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THE BURDEN OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS INFECTIONS AMONG HOSPITALISED PATIENTS IN SINGAPORE

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ABSTRACT

Background: MRSA has caused enormous burden to affected Western patients and society. However, only limited study results originated from the Asia-Pacific populations.

Aim: To assess the burden of Methicillin-resistant S. aureus infections (MRSA) among patients from a large tertiary care hospital in Singapore.

Methods: Retrospective study using data from the hospital discharge database to identify patients with MRSA and Methicillin-sensitive S. aureus infections (MSSA) using International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Australian Modification (ICD-9-AM) codes.

Findings: Amongst 543,068 hospitalized patients between 2004 and 2010, 8,664(1.6%) were infected with S. Aureus, including 4,868(0.9%) with MRSA. Compared with uninfected controls, MRSA patients had longer hospital stay (geometric mean, GM, 12.2 vs. 3.0 days), higher hospitalization costs (GM, $6294.7 vs. $2295.7), higher in-hospital mortality rate (7.8% vs. 2.8%) and higher 30-day all-cause unscheduled readmission rate (36.3% vs. 23.7%, all p<0.001). The difference still existed after adjustment for age groups, gender, ethnicity, medical management, and Charlson comorbidity index. Similarly, MRSA patients had longer hospital stay, higher hospitalization costs, higher in-hospital mortality rate and 30-day all-cause unscheduled readmission rate compared with patients with MSSA.

Conclusion: MRSA infection was associated with poor clinical outcomes and higher economic burden in this population. Prevention and control measures should be implemented both inside and outside the hospital setting.

Key words: MRSA, length of stay, hospitalization cost, unscheduled readmission, hospital mortality, ICD-9-AM.

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INTRODUCTION

Since it was first reported as a nosocomial pathogen in US hospitals, Methicillin resistant Staphylococcus aureus (MRSA) infection has rapidly increased to epidemic proportions worldwide.1 The estimated number of S. aureus–related hospitalizations in US increased by 62% (or about 8.4% per year) from 294,570 in 1999 to 477,927 in 2005, and the estimated number of MRSA-related hospitalizations more than doubled from 127,036 to 278,203 over the same period (a rise of 14% per year).2 Infections by MRSA are estimated to cause 19,000 deaths among hospitalized patients in the US annually, similar to deaths due to AIDS, tuberculosis, and viral hepatitis combined.3 4 In the European Union (EU), MRSA infections are estimated to affect more than 150,000 patients annually, resulting in additional in-hospital costs of EUR380 million for EU healthcare systems.5 Furthermore, MRSA has been found to be independently associated with hospitalization costs and increased length of stay in patients with S. aureus infections (including bacteraemia, surgical site infections, and ventilator-associated pneumonia).6-8

Most studies to date have suffered from one or more limitations: Selected ones have only encompassed one type of S. aureus infection, whereas others have quantified costs for only short periods with limited sample sizes. Moreover, others have presented only hospital charges without other outcomes such as hospital length of stay and readmission.9-11 Almost all studies have originated in the USA and European countries, with very few from the Asia-Pacific region. As different countries differ along many dimensions, including different genetic profiles, different climates and bacterial floras, different practices of antibiotics use, healthcare delivery and financing systems, the burden of MRSA infections may be substantially different across countries and cannot be directly extrapolated from one to the other7 8 12

Knowledge of the burden of S. aureus infection in the local patient population, especially MRSA, will be helpful to medical personnel and hospital administrators to understand and possibly reduce the impact of such infections, and to evaluate cost-effectiveness of interventions. Thus, this study aims to assess the burden of MRSA infection among hospitalized patients from a large tertiary care hospital in Singapore, by comparing patients with MRSA to both

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patients with MSSA and to patients without nosocomial infections. The outcomes used to assess the burden were hospital length of stay, 30-day all-cause re-admission, in-hospital mortality and cost of care.

