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

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# Public Health

## Length of stay, hospitalization cost, and in-hospital mortality of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* bacteremia in Japan --Manuscript Draft--

<b>Manuscript Number:</b>	PUHE-D-21-01030R1
<b>Article Type:</b>	Original Research
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<b>Abstract:</b>	<p><b>Objectives</b> To examine the length of stay, hospitalization cost, and case fatality of methicillin-susceptible and -resistant <i>Staphylococcus aureus</i> (MSSA and MRSA) bacteremia in Japan.</p> <p><b>Study design</b> Retrospective cohort study. Patients with a diagnosis of <i>Staphylococcus aureus</i> bacteremia admitted to a tertiary care hospital (National Center for Global Health and Medicine [NCGM]) in Tokyo, Japan, between 1<sup>st</sup> January 2016 and 31<sup>st</sup> December 2020 .</p> <p><b>Methods</b> 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), hospitalization cost, hospitalization cost per day, and clinical outcome were compared after propensity score matching.</p> <p><b>Results</b> Median LoS was 46 (IQR 28.5-64.5) days in the MSSA group and 66 (IQR 40-91) days in the MRSA group ( <math>p = 0.020</math>). Median LoS-after was 38 (IQR 25-62.5) days and 45 (IQR 24-63) days ( <math>p = 0.691</math>), respectively. Median hospitalization 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) ( <math>p = 0.036</math>) but cost per day was not (MRSA: 528.9 [IQR 374.9-647.4] USD; MSSA: 455.6 [IQR 359.2-701.7] USD; <math>p = 0.990</math>). Case fatality rate was higher in the MRSA group than in the MSSA group (22/60 vs. 9/60, <math>p = 0.012</math>).</p> <p><b>Conclusions</b> Patients with MRSA bacteremia had longer LoS and higher costs than those with MSSA bacteremia. However, LoS-after and hospitalization cost per day were not different. The longer LoS than that of other countries might contribute to the higher disease burden of <i>S. aureus</i> bacteremia in Japan.</p>

1 **Length of stay, hospitalization cost, and in-hospital mortality of**  
2 **methicillin-susceptible and methicillin-resistant *Staphylococcus aureus***  
3 **bacteremia in Japan**

4

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7

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19 **Acknowledgments**

20 **Statements of ethical approval:** This study was approved by the Ethics Committee of  
21 National Center for Global Health and Medicine, Tokyo, Japan (approval number,  
22 NCGM-G-003606-00).

23

24 **Funding:** This study was supported by a Ministry of Health, Labour and Welfare  
25 (MHLW) research grant of Japan (20HA2003).

26

27 **Competing interests:** We declare no competing interests.

28

29 **Data sharing:** Data used in this study are available from the corresponding author upon  
30 reasonable request.

31

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

36

Resubmission Manuscript

Manuscript Number: PUHE-D-21-01030

Article Title: Length of stay, hospitalization cost, and in-hospital mortality of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* bacteremia in Japan

June 28, 2021

Andrew Lee, Joanne Morling

Editors-in-Chief

*Public Health*

Dear Drs. Lee and Morling,

Thank you very much for giving us the opportunity to revise our manuscript. We appreciate the reviewers' careful review and constructive suggestions. Please find our point-by-point responses to the comments below in blue italics. Changes made in the main body of the manuscript are indicated using Track Changes.

We hope that the manuscript is now suitable for publication in *Public Health*

and look forward to hearing from you.

Sincerely,

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In addition to the reviewer comments below the Editor suggests that the methods section also needs to be revised to add more detail so that the analysis can be replicated by others (more detail on what analysis was carried out exactly). However, the Editor highlights that it also needs to be succinct.

*We appreciate the Editor's suggestion and have substantially revised the "Methods". It is now divided into the following subsections: "Data source and curation", "Definition of cases", "Hospitalization cost", "Statistical analysis" and "Ethics approval". More detailed information was added to each subsection in response to the reviewers' comments. We have endeavoured to be as succinct as possible. In addition, we have uploaded the R code used in this study to enable readers to replicate the results. It is difficult for us to make our data publicly available due to ethical concerns, but the data will be available upon reasonable request to the corresponding author.*

Reviewer #1: Abstract/ Methodology - Line 13 and Line 60 - please mention exact study dates Eg. 1st January 2016 - 31st December 2020

*Thank you for your suggestion. Our study period ran from 1 January 2016 to 31 December 2020, as you expected.*

Methodology:

Please provide what definition was used for MRSA and MSSA bacteremia in this study, were ICD-10 codes used? Or a clinical definition?

*We appreciate your comment. We followed the definitions provided by the Japan Nosocomial Infections Survey (JANIS), which are based on those of the Clinical Laboratory Standards Institute (CLSI). The definitions have been detailed in the main manuscript text.*

Mention more in detail about data linkage, how data was extracted and stored, who had access, was the data linkage key available, was data de-identified or not?

Please include a section on how costing was done to arrive at hospitalization costs

*Thank you very much for your constructive suggestion. The data aggregation process has now been detailed in the “Data source and curation” subsection in the “Methods”.*



*As for costing, please refer to the “Hospitalization cost” subsection in the “Methods”, where we describe the component of cost in this study. It includes drug cost, treatment and operation cost, examination cost and accommodation cost.*

Results:

I see that authors have reported costs in USD to allow for international comparison, would be good to have the same results mentioned in JPY as well for Japanese readers of the article.

*We have made the appropriate change.*

Discussion:

Lines 158, 160 - mentions case fatality risk - I would suggest using the term case fatality rate

*We have used your suggested term.*

Include which component of hospitalization cost in both groups was high - was it bed

charge, treatment cost, etc?? Would be a value add to the analysis which has been done, if this can be described

*Thank you for your insightful comment. We have added a new figure (Figure 3) that shows the breakdown of the accumulated hospitalization cost between 2016 and 2020. Accommodation cost accounted for 59.1% of the total cost in the MSSA group. Similarly, the accommodation cost accounted for 52.6% of the total cost in the MRSA group.*

Curious to know why Japan has such high LoS - I do acknowledge that authors have touched upon it briefly and recommended further research

*We appreciate your suggestion. One of our key references (Tiessen et al., DOI: 10.1177/0951484813512287) stated that “non-clinical factors contribute to sustained international differences in length of stay. These factors may include professional or cultural norms, differing payment schemes and access to long-term care facilities”. We agree with their viewpoint and have discussed this aspect in the revised manuscript.*

## Reviewer #2: Comments

1. The revised introduction should state the contribution of the paper to the earlier empirical literature.

*Thank you for your insightful suggestion. We have added a more detailed explanation of the contribution of the present study. As described in the original manuscript, information on LoS and hospitalization cost is not widely available in Japan. This made it difficult for us to appropriately assess the burden of each disease. Our results might be used as an indicator in the evaluation of disease burden in the context of an international comparison.*

