (21.5)	0.001†
Hypertension	302 (13.6)	1050 (23.7)	<0.001†
Procedure, n (%)			
Total joint replacement	10 (0.5)	23 (0.5)	0.71
Coronary artery bypass graft	18 (0.8)	37 (0.8)	0.92
Laparoscopy	6 (0.3)	13 (0.3)	0.87
Medication, n (%)			
Antigout preparations	162 (7.3)	334 (7.5)	0.74
Antineoplastic agents	116 (5.2)	251 (5.7)	0.47
Statins	81 (3.7)	204 (4.6)	0.07
Streptokinase	14 (0.6)	16 (0.4)	0.12

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; IQR, interquartile range. *Eight out of 15 primary specialties with the most patients were listed. †Statistically significant, after Bonferroni correction ($P<0.05/12=0.0042$).

Table 8. Excess risks for mortality and new-onset organ failure in patients with *A. baumannii* HAIs

Outcomes	Endpoint of Observation*	*A. baumannii* HAI Patients	Matched Patients without HAIs	Excess Risk (%)	OR	Adjusted OR‡
Mortality	Number at risk#	2213	4426	-	-	-
	Discharge	731 (33.0)	508 (11.5)	21.6	4.6†	4.4†
	30-day after discharge	909 (41.1)	790 (17.8)	23.2	3.9†	3.8†
	one-year	1377 (62.2)	1827 (41.3)	20.9	3.1†	3.1†
Chronic ventilator dependence	Number at risk#	2163	4326	-	-	-
	Discharge	250 (11.6)	129 (3.0)	8.6	5.4†	5.4†
	30-day after discharge	312 (14.4)	167 (3.9)	10.6	5.2†	5.2†
	one-year	373 (17.2)	303 (7.0)	10.2	3.3†	3.3†
Dialysis-dependent end-stage renal disease	Number at risk#	2152	4304	-	-	-
	Discharge	17 (0.8)	18 (0.4)	0.4	2.0	2.5
	30-day after discharge	23 (1.1)	30 (0.7)	0.4	1.6	2.0
	one-year	32 (1.5)	55 (1.3)	0.2	1.2	1.5

Abbreviations: HAI, healthcare-associated infection; OR, odds ratio.

* Follow-up duration from index date to endpoint of observation.

Number at risk: the number of patients who have not yet developed the outcomes at admission.

‡ Adjusted for ischemic heart disease, diabetes mellitus and hypertension.

† Statistically significant, after Bonferroni correction (all $P<0.05/18=0.0028$).

Table 9. Subgroup analysis of excess one-year mortality

Variables	*A. baumannii* HAI Patients		Matched Patients without HAIs		% Difference	*P* value
	n	Event (%)	n	Event (%)		
One-year mortality, n (%)	2213	1,377 (62.2)	4426	1827 (41.4)	20.9	<0.001†
By site of infection of index *A. baumannii* HAI cases						
Pneumonia	848	603 (71.1)	1696	720 (42.5)	28.7	<0.001†
Bloodstream infection	584	363 (62.2)	1168	517 (44.3)	17.9	<0.001†
Urinary tract infection	509	277 (54.4)	1018	408 (40.1)	14.3	<0.001†
Surgical site infection	75	32 (42.7)	150	32 (21.3)	21.3	<0.001†
Others	197	102 (51.8)	394	150 (38.1)	13.7	<0.001†
By antimicrobial resistance of index *A. baumannii* HAI cases						
CSAB	1177	666 (56.6)	2354	969 (41.2)	15.4	<0.001†
CRAB	1036	711 (68.6)	2072	858 (41.4)	27.2	<0.001†
By presence of severe illnesses* at admission of index *A. baumannii* HAI cases						
No	1676	976 (58.2)	3352	1156 (34.5)	23.7	<0.001†
Yes	537	401 (74.7)	1074	671 (62.5)	12.2	<0.001†

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; CSAB, carbapenem-susceptible *A. baumannii*; CRAB, carbapenem- resistant *A. baumannii*.

[*] Any of the 7 classes of severe illnesses (cancer, dialysis-dependent end stage renal disease, liver cirrhosis with complications, chronic ventilator dependence, generalized autoimmune syndrome, spinal injury/myeleterosis, and major trauma). [†] Statistically significant, after Bonferroni correction ($P<0.05/10=0.005$).