METHODS

DATA SOURCE

Singapore General Hospital (SGH) is the largest acute tertiary care hospital in Singapore with 1600 beds, serving approximately a quarter of the Singapore population of 5.08 million.13 Each year, SGH manages approximately 80,000 inpatients. Data from all hospitalized patients aged 21 years and above admitted into SGH from January 1, 2004 to December 31, 2010 was collected from the hospital's data warehouse at the Information Technology Department, Singapore Health Services Group, Singapore. This included demographic information such as age, gender, ethnicity; and clinical characteristics, including hospital admission and discharge date; up to 10 International Statistical Classification of Diseases and Related Health Problems 9th Revision, Australian Modification (ICD-9-AM) Diagnosis Codes; up to 10 ICD-9-AM Procedure Codes; discharge status; and disposition at discharge. Data relating to patients who were readmitted to the hospital within 30 days of the first discharge was extracted. Available hospitalization cost of care data including investigation, medication, treatment and facility charges was also extracted based on hospital service codes as secondary cost endpoints. The protocol for this study was approved by the Ethics Committee of the Singapore General Hospital with exemption from the requirement for informed consent.

CASE DEFINITION

A S. aureus infection was deemed to be present by the occurrence of any of the following ICD-9-AM codes in the patient's discharge data: S. aureus infection (code 041.11), S. aureus septicemia (code 038.11), or pneumonia due to S. aureus (code 482.41), as outlined previously.2 14 MRSA infection was deemed to be present if any of the ICD-9-AM code for MRSA (code V09.0) in the database was found, either alone or in conjunction with an ICD-9-AM code for S. aureus infection (code 041.11), S. aureus septicemia (code 038.11), or pneumonia due to S. aureus (code 482.41). Medical records that contained multiple S. aureus–related ICD-9-AM codes were counted only once.2 14

The presence of surgical and medical conditions was determined based on the

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occurrences of ICD-9-AM diagnostic codes and procedure codes.15 16 Chronic comorbid conditions were identified and then used to calculate the Deyo's adaptation of Charlson Comorbidity Index (CCI).17

STATISTICAL ANALYSIS

Categorical variables were reported as percentages, and continuous variables as mean and standard deviation (SD) with the exception of hospitalization cost and length of stay (LOS) where geometric mean (GM) and 95% confidence interval (CI) were used given the skewed distributions of these variables. Comparisons of categorical variables among MRSA, MSSA and control patients were analyzed using the Chi-square test. Comparisons of LOS and hospitalization cost among the three groups were analyzed using the Kruskal Wallis test. All hospitalization costs were converted to year 2010 US dollars for presentation based on the Annual Average Rates of Exchange, Singapore [2010].18

Generalized Estimating Equation (GEE) model, an extension of generalized linear model regression analysis, was used to assess the association of these clinical outcomes with MRSA infection after adjusting for age groups, gender, ethnicity, medical management, and CCI groups. This model correctly accounts for the within-patient correlation due to multiple visits from the same patients.19 As very small percentage (<1%) of patients experienced a repeated admission for more than 20 times over the study period, only the first 19 readmission of these patients were selected for the regression analysis. We considered the model with lowest Quasi-likelihood Information Criterion (QIC) to be the most parsimonious model among the competing models with different correlation structures (exchangeable, auto-regressive, unstructured etc.).19 Using the estimates from the regression models, we present adjusted in-hospital mortality rate, 30-day all-cause unscheduled readmission rate, length of stay and hospitalization costs among MRSA, MSSA and uninfected control patients.

All tests were two-sided, with $p<0.05$ considered statistically significant. Data analysis was performed using STATA Version 10.0 (StataCorp, College Station, TX, USA).