2. The revised introduction should motivate the empirical context of the study.

*As in our answer to the previous question, we have few data on LoS and hospitalization cost, which makes it difficult to estimate the precise burden of disease. For example, we know that our LoS is longer than in other countries by comparison with OECD evidence but we do not know to what extent. Our results elucidate to what extent the LoS of*

*bacteremia is longer, which will enable us to more precisely estimate the disease burden of bacteremia.*

3. What is the external validity of the findings that are presented in the paper?

*We thank you for giving us an opportunity to discuss this issue. As we explained in the “Discussion”, one of the limitations of our results is they are based on data from a single national centre hospital. The next step would be a multicenter study. Nevertheless, our results are the first step in elucidating the difference in LoS between Japan and other countries because other studies also found a longer LoS in Japan for other diseases compared with other countries. Furthermore, the causes of this difference would also be an interesting topic for further consideration.*

4. Are all relevant (economic) costs captured in the study?

*Thank you for giving us a chance to explain this aspect in more detail. We have added a “Hospitalization cost” subsection to the “Methods” and described the component of cost in this study. It includes drug cost, treatment and operation cost, examination cost,*

*accommodation cost and other expenses. In other words, “hospitalization cost” in this study refers to the cost paid by acute healthcare facilities and does not include the cost of long-term care and expenses paid by patients (e.g., transportation fees). As described in the original manuscript, “direct costs from the healthcare payer perspective” were captured in this study.*

5. The paper should state more practical policy lessons that stem from the estimation results that are presented in the paper.

*Thank you for your suggestion. As now stated in the last paragraph, we can reduce the disease burden of S. aureus bacteremia if the LoS in Japan is unnecessary longer than that in other countries. However, it will be important to examine why the LoS is so long in Japan to take appropriate countermeasures.*

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1 **Length of stay, hospitalization cost, and in-hospital mortality of**  
2 **methicillin-susceptible and methicillin-resistant *Staphylococcus aureus***  
3 **bacteremia in Japan**

4 **Summary**

5 **Objectives**

6 To examine the length of stay, hospitalization cost, and case fatality of methicillin-  
7 susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA) bacteremia in  
8 Japan.

9 **Study design**

10 Retrospective cohort study.

11 Patients with a diagnosis of *Staphylococcus aureus* bacteremia admitted to a tertiary  
12 care hospital (National Center for Global Health and Medicine [NCGM]) in Tokyo,  
13 Japan, between 1<sup>st</sup> January 2016 and 31<sup>st</sup> December 2020.

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14 **Methods**

15 We combined Japan Nosocomial Infections Surveillance data and Diagnosis Procedure  
16 Combination data at NCGM from 2016 to 2020. The data were stratified into MSSA  
17 and MRSA groups. Length of stay (LoS), LoS after submission of a blood culture  
18 specimen (LoS-after), hospitalization cost, hospitalization cost per day, and clinical

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19 outcome were compared after propensity score matching.

20 **Results**

21 Median LoS was 46 (IQR 28.5-64.5) days in the MSSA group and 66 (IQR 40-91) days  
22 in the MRSA group ( $p = 0.020$ ). Median LoS-after was 38 (IQR 25-62.5) days and 45  
23 (IQR 24-63) days ( $p = 0.691$ ), respectively. Median hospitalization cost was  
24 significantly higher in the MRSA group (26,035 [IQR 18,154-47,362] USD) than in the  
25 MSSA group (19,823 [IQR 13,764-32,042] USD) ( $p = 0.036$ ) but cost per day was not  
26 (MRSA: 528.9 [IQR 374.9-647.4] USD; MSSA: 455.6 [IQR 359.2-701.7] USD;  $p = 0.$   
27 990). Case ~~fatality risk~~fatality rate was higher in the MRSA group than in the MSSA  
28 group (22/60 vs. 9/60,  $p = 0.012$ ).

29 **Conclusions**

30 Patients with MRSA bacteremia had longer LoS and higher costs than those with MSSA  
31 bacteremia. However, LoS-after and hospitalization cost per day were not different. The  
32 longer LoS than that of other countries might contribute to the higher disease burden of  
33 *S. aureus* bacteremia in Japan.

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35 **Keywords:** MRSA, bacteremia, Hlength of stay, hospitalization cost, Japan

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37 **Introduction**

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

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

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55 other developed countries.

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

## 63 **Methods**

### 64 Data source and curation

65 We obtained Japan Nosocomial Infections Surveillance (JANIS)<sup>14</sup> data which include  
66 information about microorganisms and Diagnosis Procedure Combination (DPC) data  
67 which includes information on patients' background, hospitalization cost, and LoS  
68 recorded between 1 January 2016 and 31 December 2020 from ~~the~~ National Center for  
69 Global Health and Medicine (NCGM).

70 The data were stored on a hard disk in a locked cabinet and only the authors of  
71 this study had access to them. The data were de-identified and we extracted only cases  
72 with a diagnosis of blood stream infections and a detection record of *S. aureus* from a

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73 blood culture specimen during the same admission period. We next merged the JANIS  
74 data and DPC data by sex, age, date of birth, date of admission, and date of discharge  
75 and then stratified the merged data into MSSA and MRSA groups.

76 ~~After extracting the data of patients diagnosed as having bacteremia and whose~~  
77 ~~blood culture results were positive for *S. aureus*, we stratified cases into a methicillin-~~  
78 ~~susceptible (MSSA) group and a methicillin-resistant (MRSA) group.~~

80 Definition of cases

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

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

90 Hospitalization cost

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91 We defined hospitalization cost in this study as direct costs from the healthcare payer  
92 perspective and then obtained the hospitalization cost of each blood stream infection  
93 case through aggregation: 1) prescription cost of drugs; 2) treatment and operation cost;  
94 3) examination cost including image inspections; 4) accommodation cost; and 5) other  
95 expenses.

96  
97 Statistical analysis

98 LoS, LoS after submission of a blood culture specimen (LoS-after), total hospitalization  
99 cost, hospitalization cost per day (~~direct costs from healthcare payer perspective~~), and  
100 clinical outcome were compared between the groups after propensity score matching  
101 (one-to-one nearest matching, caliper = 0.20) to adjust for the influence of age and  
102 sex.<sup>16,17</sup> An absolute standardized mean difference of each covariate (age and sex) above  
103 10% in matched data was regarded as a clinically significant difference, and all such  
104 differences were within 10%. In addition, we aggregated the data of all patients  
105 admitted to NCGM in the observation period to calculate the LoS and hospitalization  
106 cost for all causes of admission.