Table 10. Subgroup analysis of excess hospital stay and costs

Variables	*A. baumannii* HAI Patients		Matched Patients without HAIs		Mean Difference	*P* value
	n	Mean (SD)	n	Mean (SD)		
Length of stay, mean (SD), days	2213	35.5 (17.5)	4426	25.6 (16.4)	9.9	<0.001†
By site of infection of index *A. baumannii* HAI cases						
Pneumonia	848	35.6 (16.6)	1696	23.3 (15.2)	12.3	<0.001†
Bloodstream infection	584	31.9 (17.9)	1168	24.5 (16.4)	7.4	<0.001†
Urinary tract infection	509	38.7 (17.3)	1018	30.7 (17.3)	8.0	<0.001†
Surgical site infection	75	39.0 (18.4)	150	25.8 (17.1)	13.2	<0.001†
Others	197	35.9 (17.8)	394	25.6 (16.1)	10.3	<0.001†
By antimicrobial resistance of index *A. baumannii* HAI cases						
CSAB	1177	33.7 (17.1)	2354	24.1 (15.9)	9.6	<0.001†
CRAB	1036	37.6 (17.6)	2072	27.3 (16.8)	10.3	<0.001†
By presence of severe illnesses* at admission of index *A. baumannii* HAI cases						
No	1676	36.1 (17.6)	3352	25.5 (16.4)	10.6	<0.001†
Yes	537	33.7 (16.9)	1074	26.0 (16.5)	7.7	<0.001†

Cost of hospitalization, mean (SD), in US dollars [‡]	2213	12047 (8581)	4426	5951 (6009)	6096	<0.001[†]
By site of infection of index *A. baumannii* HAI cases						
Pneumonia	848	12567 (7806)	1696	5260 (5540)	7306	<0.001[†]
Bloodstream infection	584	11361 (9090)	1168	5766 (5842)	5595	<0.001[†]
Urinary tract infection	509	11017 (7936)	1018	7235 (6803)	3782	<0.001[†]
Surgical site infection	75	14830 (11916)	150	6627 (7163)	8204	<0.001[†]
Others	197	13446 (9733)	394	5896 (5201)	7549	<0.001[†]
By antimicrobial resistance of index *A. baumannii* HAI cases						
CSAB	1177	10324 (7881)	2354	5404 (5693)	4921	<0.001[†]
CRAB	1036	14004 (8921)	2072	6572 (6293)	7432	<0.001[†]
By presence of severe illnesses[*] at admission of index *A. baumannii* HAI cases						
No	1676	12401 (8800)	3352	5950 (5990)	6451	<0.001[†]
Yes	537	10942 (7760)	1074	5952 (6071)	4989	<0.001[†]

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; CSAB, carbapenem-susceptible *A. baumannii*; CRAB, carbapenem- resistant *A. baumannii*.

[*]Any of the 7 classes of severe illnesses (cancer, dialysis-dependent end stage renal disease, liver cirrhosis with complications, chronic ventilator dependence, generalized autoimmune syndrome, spinal injury/myeleterosis, and major trauma). [‡] At an exchange rate of 30 New Taiwan Dollars (NT$s) / US$. [†] Statistically significant, after Bonferroni correction ($P<0.05/20=0.0025$).

Table 11. Excess one-year mortality and disability attribute to carbapenem resistance

Outcomes	CRAB matched group				CSAB matched group				Attributable difference of excess risk	Adjusted OR‡
	no. of pairs#	CRAB HAI Patients	Matched Patients without HAIs	Excess Risk	no. of pairs#	CSAB HAI Patients	Matched Patients without HAIs	Excess Risk		
Mortality, %										
Overall	1036	68.6	41.4	27.2	1177	56.6	41.2	15.4	11.8†	1.7‡
Pneumonia	449	73.9	43.2	30.7	399	67.9	41.6	26.3	4.4	1.3
Bloodstream infection	178	78.1	41.0	37.1	406	55.2	45.7	9.5	27.6†	3.0‡
Urinary tract infection	277	61.7	41.7	20.0	232	45.7	38.1	7.6	12.4	1.9‡
Surgical site infection	31	38.7	19.4	19.3	44	45.5	22.7	22.8	-3.5	0.8
Other	101	56.4	40.1	16.3	96	46.9	25.5	21.4	-5.1	0.7
New-onset chronic ventilator dependence, %										
Overall	1007	21.1	8.1	13.0	1156	13.9	6.1	7.8	5.2†	1.7‡
Pneumonia	435	23.7	8.6	15.1	391	16.6	6.9	9.7	5.4	1.6
Bloodstream infection	174	14.4	5.8	8.6	404	10.1	5.2	4.9	3.7	1.5
Urinary tract infection	268	22.4	10.3	12.1	223	17.9	6.3	11.6	0.5	1.3
Surgical site infection	30	10.0	3.0	7.0	44	11.4	5.7	5.7	1.3	1.2
Other	100	21.0	6.0	15.0	94	10.6	5.9	4.7	10.3	2.3

Abbreviation: HAI, healthcare-associated infection; CRAB, carbapenem resistant *A. baumannii*; CSAB, carbapenem susceptible *A. baunammii*.
† Statistically significant, after Bonferroni correction ($P<0.05/12=0.0042$).
# Number at risk: the number of patients who have not yet developed the outcomes at admission.
‡ Adjusted for ischemic heart disease, diabetes mellitus and hypertension.

