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Original Research

Length of stay, hospitalisation costs and in-hospital mortality of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* bacteremia in Japan

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ABSTRACT

Objectives: To examine the length of stay, hospitalisation costs and case fatality of methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA) bacteremia in Japan.
Study design: Retrospective cohort study. Patients with a diagnosis of *S. aureus* bacteremia who were admitted to a tertiary care hospital (the National Centre for Global Health and Medicine [NCGM]) in Tokyo, Japan, between 1st January 2016 and 31st December 2020 were included in the study.
Methods: We combined Japan Nosocomial Infections Surveillance data and Diagnosis Procedure Combination data at NCGM from 2016 to 2020. The data were stratified into MSSA and MRSA groups. Length of stay (LoS), LoS after submission of a blood culture specimen (LoS-after), hospitalisation cost, hospitalisation costs per day and clinical outcome were compared after propensity score matching.
Results: Median LoS was 46 (interquartile range [IQR] 28.5–64.5) days in the MSSA group and 66 (IQR 40–91) days in the MRSA group ($P = 0.020$). Median LoS-after was 38 (IQR 25–62.5) days and 45 (IQR 24–63) days ($P = 0.691$) in the MSSA and MRSA groups, respectively. Median hospitalisation cost was significantly higher in the MRSA group (26,035 [IQR 18,154–47,362] USD) than in the MSSA group (19,823 [IQR 13,764–32,042] USD) ($P = 0.036$), but cost per day was not (MRSA: 528.9 [IQR 374.9–647.4] USD; MSSA: 455.6 [IQR 359.2–701.7] USD; $P = 0.990$). Case fatality rate was higher in the MRSA group than in the MSSA group (22/60 vs 9/60, $P = 0.012$).
Conclusions: Patients with MRSA bacteremia had longer LoS and higher costs than those with MSSA bacteremia. However, LoS-after and hospitalisation costs per day were not different. The longer LoS of patients in Japan compared with other countries might contribute to the higher disease burden of *S. aureus* bacteremia in Japan.

Introduction

Staphylococcus aureus is one of the most important causes of bacteremia and poses a substantial burden to society.[1–6] Because *S. aureus* bacteremia requires long-term parenteral antibiotic therapy, its disease burden is not limited to high mortality but also extends to economic aspects.[7,8] In addition, methicillin-resistant strains (MRSA) might have a heavier burden than susceptible strains (MSSA).[9] However, to our knowledge, there is no solid evidence on the difference in the disease burden of bacteremia between MRSA and MSSA.

Length of stay (LoS) and hospitalisation cost are important indicators for estimating the burden of diseases on healthcare facilities. According to the Organisation for Economic Co-operation and Development (OECD), there is wide international variation in LoS, with Japan showing a markedly longer LoS than the worldwide average (16.1 days vs 6.6 days in 2018).[10] Although we know that the disease burden due to LoS is larger in Japan than in other countries, few studies have investigated LoS in Japan in detail. For hospitalisation costs, scarce evidence is available from Japan. Only a few previous studies have reported hospitalisation costs in Japan, but they focused on specific diseases other than bacteremia.[11–13] Consequently, it is difficult to estimate the actual disease burden

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of bacteremia in Japan and to compare it with other developed countries.

The main objective of this study was to examine the outcomes of MRSA and MSSA bacteremia in terms of LoS, hospitalisation cost and case fatality in a tertiary care hospital in Japan. These results will provide novel evidence on LoS and hospitalisation cost and allow comparisons in the area of infectious diseases. Such evidence will enable us to more precisely estimate the burden of each disease and will be a good indicator for health policy decision-makers.

Methods

Data source and curation

We obtained Japan Nosocomial Infections Surveillance (JANIS)[14] data, which include information on microorganisms, and Diagnosis Procedure Combination (DPC) data, including information on patients' background, hospitalisation cost and LoS recorded between 1st January 2016 and 31st December 2020 from the National Centre for Global Health and Medicine (NCGM).

The data were stored on a hard disk in a locked cabinet, and only the authors of this study had access to the information. The data were de-identified, and we extracted only cases with a diagnosis of bloodstream infection and a detection record of *S. aureus* from a blood culture specimen during the same admission period. Next, we merged the JANIS data and DPC data by sex, age, date of birth, date of admission and date of discharge and then stratified the merged data into MSSA and MRSA groups.