107 Two-sided *p* values less than 0.05 were considered statistically significant. All  
108 statistical analyses were performed using R version 4.0.3.<sup>18</sup> \_

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110 **Ethics approval**

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

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114 **Results**

115 Table 1 shows the LoS and hospitalization cost of all patients admitted to NCGM  
116 between 2016 and 2020 (i.e., not limited to those with *S. aureus* bacteremia). In total,  
117 median hospitalization cost per patient was 5,162 (interquartile range [IQR] 2,745-  
118 10,142) USD and median LoS was 7 (IQR 3-15) days. Among all age groups, neonatal  
119 patients had the highest hospitalization cost (median 14,432 USD; IQR 8,162-28,311  
120 USD) and the longest LoS (median 13 days; IQR 8-29 days).

121

122 (Table 1)

123

124 In the population of interest, median LoS was 46 (IQR 28.5–64.5) days in the  
125 MSSA group and 66 (IQR 40-91) days in the MRSA group. Median LoS-after was 38  
126 (IQR 25–62.5) days in the MSSA group and 45 (IQR 24-63) days in the MRSA group.

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10 127 Median hospitalization cost and cost per day were respectively 19,823 (IQR 13,764–  
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12 128 32,042) USD and 455.6 (IQR 359.2–701.7) USD in the MSSA group and 26,035 (IQR  
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14 129 18,154–47,362) USD and 528.9 (IQR 374.9–647.4) USD in the MRSA group.

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17 130 The Wilcoxon rank sum test revealed that LoS and hospitalization cost significantly  
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19 131 differed between the groups ( $p = 0.020$  and  $0.036$ , respectively), unlike LoS-after and  
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21 132 hospitalization cost per day ( $p = 0.691$  and  $0.990$ , respectively). The case fatality rate  
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24 133 was higher in the MRSA group (22/60) than in the MSSA group (9/60) according to  
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26 134 Fisher's exact test ( $p = 0.012$ ). Table 2 shows the results before propensity score  
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29 135 matching, and Table 3 shows the results after matching. Figures 1 and 2 are violin plots  
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31 136 of LoS and hospitalization cost by strain, respectively.

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36 138 (Table 2)  
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Figure 3 describes the breakdown of hospitalization cost for each group.

(Figure 3)

Accommodation cost accounted for more than half of the total hospitalization 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 hospitalization cost between MSSA and MRSA in Japan. In our results, median LoS of all-cause admission was substantially shorter than reported by the OECD.<sup>10</sup> 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

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10 163 days reported by the OECD would be greatly influenced by outliers (i.e., the extremely  
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12 164 long LoS of some patients). Nevertheless, 7 days is longer than the average LoS  
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14 165 worldwide (6.6 days) and that ~~in~~ the US (5.5 days).<sup>10</sup>  
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17 166 Notably, the LoS of patients with *S. aureus* bacteremia in Japan is substantially  
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19 167 longer than that in other countries. Cosgrove and colleagues reported that the median  
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21 168 LoS for MSSA and MRSA bacteremia in the US was 7 and 9 days, respectively.<sup>19</sup>  
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23 169 According to Thampi and colleagues, the median LoS of such patients in Canada was  
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25 170 14 and 22.5 days, respectively.<sup>20</sup> Another study from the Greater Toronto area found a  
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27 171 median LoS for *S. aureus* bacteremia of 17 days.<sup>21</sup> In contrast, our results indicated that  
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29 172 patients with *S. aureus* bacteremia in Japan are hospitalized for a median 49 days, which  
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32 173 is about three times as long as that reported previously in other countries. Even when  
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34 174 the data are limited to LoS-after (i.e., LoS after submission of a blood culture), this  
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36 175 amounts to twice as long as that reported previously in other countries. Given these  
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38 176 results, it is not difficult to imagine that the disease burden of *S. aureus* bacteremia will  
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41 177 be greater in Japan than in other countries.  
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46 178 The cause of the considerable international differences in LoS is not clear, but,  
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48 179 Tiessen and colleagues have obtained some interesting results.<sup>22</sup> Although their study  
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51 180 examined the LoS of acute myocardial infarction, they observed a trend similar to that  
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181 of our results. In their opinion, their results can be explained by nonclinical factors such  
182 as professional/cultural norms and differences in healthcare schemes. For instance,  
183 acute care hospitals in Japan are generally equipped with a larger supply of acute care  
184 beds but, a small supply of long-term care beds. This combination should theoretically  
185 result in longer acute care stays. In addition, hospital ownership in Japan would also  
186 influence the results. Private for-profit organizations perhaps act to fill their capacity,  
187 which is higher than that of their counterpart, to maximize revenues. These hypotheses  
188 should be carefully examined in future work.

189       Meanwhile, we should also note that, although there was a difference in total LoS  
190 between MSSA and MRSA in our study, there was no substantial difference in LoS-  
191 after. This is a markedly different result from that of previous studies.<sup>9,23</sup> Generally  
192 speaking, the presence of antibiotic resistance appears to increase LoS and  
193 hospitalization costs. This phenomenon is probably related to Japanese healthcare  
194 systems and customs. Because residence in a long-term care facility is one of the risk  
195 factors of MRSA infection,<sup>24</sup> the longer LoS might be attributable to an increase in  
196 novel MRSA bacteremia because patients who tend to stay in the hospital longer also  
197 tend to be infected with MRSA. It is possible that the long LoS in Japan is not only  
198 unnecessary, but also increases the number of infected cases. Because the LoS-after in



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10 199 Japan is substantially longer than the appropriate duration of antibiotic therapy for *S.*  
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12 200 *aureus* bacteremia,<sup>25</sup> the difference in the recommended duration of antibiotic therapy  
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14 201 between MSSA and MRSA does not explain the difference in LoS-after between these  
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17 202 strains.

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19 203 The hospitalization cost of *S. aureus* bacteremia in Japan is neither expensive nor  
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22 204 cheap compared with other developed countries. Thampi and colleagues reported that *S.*  
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24 205 *aureus* bacteremia costs about 12,000 USD per case in Canada.<sup>20</sup> In contrast, it costs  
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26 206 more than 37,000 USD in the US.<sup>23</sup> As described above, the LoS in Japan is clearly  
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29 207 longer than that in these countries, but the hospitalization cost per day in Japan may be  
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32 208 less expensive. In addition, the hospitalization cost per day in Japan is not substantially  
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34 209 different between MSSA and MRSA. This result is compatible with that of a recent  
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36 210 study from the US,<sup>26</sup> although it contradicts the results of older studies.<sup>19,27-31</sup>

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39 211 In terms of the clinical outcome of *S. aureus* bacteremia, the case ~~fatality~~  
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41 212 ~~risk~~fatality rate of 24.5% in this study is also similar to that in previous studies.<sup>21,32</sup>  
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44 213 However, the difference in the case ~~fatality~~ ~~risk~~fatality rate between MSSA and MRSA  
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46 214 is clear in our study, in contrast to a recent study.<sup>26</sup> This can be attributed to the nature  
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49 215 of our data, which are a combination of microbiological test results and patients' claim  
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51 216 data ~~and~~, which made it difficult to adjust for confounding factors associated with  
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217 prognosis.