RESULTS

Of 543,068 hospitalized patients from 2004 to 2010, 276581 (51%) patients involved only 1 admission, 100075 (18.4%) patients involved 2 admissions, and 166412 (30.6%)

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patients involved 3 and more admissions over the study period. Of all the patients, 8,664 (1.6%) were infected with S. aureus, in which 4,868 (0.9%) had MRSA. MRSA patients were older compared to MSSA patients and uninfected controls (p<0.001). Patients with S. aureus infection were more likely to be male and more likely to be surgically managed compared to control patients (all p<0.001). MRSA patient were more likely to be admitted to ICU (8.2%), followed by MSSA (6.7%), and control patients (3.1%, all p<0.001 within group comparisons). Similarly, MRSA patients experienced highest grades of comorbidity, followed by MSSA patients, and control patients (all p<0.001 within group comparisons). The demographic and clinical characteristics of all patients are shown in Table 1.

Clinical outcomes and resource utilization before adjustment. MRSA patients had highest in-hospital mortality (7.8%), followed by MSSA patients (5.6%) and control patients (2.8%, all p<0.001). For the 30-day all-cause unscheduled readmission rates, MRSA patients (36.3%, p<0.001) had higher rates compared to other patients, but similar rates for MSSA and control patients (24.5% and 23.7%, P>0.05). As for resource utilization, MRSA patients had longest hospital stay (GM, 12.2 days) and highest hospitalization cost (GM, $6294.7), followed by MSSA patients (9.8 days and $4915.8) and control patients (3.0days and $2295.7; all p<0.001) (Table 2). The clinical outcomes and resource utilization among the three groups of patients are shown in Table 2.

Multivariate analysis results of hospital clinical outcomes and resource utilization. GEE model was used to account for the correlation of multiple visits by the same patient. The regression model is also adjusted for age groups, gender, ethnicity, medical management, and CCI grades. MRSA patients had the highest in-hospital mortality (MRSA 12.2%, MSSA 7.3% and controls 1.1%), longest hospital stay (GM, 18.5, 15.9 and 4.5 days) and highest hospitalization cost (GM, $9760.1, $8327.5 and $3340.1), followed by MSSA patients, and then control patients (all comparison between groups were p<0.001; Table 2). As for 30-day all-cause unscheduled readmission rate, MRSA patients (58.4%, p<0.001) had higher rates compared to other patients, but MSSA and control patients (21.3% and 22.7 %, P>0.05) showed similar rates.

As for the detailed secondary hospitalization cost endpoints, similarly, MRSA patients had significant highest

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investigation, medication, treatment, and facility cost, followed by MSSA patients and control patients (all p<0.001). The significantly different secondary hospitalization cost endpoints persisted even after adjustment for the same parameters (Table 3).

DISCUSSION:

We found that patients with MRSA had significantly increased in-hospital mortality and 30-day all-cause unscheduled readmission rates compared with both MSSA and with control patients. The in-hospital mortality rates were 7.8% for MRSA, 5.6% for MSSA and 2.8% for control patients (p<0.001). The 30-day all-cause unscheduled readmission rates were 36.3% for MRSA patients, 24.5% and 23.7% for MSSA and control patients (p<0.001). At the same time, MRSA patients also had the longest hospital stay (12.2 days), and highest hospitalization cost ($6294.7), followed by MSSA (9.8 days and $4915.8) and then control patients (3.0 days and $2295.7, all p<0.001). These differences were still statistically significant even after adjustment for age groups, gender, ethnicity, medical management, and CCI grades.

Our findings are consistent with previous reports of in-hospital mortality due to MRSA infections, where figures ranging from 4.7% to 8.8% have been reported.2 20 21 It is slightly higher than that reported in Illinois, USA, which reported mortality rates of 1.9% to 3.4% form 2002 to 2007.22 However, there are also other studies which have reported mortality rates as high as 17.8% to 39%.3 23 Meta-analyses have also found that mortality is almost doubled in patients with MRSA-associated bacteraemia compared with MSSA.5 24 25 Different patient selection criteria, including age, comorbidities, ineffective antibiotics usage, and the virulence of the MRSA organism itself, have been suggested to contribute to these differences.4 24

Our study results differ from those from a previous study of local patient population.8 In the study, Pada et al. reported that nosocomial MRSA infection was independently associated with in-hospital death (14.4% vs. 1.4%), longer hospital stay (median, 32 days vs. 7 days), and higher hospitalization costs (median, US$18,129.89 vs. US$4,490.47) compared with MSSA infection.8 The above mentioned study selected a limited number of patients with clinically significant healthcare-associated MRSA infections classified according to the former National Nosocomial Infections

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Surveillance System definitions. In contrast, our study selected patients based on discharge ICD-9-AM codes over a much longer period of time and covered all types of MRSA infections, including patients with MRSA colonization. Although coding inaccuracies is inevitable within a large administrative database like the one we used, these are unlikely to explain the huge difference (14.4% vs. 7.8%) in mortality rates between the two studies.