Table 12. Excess hospital stay and costs attribute to carbapenem resistance

Outcomes	CRAB matched group				CSAB matched group				Attributable difference of mean difference
	no. of pairs[#]	CRAB HAI Patients	Matched Patients without HAIs	Mean difference	no. of pairs[#]	CSAB HAI Patients	Matched Patients without HAIs	Mean difference	
Length of stay, days									
Overall	1036	37.6	27.3	10.3	1177	33.7	24.1	9.6	0.7[†]
Pneumonia	449	36.4	23.8	12.6	399	34.8	22.7	12.1	0.5
Bloodstream infection	178	33.9	27.0	6.9	406	31.1	23.4	7.7	-0.8
Urinary tract infection	277	40.7	32.7	8.0	232	36.4	28.4	8.1	-0.1
Surgical site infection	31	47.6	29.5	18.1	44	33.0	23.2	9.8	8.3[†]
Other	101	38.5	28.0	10.5	96	33.3	23.0	10.3	0.2
Cost of hospitalization, in US dollars [&]									
Overall	1036	14004	6572	7432	1177	10324	5404	4921	2511[†]
Pneumonia	449	13748	5666	8082	399	11237	4804	6433	1649[†]
Bloodstream infection	178	15294	6680	8614	406	9637	5365	4272	4342[†]
Urinary tract infection	277	12360	7824	4536	232	9414	6532	2882	1654[†]
Surgical site infection	31	20059	7950	12109	44	11147	5694	5453	6656[†]

Other	101	15520	6558	8962	96	11264	5200	6064	2898[†]

Abbreviation: HAI, healthcare-associated infection; CRAB, carbapenem resistant *A. baumannii*; CSAB, carbapenem susceptible *A. baunammii*.

[&] At an exchange rate of 30 New Taiwan Dollars (NT$s) / US$.

[†] Statistically significant, after Bonferroni correction ($P<0.05/12=0.0042$).

Number at risk: the number of patients who have not yet developed the outcomes at admission.