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

230 Despite these limitations, our results provide necessary evidence for international  
231 comparisons of the disease burden of *S. aureus* bacteremia. At our hospital in Japan,  
232 patients with MRSA bacteremia had longer hospital stays and higher costs than those  
233 with MSSA bacteremia. However, the LoS-after and hospitalization cost per day did not  
234 differ. Furthermore, the markedly longer LoS in Japan compared with other countries

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10 235 would be of major interest. Further studies of this long LoS in Japan and its reasons  
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12 236 based on multicenter, national-level data are necessary because a longer LoS would be a  
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14 237 major cause of heavier disease burden for the same disease in Japan compared with  
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17 238 other countries. These novel findings might contribute to reduce the burden and medical  
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19 239 expenses of *S. aureus* bacteremia in Japan because the LoS in Japan may be  
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22 240 unnecessarily longer than that in other countries and causes additional productivity loss  
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24 241 and medical costs.

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29 243 **Acknowledgments**

30  
31 244 *Statements of ethical approval:* This study was approved by the Ethics Committee of  
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48 251 *Competing interests:* We declare no competing interests.

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253 **Data sharing:** Data used in this study are available from the corresponding author upon  
254 reasonable request.

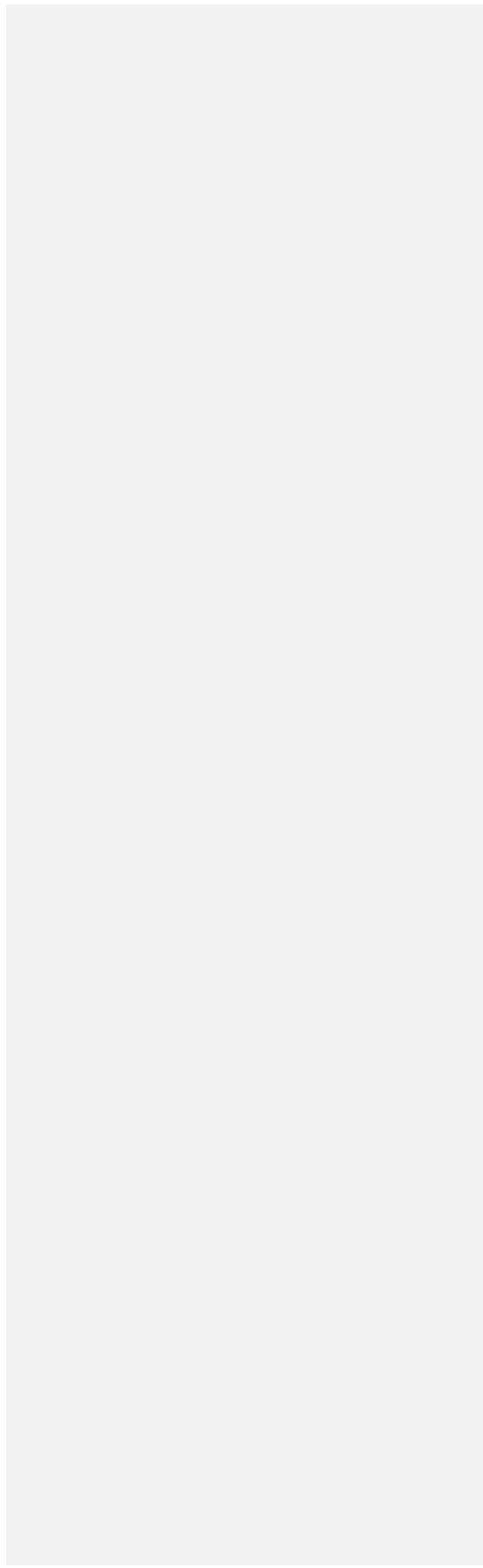
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256 **Contributors:** ST and NO conceived the study. JY collected and managed the data. ST  
257 performed statistical analyses and drafted the first draft of the manuscript. NM, JY, and  
258 NO critically reviewed the manuscript and all authors approved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

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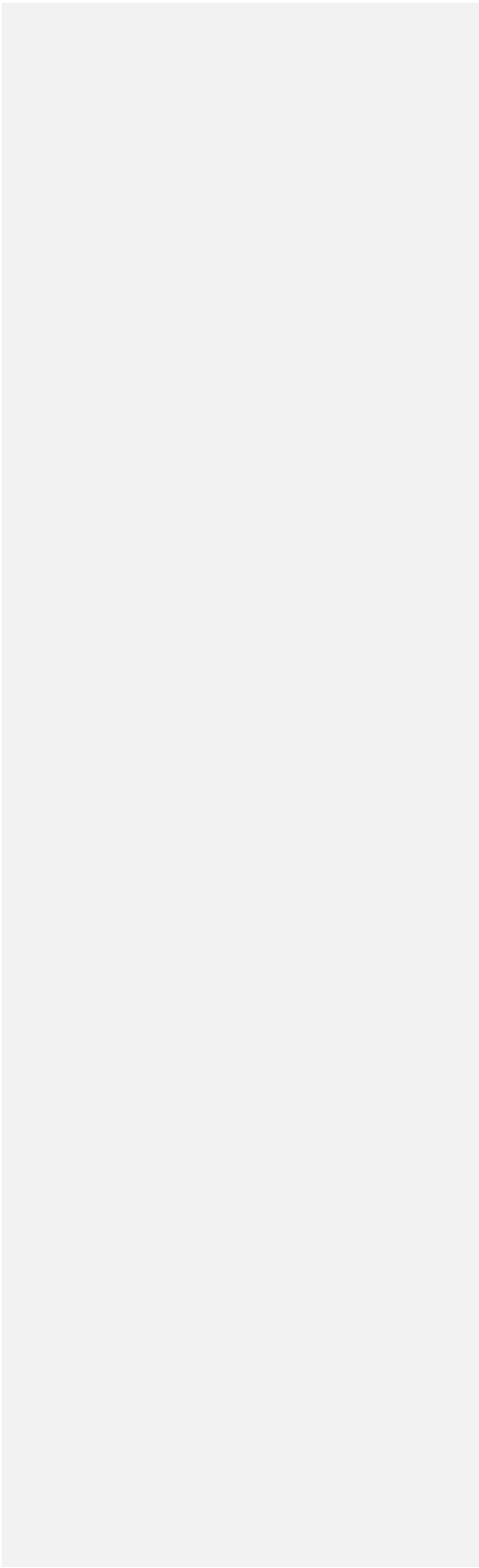
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388 **Table 1. Cost and length of stay of all patients in the National Center for Global**  
389 **Health and Medicine, 2016-2020**