Besides effects on mortality, many studies have found that MRSA infections cause significant additional financial burden over MSSA infections and non-S. aureus infected control patients. Cosgrove and colleagues noted that bacteraemic patients with MRSA cost $26,424 and those with MSSA $19,212.26 Other studies have also reported an increase in costs for MRSA infections when compared with MSSA infections, which varied from one to three fold increment.7 27 28 In our study, we found an almost tripled hospitalization cost of patients with MRSA compared with control patients, with doubled cost for patients with MSSA after adjustment for co-morbidities and other factors. The increased cost occurred in all secondary hospitalization cost endpoints including investigations, medications, treatment and facility costs, indicating a burden on all hospital sectors.

Several explanations have been proposed for the increased hospitalization cost of MRSA. One explanation could be underlying severity of illness. In our study, we applied the CCI to adjust for severity of diseases in all three groups to exclude the possible effect. The CCI has been used as a measure of underlying disease in several studies examining the impact on outcome or costs of patients with MRSA or Clostridium difficile.29 30 Other explanations include prolonged hospital stay, occupation of isolation rooms, and prolonged ICU stay and ventilation for surgical and critically ill patients.5 7 26-28 31 Shorr et al. reported prolonged hospitalisation, prolonged ventilation, and longer stay on ICU in MRSA patients after multivariate analysis.32 Our findings support this explanation. Furthermore, these increased costs might reflect the increased antibiotics utilization to treat MRSA infection. Medication data presented the largest relative increase, and might reflect a higher demand for more expensive drugs in these patients such as vancomycin and linezolid.33 Once again, our study results endorse this explanation.

Our assessments of the 30-day all-cause unscheduled readmission rate due to MRSA are unique. The 30-day all-cause unscheduled readmission rate in patients with MRSA was about 50% more than that in

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MSSA and control patients (36.3%, 24.5% and 23.7%). To the best of our knowledge, our study is the first study in Asian patient population to measure and report significantly increased 30-day all-cause unscheduled readmission rate due to MRSA infection by using a large administrative database. Our study results are in agreement with similar readmission measurements done by other studies with small numbers of subjects. MRSA infections have previously been reported to result in a readmission rate of 40% (all readmission over 4 years)34, and surgical site infections due to MRSA were found to result in a 35-fold increased risk of hospital 90-days readmission compared to uninfected controls.35 Older age and higher disease severity in patients with MRSA have been acknowledged as key risk factors for the higher rate in readmission2 3, and a local study of patients aged 65 and above has shown that nosocomial infection is a risk factor for unplanned patient readmission to hospital within 15 days of discharge.36 However, in our study, the higher readmission rate remained even after adjustment for these factors.

This study further highlights the importance of implementation of MRSA reduction strategies in the hospital setting. Our hospital has ongoing active surveillance as a measure to monitor the number of patients with MRSA. Intensive Hand Hygiene Program for all hospital staff has also been implemented in SGH. The Program includes the multimodal strategy recommended in the World Health Organization (WHO) guidelines e.g. system changes, from hand washing to greater use of the alcohol hand rub agents, as well as ensuring that staff have easy access to hand rub agents at the point of care. This perhaps mirrored by the relative lower MRSA rate reported in our study. The success of the Hand Hygiene Program has earned the hospital recognition as a Global Hand Hygiene Expert Centre by the WHO in 2011.37

Strengths of our study include the inclusion of a large multiethnic population sample over many years, which allows for a robust estimate and control for potential confounding variables (including patient demographics and comorbid conditions). It should be acknowledged that there may be other unmeasured confounders that could explain at least part of the outcome differences among the 3 patient groups. The hospital discharge data are reliable and extensive use in various analyses in health services research.38 As all the data came from a single hospital, there is less risk of coding discrepancies and non-uniformity in the calculation of hospitalization costs.