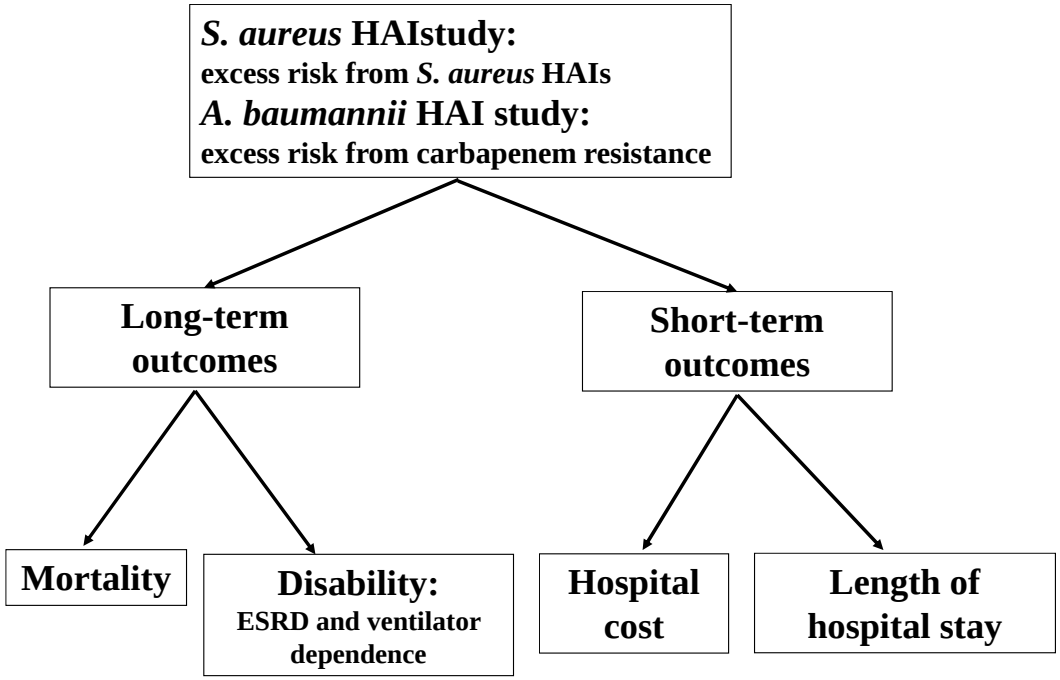

Figure 1. Objectives of the *S. aureus* /*A. baumannii* HAI study

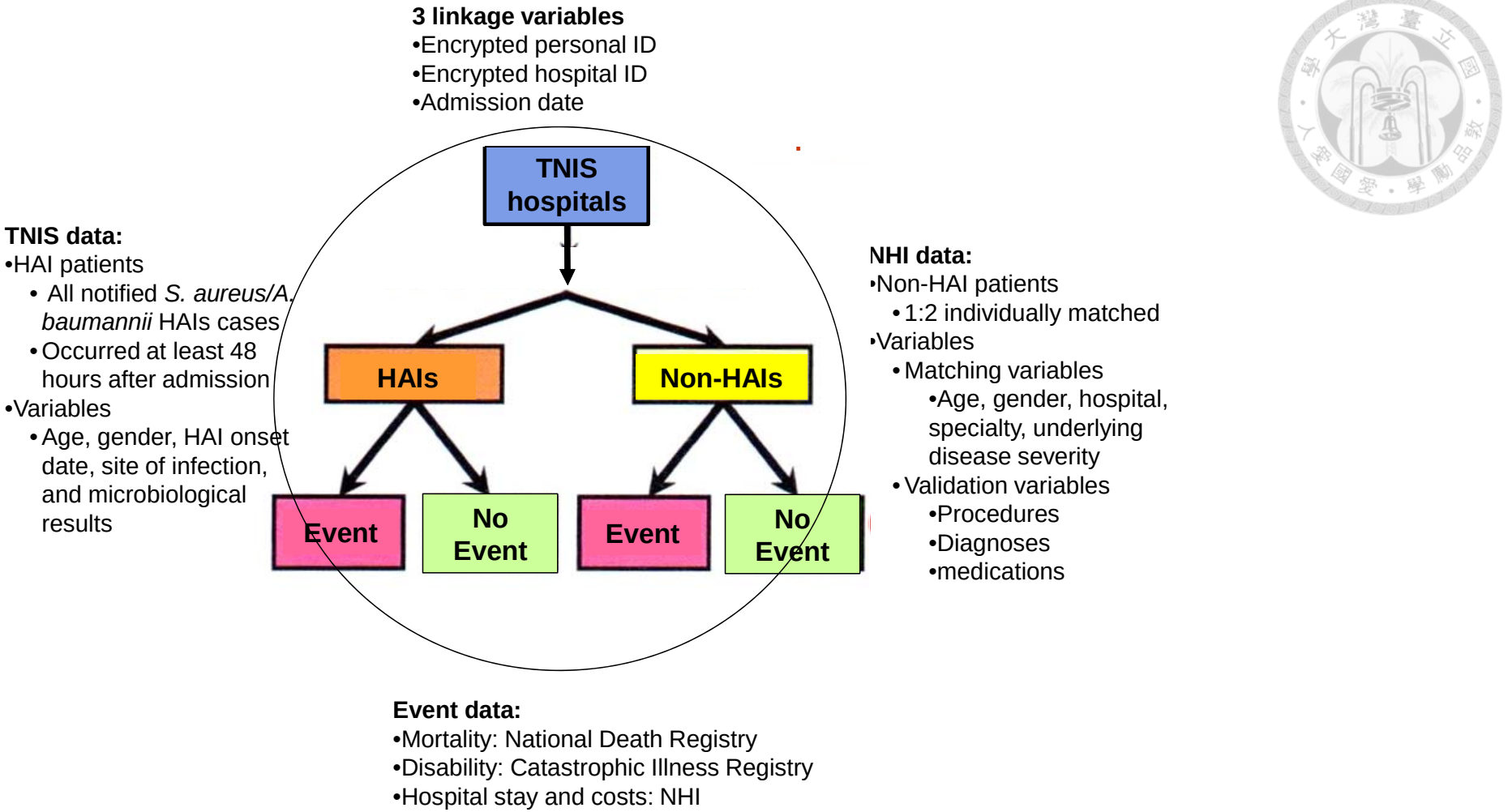

Figure 2. Framework of study sources