Age group	Cost (USD*)	<u>Cost (JPY)</u>	Length of stay (days)
Neonates	14432 (8162-28311)	<u>1587565 (897835-3114155)</u>	13 (8-29)
Infants	4553 (3446-6390)	<u>500870 (379080-702890)</u>	6 (4-8)
1-14 years	5145 (3605-6921)	<u>566000 (396555-761280)</u>	5 (3-7)
15-64 years	4808 (2529-9143)	<u>528882 (278230-1005783)</u>	7 (3-13)
65-89 years	5219 (2696-11235)	<u>574105 (296603-1235814)</u>	8 (2-17)
90 years and older	6969 (3706-13010)	<u>766628 (407668-1431061)</u>	12 (5-25)
<b>Total</b>	<b>5162 (2745-10142)</b>	<b><u>567800 (301936-1115629)</u></b>	<b>7 (3-15)</b>

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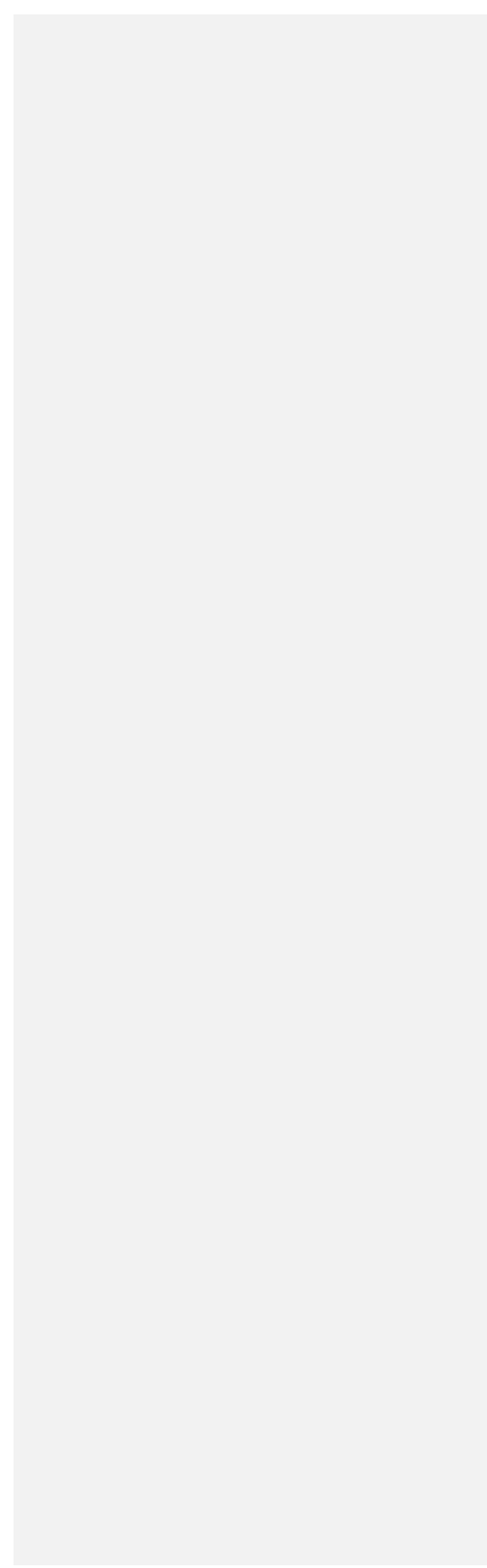
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390 Values are shown as the median (interquartile range).

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393 **Table 2. Length of stay, hospitalization cost, and in-hospital mortality of patients**  
 394 **with *S. aureus* bacteremia in the National Center for Global Health and Medicine,**  
 395 **2016-2020**

	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)*	32 (22-59.5)	43 (23-62)	32 (17-56)
Hospitalization cost (USD)**	20884 (13880- 33951)	27798 (18252- 47543)	22902 (15699- 43330)
<b><u>Hospitalization cost</u></b> <b><u>(JPY)</u></b>	<b><u>2297240</u></b> <b><u>(1526856-</u></b>	<b><u>3057807</u></b> <b><u>(2007727-</u></b>	<b><u>2519214</u></b> <b><u>(1726905-</u></b>
<b><u>Hospitalization cost per</u></b> <b><u>day (USD)**</u></b>	<b><u>3734595)</u></b> <b><u>401 (150-1111)</u></b>	<b><u>5229778)</u></b> <b><u>496 (231-1215)</u></b>	<b><u>4766352)</u></b> <b><u>488 (374-719)</u></b>
<b><u>Hospitalization cost per</u></b> <b><u>day (JPY)</u></b>	<b><u>44085 (16527-</u></b>	<b><u>54518 (25374-</u></b>	<b><u>53651 (41181-</u></b>
<b>In-hospital death</b>	<b>12 (14.3)</b>	<b>24 (38.1)</b>	<b>36 (24.5)</b>

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- 396 MSSA, methicillin-susceptible *Staphylococcus aureus*; ~~MRSARF~~, methicillin-resistant
- 397 *Staphylococcus aureus*; LoS, length of stay.
- 398 Values are shown as the median (interquartile range) or number (percentage).
- 399 \*Length of stay after blood culture submission.
- 400 \*\*1 USD = 110 JPY.

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

	MSSA (n=60)	MRSA (n=60)	<i>p</i> -value <sup>†</sup>
Age	76 (66-83)	76.5 (65.5-89)	0.303
Male	33 (55.0)	32 (53.3)	1.0
LoS (days)	46 (28.5-64.5)	66 (40-91)	0.020
LoS-after (days)*	38 (25-62.5)	45 (24-63)	0.691
Hospitalization cost (USD)**	19823 (13764- 32042)	26035 (18154- 47362)	0.036
<u>Hospitalization cost</u> <u>(JPY)</u>	<u>2180493</u> <u>(1514005-</u> <u>3524635)</u>	<u>2863872</u> <u>(1996922-</u> <u>5209858)</u>	<u>0.036</u>
Hospitalization cost per day (USD)**	456 (359-702)	529 (375-647)	0.990
<u>Hospitalization cost per</u> <u>day (JPY)</u>	<u>50113 (39516-</u> <u>77191)</u>	<u>58174 (41238-</u> <u>71212)</u>	<u>0.990</u>
In-hospital death	9 (15.0)	22 (36.7)	0.012

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403 MSSA, methicillin-susceptible *Staphylococcus aureus*; ~~MRSARF~~, methicillin-resistant

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404 *Staphylococcus aureus*; LoS, length of stay.

405 Values are shown as median (interquartile range) or an absolute number (percentage).

406 \*Length of stay after blood culture submission.

407 \*\*1 USD = 110 JPY.

408 †Mann-Whitney test for continuous variables and Fischer’s exact test for binary

409 variables.