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However, the study also has several limitations. The hospital dataset is administrative in nature and not specifically designed to track infection prevalence. This problem was partly mitigated by the quality control processes instituted by the hospital which uses these data for planning and financing purposes. We are not able to differentiate MRSA colonization from infection based on the discharge database. Thus, the presented results might underestimate the real burden of MRSA infection. Moreover, our discharge database is limited to only the duration of hospital stay and does not provide patient level information regarding patient transfers, or mortality following discharge. The in-hospital mortality provides only limited information on the crude mortality of patients with MRSA infections as we did not assess whether the primary cause of death was MRSA. A 30-day or 6-month mortality rate is likely a better measurement of the true mortality rate due to MRSA infections.6 Correspondingly, we could only assess readmissions within our hospital. We do not know how frequently patients were admitted to other hospitals, a potential problem in most research of this type reported to date.39 Lastly, as the uninfected control patients may have other nosocomial infection, thus, our results may be conservative in presenting the effects of MRSA infection. However, it is possible that MRSA and MSSA patients may have also suffered from the same nosocomial infections, which may offset the resulted confounding effect.

In conclusion, our study showed that patients with MRSA experienced poorer clinical outcomes and incurred a heavier economic burden, compared to both patients with MSSA and patients without nosocomial infections. Control measures should be implemented to prevent MRSA transmission both inside and outside the hospital setting.

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Table 1 The demographic, clinical characteristics among patients with MRSA, MSSA and controls

	Controls, n= 534404	MSSA, n=3796	MRSA, n=4868	p
Age, mean year (SD)	57.2 (17.9)	57.4 (16.7)	63.7 (16.4)*#	<0.001
<65, %	37.3	35.1	50.7	<0.001
≥65, %	62.7	64.9	49.3	
Male sex, %	50.2	57.9	58.6	<0.001
Ethnicity, %				
Chinese	72.3	64.0	71.8	<0.001
Malay	11.8	19.2	13.9	
Indian	9.7	11.6	9.8	
Others	6.2	5.2	4.4	
Medical condition, %	70.0	54.0	57.3	<0.001
Surgical condition, %	30.0	46.0	42.7	
ICU admission, %	3.1	6.7	8.2	<0.001
Charlson Comorbidity Index, %				
None	47.2	32.9	26.7	<0.001
Low	31.8	37.3	42.7	
Moderate	11.2	19.2	19.5	
High	9.8	10.6	11.1	

MSSA, Methicillin-sensitive Staphylococcus aureus; MRSA, Methicillin-resistant Staphylococcus aureus. SD, standard deviation. p value was calculated using Chi-Square test except age was calculated using one way
analysis of variance. *p<0.05 vs. Controls by post-hoc Scheffe tests; #p<0.05 vs. MSSA by post-hoc Scheffe tests.

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Table 2 The length of stay, total hospitalization cost and outcomes of care among patients with MRSA, MSSA and controls

	Controls, n= 534404	MSSA, n=3796	MRSA, n=4868	p
Length of stay, day[†]				
Un-adjusted mean (95% CI)	3.0 (3.0, 3.0)	9.8 (9.4, 10.1)*	12.2 (11.9, 12.6)*#	<0.001
Adjusted mean (95% CI)	4.5 (4.5, 4.5)	15.9 (15.8, 16.0)*	18.5 (18.4, 18.5)*#	<0.001
Total hospitalization cost, $[†]				
Un-adjusted mean (95% CI)	2295.7 (2289.5, 2301.9)	4915.8 (4749.2, 5088.4)*	6294.7 (6121.1, 6473.1)*#	<0.001
Adjusted mean (95% CI)	3340.1 (3334.4, 3345.7)	8327.5 (8243.2, 8412.7)*	9760.1 (9689.2, 9831.4)*#	<0.001
Unscheduled readmission, %				
Un-adjusted	23.7	24.5	36.3*#	<0.001
Adjusted	22.7	21.3	58.4*#	<0.001
Hospital mortality, %				
Un-adjusted	2.8	5.6*	7.8*#	<0.001
Adjusted	1.1	7.3*	12.2*#	<0.001