Definition of cases

Each *S. aureus* detected from a blood specimen was counted as one case of bloodstream infection. To avoid duplication from the same patient, we included only one specimen from the same admission data (i.e. if one patient was admitted twice for *S. aureus* bacteremia in different years, they were counted as two cases).

The criteria for judging the antimicrobial susceptibility of each bacterium were in accordance with the regulations of JANIS, which follows the criteria defined by the Clinical Laboratory Standards Institute (CLSI).[15] MRSA was defined as *S. aureus* resistant to oxacillin and/or cefoxitin.

Hospitalisation cost

We defined hospitalisation cost in this study as direct costs from the healthcare payer perspective and then obtained the hospitalisation cost of each bloodstream infection case through the aggregation of the following: 1 prescription cost of drugs; 2 treatment and operation cost; 3 examination cost, including image inspections; 4 accommodation cost; and 5 other expenses.

Statistical analyses

LoS, LoS after submission of a blood culture specimen (LoS-after), total hospitalisation cost, hospitalisation cost per day and clinical outcome were compared between the groups after propensity score matching (one-to-one nearest matching, caliper = 0.20) to adjust for the influence of age and sex.[16,17] An absolute standardised mean difference of each covariate (age and sex) above 10% in matched data was regarded as a clinically significant difference, and all such differences were within 10%. In addition, we aggregated the data of all patients admitted to NCGM in the observation period to calculate the LoS and hospitalisation cost for all causes of admission.

Two-sided p values less than 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.0.3.[18]

Ethical approval

This study was approved by the Ethics Committee of the National Centre for Global Health and Medicine, Tokyo, Japan (approval number, NCGM-G-003606-00).

Results

Table 1 shows the LoS and hospitalisation cost of all patients admitted to NCGM between 2016 and 2020 (i.e. not limited to those with *S. aureus* bacteremia). In total, the median hospitalisation cost per patient was 5162 (interquartile range [IQR] 2745–10,142) USD, and median LoS was 7 (IQR 3–15) days. Among all age groups, neonatal patients had the highest hospitalisation cost (median 14,432 USD; IQR 8162–28,311 USD) and the longest LoS (median 13 days; IQR 8–29 days).

In the population of interest, the median LoS was 46 (IQR 28.5–64.5) days in the MSSA group and 66 (IQR 40–91) days in the MRSA group. Median LoS-after was 38 (IQR 25–62.5) days in the MSSA group and 45 (IQR 24–63) days in the MRSA group. Median hospitalisation cost and cost per day were 19,823 (IQR 13,764–32,042) USD and 455.6 (IQR 359.2–701.7) USD, respectively, in the MSSA group and 26,035 (IQR 18,154–47,362) USD and 528.9 (IQR 374.9–647.4) USD, respectively, in the MRSA group.

The Wilcoxon rank-sum test revealed that LoS and hospitalisation cost significantly differed between the groups ($p = 0.020$ and 0.036, respectively), unlike LoS-after and hospitalisation cost per day ($p = 0.691$ and 0.990, respectively). The case fatality rate was higher in the MRSA group (22/60) than in the MSSA group (9/60), according to Fisher's exact test ($p = 0.012$). Table 2 shows the results before propensity score matching, and Table 3 shows the results after matching. Figs. 1 and 2 are violin plots of LoS and hospitalisation cost by strain, respectively.

Table 1
Cost and length of stay of all patients in the National Centre for Global Health and Medicine, 2016–2020.

Age group	Cost [median (interquartile range)]		Length of stay in days [median (interquartile range)]
	USD[a]	JPY	
Neonates	14,432 (8162–28,311)	1,587,565 (897,835–3,114,155)	13 (8–29)
Infants	4553 (3446–6390)	500,870 (379,080–702,890)	6 (4–8)
1–14 years	5145 (3605–6921)	566,000 (396,555–761,280)	5 (3–7)
15–64 years	4808 (2529–9143)	528,882 (278,230–1,005,783)	7 (3–13)
65–89 years	5219 (2696–11,235)	574,105 (296,603–1,235,814)	8 (2–17)
90 years and older	6969 (3706–13010)	766,628 (407,668–1,431,061)	12 (5–25)
Total	5162 (2745–10,142)	567,800 (301,936–1,115,629)	7 (3–15)

[a] 1 USD = 110 JPY.

Table 2
Length of stay, hospitalisation cost and in-hospital mortality of patients with *S. aureus* bacteremia in the National Centre for Global Health and Medicine, 2016–2020.