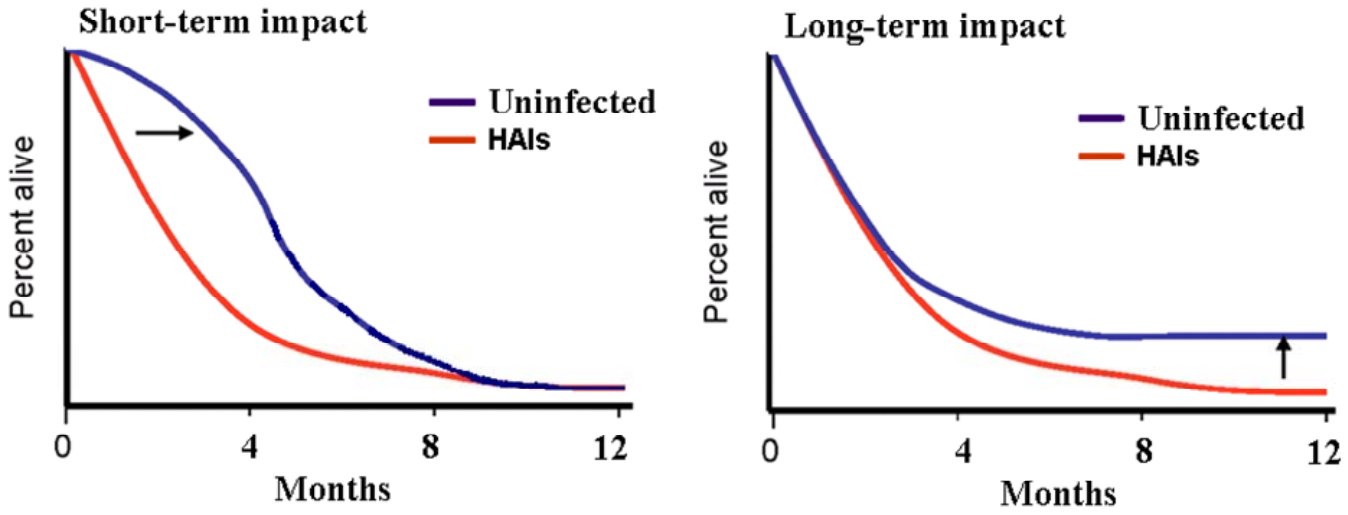

Figure 3. Short-term vs. long-term impact of HAIs

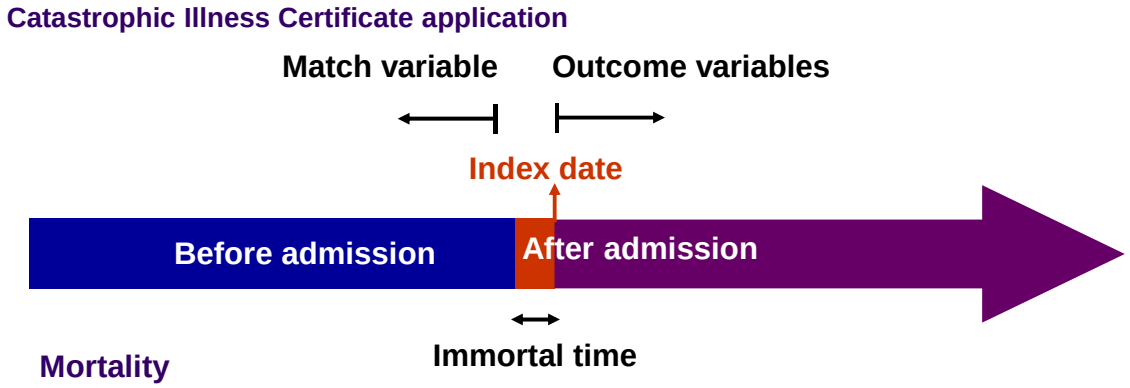

Figure 4. Ascertainment of mortality