MRSA, Methicillin-resistant Staphylococcus aureus; MSSA, Methicillin-sensitive Staphylococcus aureus. CI, confidence interval.
[†] Geometric mean (95% confidence interval); p values for unadjusted mean length of stay and hospitalization cost were calculated
using Kruskal Wallis test; p value for unadjusted hospital mortality and unscheduled readmission were calculated using Chi-Square test. p values for adjusted values were calculated using Generalized Estimating Equations (GEE) models with adjustment for the patients' age groups, gender, ethnicity, medical management, and Charlson comorbidity index.
*p<0.05 vs. Controls by post-hoc Scheffe tests; #p<0.05 vs. MSSA by post-hoc Scheffe tests.

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Table 3 The geometric mean investigation, medication, treatment and facility costs per admission among patients with MRSA, MSSA and controls

	Controls, n= 534404	MSSA, n=3796	MRSA, n=4868	p
Investigation Cost, $				
Un-adjusted mean (95% CI)	432.2 (430.7, 433.7)	978.5 (939.4, 1019.2)*	1340.5 (1300.1, 1381.4)*#	<0.001
Adjusted mean (95% CI)	716.4 (715.1, 717.6)	1890.0 (1873.1, 1907.1)*	2148.4 (2134.4, 2162.5)*#	<0.001
Medication Cost, $				
Un-adjusted mean (95% CI)	38.4 (38.2, 38.6)	177.0 (167.7, 186.9)*	346.0 (330.7, 361.9)*#	<0.001
Adjusted mean (95% CI)	198.0 (197.4, 198.6)	605.7 (599.4, 612.2)*	903.7 (898.4, 909.0)*#	<0.001
Treatment Cost, $				
Un-adjusted mean (95% CI)	503.9 (502.0, 505.7)	1279.3 (1234.1, 1326.2)*	1434.1 (1391.9, 1477.5)*#	<0.001
Adjusted mean (95% CI)	983.2 (981.6, 984.7)	2216.7 (2190.9, 2242.8)*	2368.8 (2346.9, 2390.9)*#	<0.001
Facility Cost, $				
Un-adjusted mean (95% CI)	908.6 (905.96, 911.3)	2059.4 (1990.2, 2130.9)*	2575.2 (2501.1, 2651.5)*#	<0.001
Adjusted mean (95% CI)	1420.4 (1417.6, 1422.5)	3550.3 (3512.4, 3588.6)*	4210.8 (4178.8, 4243.1)*#	<0.001
Total hospitalization cost, $				
Un-adjusted mean (95% CI)	2295.7 (2289.5, 2301.9)	4915.8 (4749.2, 5088.4)*	6294.7 (6121.1, 6473.1)*#	<0.001
Adjusted mean (95% CI)	3340.1 (3334.4, 3345.7)	8327.5 (8243.2, 8412.7)*	9760.1 (9689.2, 9831.4)*#	<0.001

MRSA, Methicillin-resistant Staphylococcus aureus; MSSA, Methicillin-sensitive Staphylococcus aureus.
Geometric mean (95% confidence interval); p value for unadjusted mean was calculated using Kruskal Wallis test;
p values for adjusted values were calculated using Generalized Estimating Equations (GEE) models with adjustment for the patients' age groups, gender, ethnicity, medical management, and Charlson comorbidity index. CI, confidence interval.
*p<0.05 vs. Controls by post-hoc Scheffe tests; #p<0.05 vs. MSSA by post-hoc Scheffe tests.

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