Variable	MSSA (n = 84)	MRSA (n = 63)	Total (n = 147)
Age	72 (50–82)	76 (64–89)	74 (58–85)
Male sex	44 (52.4)	35 (55.6)	79 (53.7)
LoS (days)	40 (27.5–64.5)	66 (37.5–87)	49 (29–76)
LoS-after (days)[a]	32 (22–59.5)	43 (23–62)	32 (17–56)
Hospitalisation cost (USD)[b]	20,884 (13,880–33,951)	27,798 (18,252–47,543)	22,902 (15,699–43,330)
Hospitalisation cost (JPY)	2,297,240 (1,526,856–3,734,595)	3,057,807 (2,007,727–5,229,778)	2,519,214 (1,726,905–4,766,352)
Hospitalisation cost per day (USD)[b]	401 (150–1111)	496 (231–1215)	488 (374–719)
Hospitalisation cost per day (JPY)	44,085 (16,527–122,191)	54,518 (25,374–133,648)	53,651 (41,181–79,102)
In-hospital death	12 (14.3)	24 (38.1)	36 (24.5)

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; LoS, length of stay.
Values are shown as the median (interquartile range) or number (percentage).
[a] Length of stay after blood culture submission.
[b] 1 USD = 110 JPY.

Table 3
Comparison of length of stay, hospitalisation cost and in-hospital mortality of MSSA and MRSA bacteremia after propensity score matching.

Variable	MSSA (n = 60)	MRSA (n = 60)	*p*-value[c]
Age	76 (66–83)	76.5 (65.5–89)	0.303
Male sex	33 (55.0)	32 (53.3)	1.0
LoS (days)	46 (28.5–64.5)	66 (40–91)	0.020
LoS-after (days)[a]	38 (25–62.5)	45 (24–63)	0.691
Hospitalisation cost (USD)[b]	19,823 (13,764–32,042)	26,035 (18,154–47,362)	0.036
Hospitalisation cost (JPY)	2,180,493 (1,514,005–3,524,635)	2,863,872 (1,996,922–5,209,858)	0.036
Hospitalisation cost per day (USD)[b]	456 (359–702)	529 (375–647)	0.990
Hospitalisation cost per day (JPY)	50,113 (39,516–77,191)	58,174 (41,238–71,212)	0.990
In-hospital death	9 (15.0)	22 (36.7)	0.012

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; LoS, length of stay.
Values are shown as median (interquartile range) or an absolute number (percentage).
[a] Length of stay after blood culture submission.
[b] 1 USD = 110 JPY.
[c] Mann-Whitney test for continuous variables and Fischer's exact test for binary variables.

Fig. 3 shows the breakdown of the hospitalisation cost for each group.

Accommodation cost accounted for more than half of the total hospitalisation cost in both groups (59.1% in the MSSA group and 52.6% in the MRSA group). The proportion of the treatment cost was higher in the MRSA group than in the MSSA group (20.6% and 13.7%, respectively).

Discussion

To our knowledge, this is the first study examining the difference in LoS and hospitalisation cost between MSSA and MRSA in Japan. In our results, the median LoS of all-cause admission was substantially shorter than reported by the OECD.[10] This difference might be due to the calculation methods used. While the OECD reported the average number of days spent by patients in hospital, which is generally measured by dividing the total number of days stayed by all inpatients during a year by the number of admissions or discharges, we used the median LoS of each patient. Therefore, the 16.1 days reported by the OECD would be greatly influenced by outliers (i.e. the extremely long LoS of some patients). Nevertheless, 7 days is longer than the average LoS worldwide (6.6 days) and the average LoS in the US (5.5 days).[10]

Notably, the LoS of patients with *S. aureus* bacteremia in Japan is substantially longer than in other countries. Cosgrove and colleagues reported that the median LoS for MSSA and MRSA bacteremia in the US was 7 and 9 days, respectively.[19] According to Thampi and colleagues, the median LoS of patients with MSSA and MRSA in Canada was 14 and 22.5 days, respectively.[20] Another study from the Greater Toronto area in Canada found a median LoS for *S. aureus* bacteremia of 17 days.[21] In contrast, our results indicated that patients with *S. aureus* bacteremia in Japan are hospitalised for a median of 49 days, which is about three times as long as that reported previously in other countries. Even when the data are limited to LoS-after (i.e. LoS after submission of a blood culture), this amounts to twice as long as that reported in other countries. Given these results, it is not difficult to imagine that the disease burden of *S. aureus* bacteremia will be greater in Japan than in other countries.