and disability outcomes

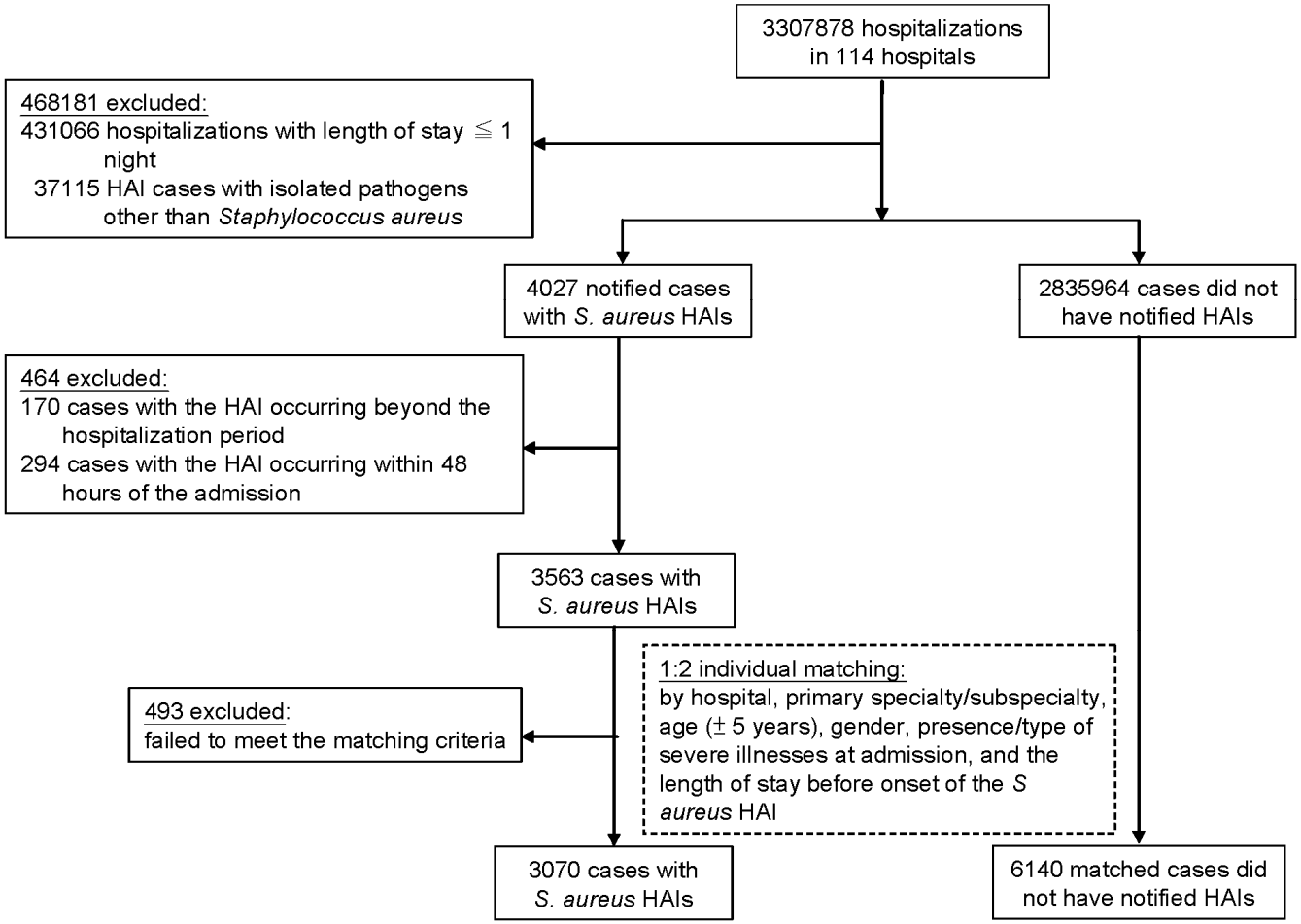

Figure 5. Flowchart of patient selection for matching

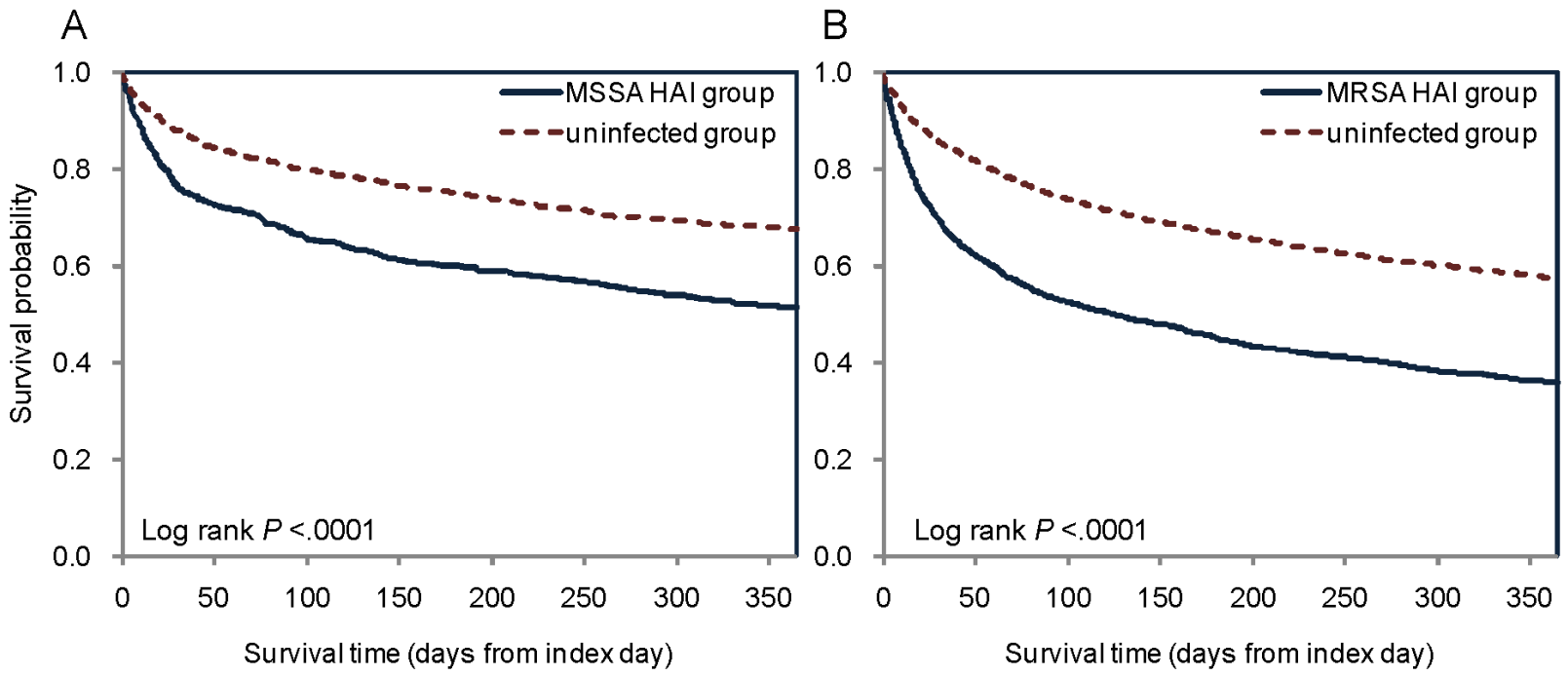

Figure 6. Kaplan-Meier survival curves (A) MSSA patients (n=869) and their matched uninfected patients (n=1738). (B) MRSA patients (n=2201) and their matched uninfected patients (n=4402)