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412 **Figure legends**

413 **Figure 1. Length of stay after blood culture submission by strain**

414 MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant  
415 *Staphylococcus aureus*.

416

417 **Figure 2. Hospitalization cost per day by strain**

418 MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant  
419 *Staphylococcus aureus*.

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421 **Figure 3. Breakdown of the total hospitalization cost from 2016 to 2020**

422 The horizontal axis represents the accumulated hospitalization cost during the study  
423 period.

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3 **1 Length of stay, hospitalization cost, and in-hospital mortality of**  
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6 **2 methicillin-susceptible and methicillin-resistant *Staphylococcus aureus***  
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9 **3 bacteremia in Japan**

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12 **4 Summary**

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15 **5 Objectives**

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19 6 To examine the length of stay, hospitalization cost, and case fatality of  
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22 7 methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA)  
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25 8 bacteremia in Japan.

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28 **9 Study design**

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32 10 Retrospective cohort study. Patients with a diagnosis of *Staphylococcus aureus*  
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35 11 bacteremia admitted to a tertiary care hospital (National Center for Global Health and  
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38 12 Medicine [NCGM]) in Tokyo, Japan, between 1<sup>st</sup> January 2016 and 31<sup>st</sup> December  
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41 13 2020.

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44 **14 Methods**

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48 15 We combined Japan Nosocomial Infections Surveillance data and Diagnosis Procedure  
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51 16 Combination data at NCGM from 2016 to 2020. The data were stratified into MSSA  
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54 17 and MRSA groups. Length of stay (LoS), LoS after submission of a blood culture  
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57 18 specimen (LoS-after), hospitalization cost, hospitalization cost per day, and clinical  
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3 19 outcome were compared after propensity score matching.  
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6 20 **Results**  
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9 21 Median LoS was 46 (IQR 28.5-64.5) days in the MSSA group and 66 (IQR 40-91) days  
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12 22 in the MRSA group ( $p = 0.020$ ). Median LoS-after was 38 (IQR 25-62.5) days and 45  
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15 23 (IQR 24-63) days ( $p = 0.691$ ), respectively. Median hospitalization cost was  
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18 24 significantly higher in the MRSA group (26,035 [IQR 18,154-47,362] USD) than in the  
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21 25 MSSA group (19,823 [IQR 13,764-32,042] USD) ( $p = 0.036$ ) but cost per day was not  
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24 26 (MRSA: 528.9 [IQR 374.9-647.4] USD; MSSA: 455.6 [IQR 359.2-701.7] USD;  $p =$   
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27 27 0.990). Case fatality rate was higher in the MRSA group than in the MSSA group (22/60  
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30 28 vs. 9/60,  $p = 0.012$ ).  
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35 29 **Conclusions**  
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38 30 Patients with MRSA bacteremia had longer LoS and higher costs than those with MSSA  
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41 31 bacteremia. However, LoS-after and hospitalization cost per day were not different. The  
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44 32 longer LoS than that of other countries might contribute to the higher disease burden of  
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47 33 *S. aureus* bacteremia in Japan.  
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53 35 **Keywords:** MRSA, bacteremia, length of stay, hospitalization cost, Japan  
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3 **37 Introduction**  
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6 **38** *Staphylococcus aureus* is one of the most important causes of bacteremia and poses a  
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9 **39** substantial burden to society.<sup>1-6</sup> Because *S. aureus* bacteremia requires long-term  
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12 **40** parenteral antibiotic therapy, its disease burden is not limited to high mortality but also  
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15 **41** extends to economic aspects.<sup>7,8</sup> In addition, methicillin-resistant strains (MRSA) might  
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18 **42** have a heavier burden than susceptible strains (MSSA).<sup>9</sup> However, to our knowledge,  
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21 **43** there is no solid evidence on the difference in the disease burden of bacteremia between  
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25 **44** MRSA and MSSA.  
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28 **45** Length of stay (LoS) and hospitalization cost are important indicators for  
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31 **46** estimating the burden of diseases on healthcare facilities. According to the Organisation  
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35 **47** for Economic Co-operation and Development (OECD), there is wide international  
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38 **48** variation in LoS, with Japan showing a markedly longer LoS than the worldwide  
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41 **49** average (16.1 days vs. 6.6 days in 2018).<sup>10</sup> Although we know that the disease burden  
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44 **50** due to LoS is larger in Japan than in other countries, few studies have investigated LoS  
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47 **51** in Japan in detail. For hospitalization cost, scarce evidence is available from Japan.  
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51 **52** Only a few previous studies have reported hospitalization costs in Japan but they  
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54 **53** focused on specific diseases other than bacteremia.<sup>11-13</sup> Consequently, it is difficult to  
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57 **54** estimate the actual disease burden of bacteremia in Japan and to compare it with that in  
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3 55 other developed countries.  
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6 56 The main objective of this study was to examine the outcomes of MRSA and  
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9 57 MSSA bacteremia in terms of LoS, hospitalization cost, and case fatality in a tertiary  
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12 58 care hospital in Japan. These results will provide novel evidence on LoS and  
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16 59 hospitalization cost and permit comparisons in the area of infectious diseases. Such  
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19 60 evidence will enable us to more precisely estimate the burden of each disease and will  
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22 61 be a good indicator for health policy decision makers.  
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## 28 63 **Methods**

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31 64 Data source and curation

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35 65 We obtained Japan Nosocomial Infections Surveillance (JANIS)<sup>14</sup> data, which include  
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38 66 information on microorganisms, and Diagnosis Procedure Combination (DPC) data,  
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41 67 which include information on patients' background, hospitalization cost, and LoS  
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44 68 recorded between 1 January 2016 and 31 December 2020 from National Center for  
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47 69 Global Health and Medicine (NCGM).

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51 70 The data were stored on a hard disk in a locked cabinet and only the authors of  
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54 71 this study had access to them. The data were de-identified and we extracted only cases  
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57 72 with a diagnosis of blood stream infection and a detection record of *S. aureus* from a  
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73 blood culture specimen during the same admission period. We next merged the JANIS  
74 data and DPC data by sex, age, date of birth, date of admission, and date of discharge  
75 and then stratified the merged data into MSSA and MRSA groups.

76

77 Definition of cases

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

82 The criteria for judging the antimicrobial susceptibility of each bacterium were  
83 in accordance with the regulations of JANIS, which follows the criteria defined by the  
84 Clinical Laboratory Standards Institute (CLSI)<sup>15</sup>. MRSA was defined as *S. aureus*  
85 resistant to oxacillin and/or ceftazidime.

86

87 Hospitalization cost

88 We defined hospitalization cost in this study as direct costs from the healthcare payer  
89 perspective and then obtained the hospitalization cost of each blood stream infection  
90 case through aggregation: 1) prescription cost of drugs; 2) treatment and operation cost;

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91 3) examination cost, including image inspections; 4) accommodation cost; and 5) other  
92 expenses.