The cause of the considerable international differences in LoS is unclear, but Tiessen and colleagues have obtained some interesting results.[22] Although their study examined the LoS of acute myocardial infarction, they observed a trend similar to that seen in our results. In their opinion, their results can be explained by nonclinical factors, such as professional/cultural norms and differences in healthcare schemes. For instance, acute care hospitals in Japan are generally equipped with a large supply of acute care beds but a small supply of long-term care beds. This combination should theoretically result in longer acute care stays. In addition, hospital ownership in Japan may also influence the results. Private for-profit organisations perhaps act to fill their capacity, which is higher than that of their counterparts, to maximise revenues. These hypotheses should be carefully examined in future work.

Meanwhile, we should also note that, although there was a difference in total LoS between MSSA and MRSA in our study, there was no substantial difference in LoS-after. This is a markedly different result from that of previous studies.[9,23] Generally speaking, the presence of antibiotic resistance appears to increase LoS and hospitalisation costs. This phenomenon is probably related to Japanese healthcare systems and customs. Because residence in a long-term care facility is one of the risk factors of MRSA infection,[24] the longer LoS might be attributable to an increase in novel MRSA bacteremia because patients who tend to stay in the hospital longer also tend to be infected with MRSA. It is possible that the long LoS in

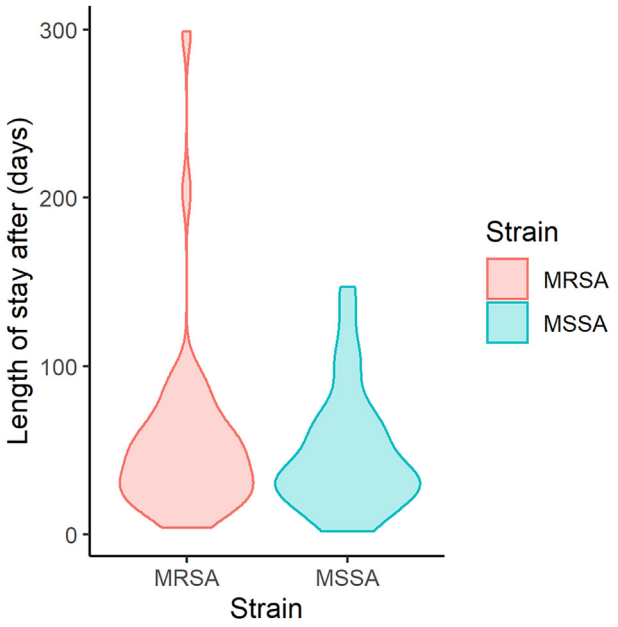

Fig. 1. Length of stay after blood culture submission by strain. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

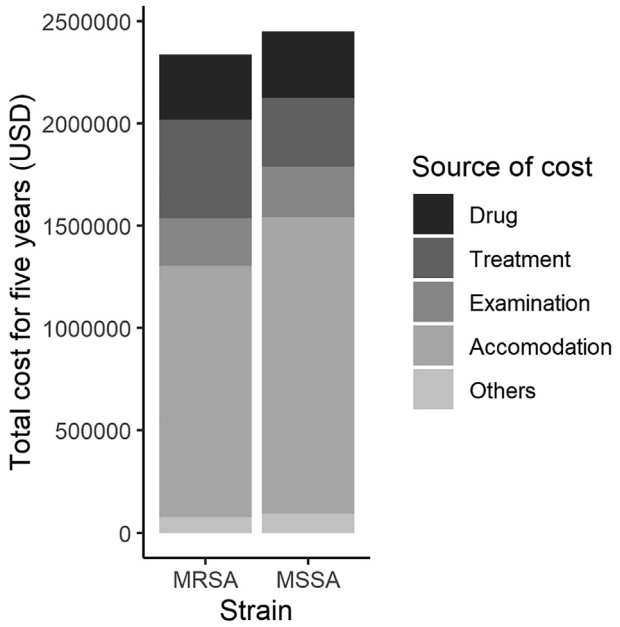

Fig. 3. Breakdown of the total hospitalisation cost from 2016 to 2020. The horizontal axis represents the accumulated hospitalisation cost during the study period.

Japan is not only unnecessary but also increases the number of infected cases. Because the LoS-after in Japan is substantially longer than the appropriate duration of antibiotic therapy for *S. aureus* bacteremia,[25] the difference in the recommended duration of antibiotic therapy between MSSA and MRSA does not explain the difference in LoS-after between these strains.