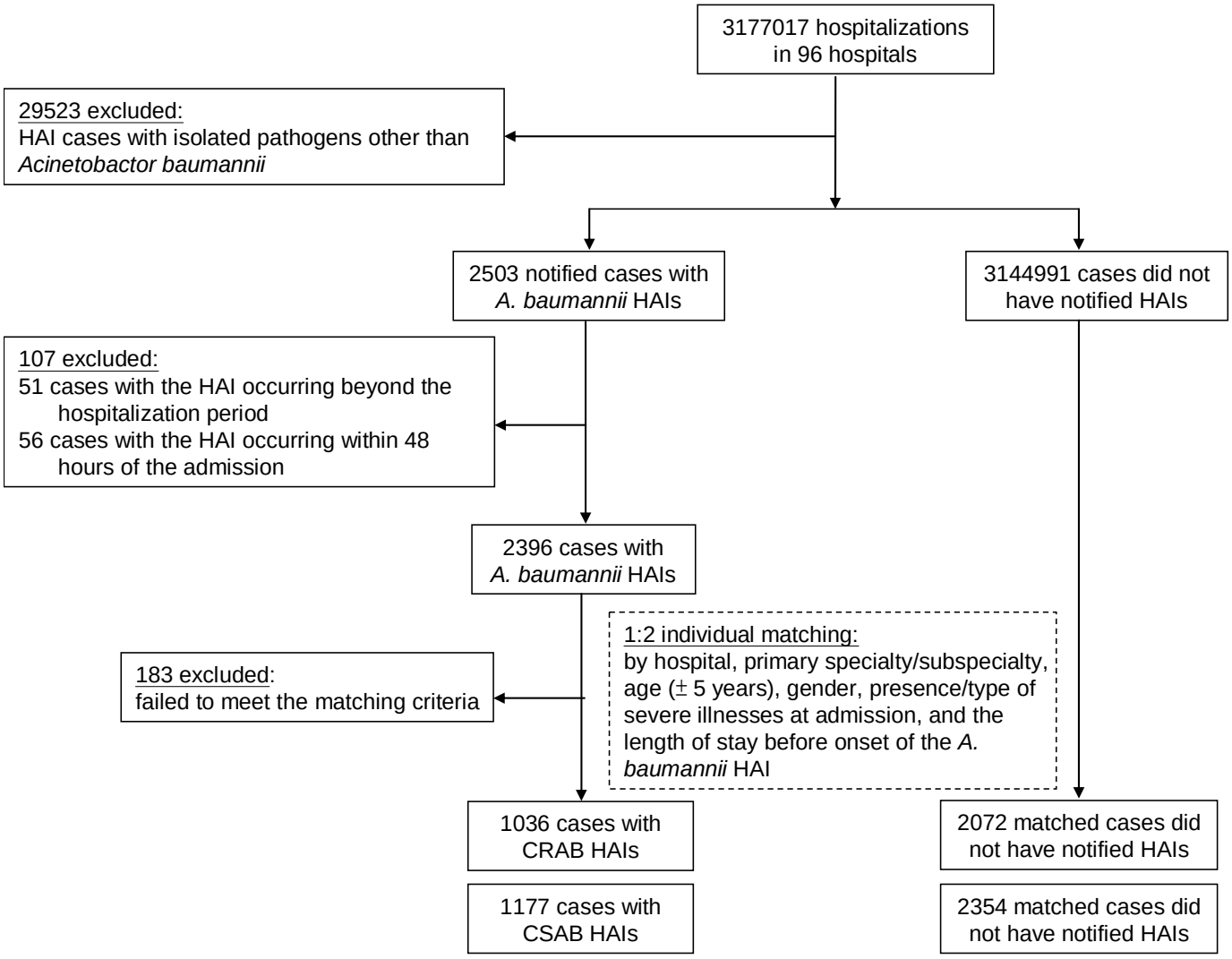

Figure 7. Flowchart of patient selection for matching

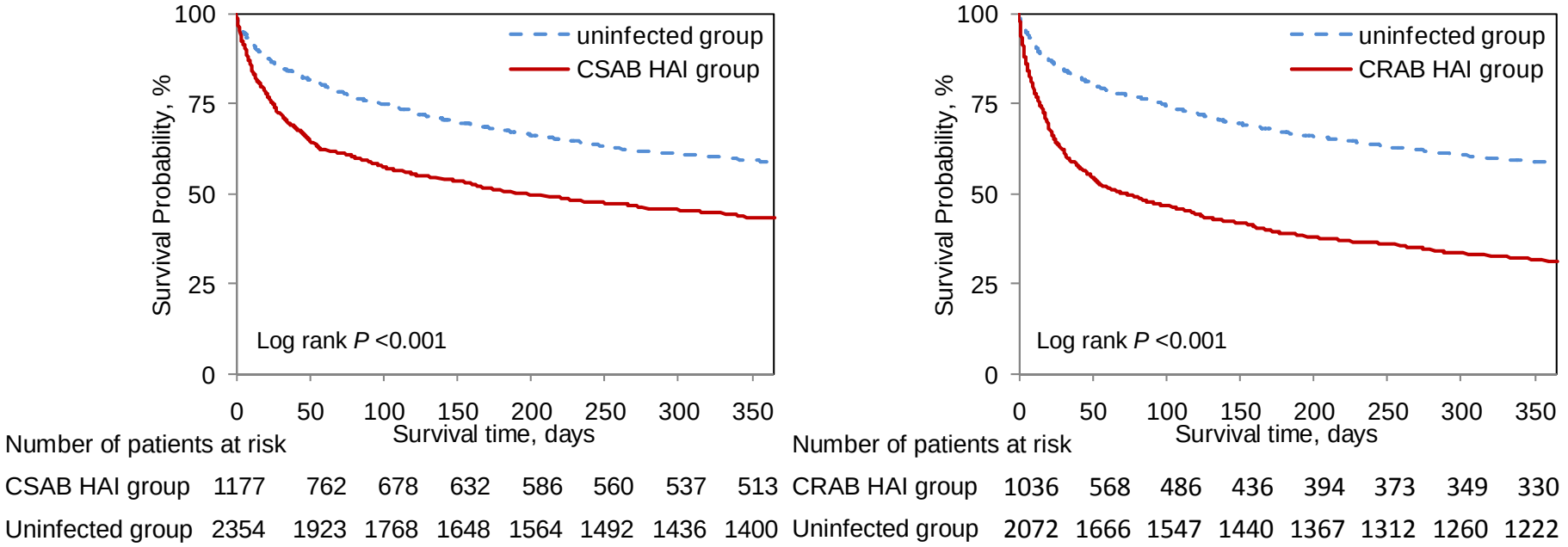

Figure 8. Kaplan-Meier survival curves (A) CSAB patients (n=1177) and their matched uninfected patients (n=2354). (B) CRAB patients (n=1036) and their matched uninfected patients (n=2072)