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94 **Statistical analysis**

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

103 Two-sided *p* values less than 0.05 were considered statistically significant. All  
104 statistical analyses were performed using R version 4.0.3.<sup>18</sup>

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106 **Ethics approval**

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

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110 **Results**

111 Table 1 shows the LoS and hospitalization cost of all patients admitted to NCGM  
112 between 2016 and 2020 (i.e., not limited to those with *S. aureus* bacteremia). In total,  
113 median hospitalization cost per patient was 5,162 (interquartile range [IQR]  
114 2,745-10,142) USD and median LoS was 7 (IQR 3-15) days. Among all age groups,  
115 neonatal patients had the highest hospitalization cost (median 14,432 USD; IQR  
116 8,162-28,311 USD) and the longest LoS (median 13 days; IQR 8-29 days).

117

118 (Table 1)

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120 In the population of interest, median LoS was 46 (IQR 28.5-64.5) days in the  
121 MSSA group and 66 (IQR 40-91) days in the MRSA group. Median LoS-after was 38  
122 (IQR 25-62.5) days in the MSSA group and 45 (IQR 24-63) days in the MRSA group.  
123 Median hospitalization cost and cost per day were respectively 19,823 (IQR  
124 13,764-32,042) USD and 455.6 (IQR 359.2-701.7) USD in the MSSA group and 26,035  
125 (IQR 18,154-47,362) USD and 528.9 (IQR 374.9-647.4) USD in the MRSA group.

126 The Wilcoxon rank sum test revealed that LoS and hospitalization cost significantly

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3 127 differed between the groups ( $p = 0.020$  and  $0.036$ , respectively), unlike LoS-after and  
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6 128 hospitalization cost per day ( $p = 0.691$  and  $0.990$ , respectively). The case fatality rate  
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9 129 was higher in the MRSA group (22/60) than in the MSSA group (9/60) according to  
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12 130 Fisher's exact test ( $p = 0.012$ ). Table 2 shows the results before propensity score  
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15 131 matching, and Table 3 shows the results after matching. Figures 1 and 2 are violin plots  
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18 132 of LoS and hospitalization cost by strain, respectively.  
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25 134 (Table 2)  
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44 140 (Figure 2)  
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51 142 Figure 3 shows the breakdown of the hospitalization cost for each group.  
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146 Accommodation cost accounted for more than half of the total hospitalization

147 cost in both groups (59.1% in the MSSA group and 52.6% in the MRSA group). The

148 proportion of the treatment cost was higher in the MRSA group than in the MSSA group

149 (20.6% and 13.7%, respectively).

150

## 151 Discussion

152 To our knowledge, this is the first study examining the difference in LoS and

153 hospitalization cost between MSSA and MRSA in Japan. In our results, median LoS of

154 all-cause admission was substantially shorter than reported by the OECD.<sup>10</sup> This

155 difference might be due to the calculation methods used. While the OECD reported the

156 average number of days spent by patients in hospital, which is generally measured by

157 dividing the total number of days stayed by all inpatients during a year by the number of

158 admissions or discharges, we used the median LoS of each patient. Therefore, the 16.1

159 days reported by the OECD would be greatly influenced by outliers (i.e., the extremely

160 long LoS of some patients). Nevertheless, 7 days is longer than the average LoS

161 worldwide (6.6 days) and that in the US (5.5 days).<sup>10</sup>

162 Notably, the LoS of patients with *S. aureus* bacteremia in Japan is substantially

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163 longer than that in other countries. Cosgrove and colleagues reported that the median  
164 LoS for MSSA and MRSA bacteremia in the US was 7 and 9 days, respectively.<sup>19</sup>  
165 According to Thampi and colleagues, the median LoS of such patients in Canada was  
166 14 and 22.5 days, respectively.<sup>20</sup> Another study from the Greater Toronto area found a  
167 median LoS for *S. aureus* bacteremia of 17 days.<sup>21</sup> In contrast, our results indicated that  
168 patients with *S. aureus* bacteremia in Japan are hospitalized for a median 49 days, which  
169 is about three times as long as that reported previously in other countries. Even when  
170 the data are limited to LoS-after (i.e., LoS after submission of a blood culture), this  
171 amounts to twice as long as that reported in other countries. Given these results, it is not  
172 difficult to imagine that the disease burden of *S. aureus* bacteremia will be greater in  
173 Japan than in other countries.

174       The cause of the considerable international differences in LoS is unclear but  
175 Tiessen and colleagues have obtained some interesting results.<sup>22</sup> Although their study  
176 examined the LoS of acute myocardial infarction, they observed a trend similar to that  
177 of our results. In their opinion, their results can be explained by nonclinical factors such  
178 as professional/cultural norms and differences in healthcare schemes. For instance,  
179 acute care hospitals in Japan are generally equipped with a large supply of acute care  
180 beds but a small supply of long-term care beds. This combination should theoretically

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181 result in longer acute care stays. In addition, hospital ownership in Japan would also  
182 influence the results. Private for-profit organizations perhaps act to fill their capacity,  
183 which is higher than that of their counterpart, to maximize revenues. These hypotheses  
184 should be carefully examined in future work.

185         Meanwhile, we should also note that, although there was a difference in total LoS  
186 between MSSA and MRSA in our study, there was no substantial difference in LoS-after.  
187 This is a markedly different result from that of previous studies.<sup>9,23</sup> Generally speaking,  
188 the presence of antibiotic resistance appears to increase LoS and hospitalization costs.  
189 This phenomenon is probably related to Japanese healthcare systems and customs.  
190 Because residence in a long-term care facility is one of the risk factors of MRSA  
191 infection,<sup>24</sup> the longer LoS might be attributable to an increase in novel MRSA  
192 bacteremia because patients who tend to stay in the hospital longer also tend to be  
193 infected with MRSA. It is possible that the long LoS in Japan is not only unnecessary,  
194 but also increases the number of infected cases. Because the LoS-after in Japan is  
195 substantially longer than the appropriate duration of antibiotic therapy for *S. aureus*  
196 bacteremia,<sup>25</sup> the difference in the recommended duration of antibiotic therapy between  
197 MSSA and MRSA does not explain the difference in LoS-after between these strains.

198         The hospitalization cost of *S. aureus* bacteremia in Japan is neither expensive nor

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199 cheap compared with other developed countries. Thampi and colleagues reported that *S.*  
200 *aureus* bacteremia costs about 12,000 USD per case in Canada.<sup>20</sup> In contrast, it costs  
201 more than 37,000 USD in the US.<sup>23</sup> As described above, the LoS in Japan is clearly  
202 longer than that in these countries, but the hospitalization cost per day in Japan may be  
203 less expensive. In addition, the hospitalization cost per day in Japan is not substantially  
204 different between MSSA and MRSA. This result is compatible with that of a recent  
205 study from the US,<sup>26</sup> although it contradicts the results of older studies.<sup>19,27-31</sup>

206 In terms of the clinical outcome of *S. aureus* bacteremia, the case fatality rate of  
207 24.5% in this study is also similar to that in previous studies.<sup>21,32</sup> However, the  
208 difference in the case fatality rate between MSSA and MRSA is clear in our study, in  
209 contrast to a recent study.<sup>26</sup> This can be attributed to the nature of our data, which are a  
210 combination of microbiological test results and patients' claim data and which made it  
211 difficult to adjust for confounding factors associated with prognosis.