The hospitalisation cost of *S. aureus* bacteremia in Japan is neither expensive nor cheap compared with other developed countries. Thampi and colleagues reported that *S. aureus* bacteremia costs about 12,000 USD per case in Canada.[20] In contrast, it costs more than 37,000 USD in the US.[23] As described above, the LoS in Japan is clearly longer than the LoS in these countries, but the hospitalisation cost per day in Japan may be less expensive. In addition, the hospitalisation cost per day in Japan is not substantially different between MSSA and MRSA. This result is compatible with that of a recent study from the US,[26] although it contradicts the results of older studies.[19,27–31]

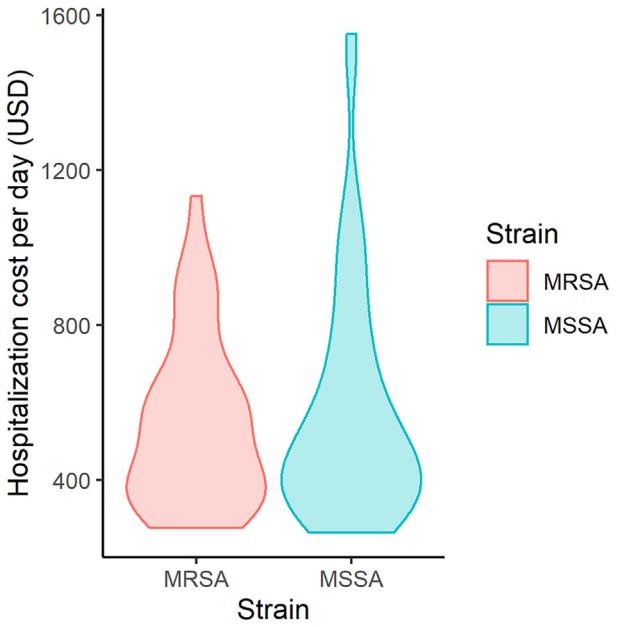

Fig. 2. Hospitalisation cost per day by strain. MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

In terms of the clinical outcome of *S. aureus* bacteremia, the case fatality rate of 24.5% in this study is also similar to that in previous studies.[21,32] However, the difference in the case fatality rate between MSSA and MRSA is clear in our study, which is in contrast to a recent study.[26] This can be attributed to the nature of our data, which are a combination of microbiological test results and patients' claim data, thus making it difficult to adjust for confounding factors associated with prognosis.

The present study has several limitations. First, our results are based on data from a single facility. Although our facility is the largest medical centre hospital in Japan in terms of infectious diseases, the number of bacteremia cases was limited, and biases due to the characteristics of the facility cannot be removed. Therefore, representativeness will be a major concern for our results. Next, as explained above, our data do not include the full characteristics of each patient. Although we adjusted for age and sex by propensity score matching, other confounding factors probably affected the results. Third, our claims data capture the cost incurred by the facility. Because the Japanese health insurance system adopts the Diagnosis Procedure Combination/Per-Diem Payment System, the claims data do not precisely reflect the actual cost paid by the government to the facility. In other words, our estimated hospitalisation cost might be overestimated if we regard the 'healthcare payer' as being the Japanese government.

Despite these limitations, our results provide the necessary evidence for international comparisons of the disease burden of *S. aureus* bacteremia. At our hospital in Japan, patients with MRSA bacteremia had longer hospital stays and higher costs than those with MSSA bacteremia. However, the LoS-after and hospitalisation cost per day did not differ. Furthermore, the markedly longer LoS in Japan compared with other countries would be of major interest. Further studies of this long LoS in Japan and its reasons based on multicentre, national-level data are necessary because a longer LoS would be a major cause of heavier disease burden in Japan compared with other countries. These novel findings might contribute to reduce the burden and medical expenses of *S. aureus*

bacteremia in Japan because the LoS in Japan may be unnecessarily longer than in other countries and cause additional productivity loss and medical costs.

Author statements

Ethical approval

This study was approved by the Ethics Committee of the National Centre for Global Health and Medicine, Tokyo, Japan (approval number, NCGM-G-003606-00).

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Competing interests

We declare no competing interests.

Data sharing

Data used in this study are available from the corresponding author upon reasonable request.

Author's contributors

ST and NO conceived the study. JY collected and managed the data. ST performed statistical analyses and drafted the first draft of the manuscript. NM, JY and NO critically reviewed the manuscript, and all authors approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.07.046.

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