212 The present study has several limitations. First, our results are based on data from a  
213 single facility. Although our facility is the largest medical center hospital in Japan in  
214 terms of infectious diseases, the number of bacteremia cases was limited and biases due  
215 to the characteristics of the facility cannot be removed. Therefore, representativeness  
216 will be a major concern for our results. Next, as explained in the previous paragraph,

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217 our data do not include the full characteristics of each patient. Although we adjusted for  
218 age and sex by propensity score matching, other confounding factors probably affected  
219 the results. Third, our claims data capture the cost incurred by the facility. Because the  
220 Japanese health insurance system adopts the Diagnosis Procedure  
221 Combination/Per-Diem Payment System, the claims data do not precisely reflect the  
222 actual cost paid by the government to the facility. In other words, our estimated  
223 hospitalization cost might be overestimated if we regard the “healthcare payer” as being  
224 the Japanese government.

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

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235 unnecessarily longer than that in other countries and cause additional productivity loss

236 and medical costs.

237

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245

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247

248 *Data sharing:* Data used in this study are available from the corresponding author upon

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250

251 *Contributors:* ST and NO conceived the study. JY collected and managed the data. ST

252 performed statistical analyses and drafted the first draft of the manuscript. NM, JY, and

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253 NO critically reviewed the manuscript and all authors approved the final version of the

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381 **Table 1. Cost and length of stay of all patients in the National Center for Global**  
 382 **Health and Medicine, 2016-2020**

Age group	Cost (USD*)	Cost (JPY)	Length of stay (days)
<b>Neonates</b>	<b>14432</b> <b>(8162-28311)</b>	<b>1587565</b> <b>(897835-3114155)</b>	<b>13 (8-29)</b>
<b>Infants</b>	<b>4553 (3446-6390)</b>	<b>500870</b> <b>(379080-702890)</b>	<b>6 (4-8)</b>
<b>1-14 years</b>	<b>5145 (3605-6921)</b>	<b>566000</b> <b>(396555-761280)</b>	<b>5 (3-7)</b>
<b>15-64 years</b>	<b>4808 (2529-9143)</b>	<b>528882</b> <b>(278230-1005783)</b>	<b>7 (3-13)</b>
<b>65-89 years</b>	<b>5219 (2696-11235)</b>	<b>574105</b> <b>(296603-1235814)</b>	<b>8 (2-17)</b>
<b>90 years and older</b>	<b>6969 (3706-13010)</b>	<b>766628</b> <b>(407668-1431061)</b>	<b>12 (5-25)</b>
<b>Total</b>	<b>5162 (2745-10142)</b>	<b>567800</b> <b>(301936-1115629)</b>	<b>7 (3-15)</b>

383 Values are shown as the median (interquartile range).

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384 \*1 USD = 110 JPY.

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386 **Table 2. Length of stay, hospitalization cost, and in-hospital mortality of patients**  
 387 **with *S. aureus* bacteremia in the National Center for Global Health and Medicine,**  
 388 **2016-2020**

	MSSA (n=84)	MRSA (n=63)	Total (n=147)
<b>Age</b>	<b>72 (50-82)</b>	<b>76 (64-89)</b>	<b>74 (58-85)</b>
<b>Male sex</b>	<b>44 (52.4)</b>	<b>35 (55.6)</b>	<b>79 (53.7)</b>
<b>LoS (days)</b>	<b>40 (27.5-64.5)</b>	<b>66 (37.5-87)</b>	<b>49 (29-76)</b>
<b>LoS-after (days)*</b>	<b>32 (22-59.5)</b>	<b>43 (23-62)</b>	<b>32 (17-56)</b>
<b>Hospitalization cost</b>	<b>20884</b>	<b>27798</b>	<b>22902</b>
<b>(USD)**</b>	<b>(13880-33951)</b>	<b>(18252-47543)</b>	<b>(15699-43330)</b>
<b>Hospitalization cost</b>	<b>2297240</b>	<b>3057807</b>	<b>2519214</b>
<b>(JPY)</b>	<b>(1526856-3734595)</b>	<b>(2007727-5229778)</b>	<b>(1726905-4766352)</b>
<b>Hospitalization cost</b>			
<b>per day (USD)**</b>	<b>401 (150-1111)</b>	<b>496 (231-1215)</b>	<b>488 (374-719)</b>
<b>Hospitalization cost</b>	<b>44085</b>	<b>54518</b>	<b>53651</b>
<b>per day (JPY)</b>	<b>(16527-122191)</b>	<b>(25374-133648)</b>	<b>(41181-79102)</b>
<b>In-hospital death</b>	<b>12 (14.3)</b>	<b>24 (38.1)</b>	<b>36 (24.5)</b>

389 MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant

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390 *Staphylococcus aureus*; LoS, length of stay.

391 Values are shown as the median (interquartile range) or number (percentage).

392 \*Length of stay after blood culture submission.

393 \*\*1 USD = 110 JPY.



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

	MSSA (n=60)	MRSA (n=60)	p-value <sup>†</sup>
<b>Age</b>	<b>76 (66-83)</b>	<b>76.5 (65.5-89)</b>	<b>0.303</b>
<b>Male sex</b>	<b>33 (55.0)</b>	<b>32 (53.3)</b>	<b>1.0</b>
<b>LoS (days)</b>	<b>46 (28.5-64.5)</b>	<b>66 (40-91)</b>	<b>0.020</b>
<b>LoS-after (days)*</b>	<b>38 (25-62.5)</b>	<b>45 (24-63)</b>	<b>0.691</b>
<b>Hospitalization cost</b>	<b>19823</b>	<b>26035</b>	<b>0.036</b>
<b>(USD)**</b>	<b>(13764-32042)</b>	<b>(18154-47362)</b>	
<b>Hospitalization cost</b>	<b>2180493</b>	<b>2863872</b>	<b>0.036</b>
<b>(JPY)</b>	<b>(1514005-3524635)</b>	<b>(1996922-5209858)</b>	
<b>Hospitalization cost</b>	<b>456 (359-702)</b>	<b>529 (375-647)</b>	<b>0.990</b>
<b>per day (USD)**</b>			
<b>Hospitalization cost</b>	<b>50113</b>	<b>58174</b>	<b>0.990</b>
<b>per day (JPY)</b>	<b>(39516-77191)</b>	<b>(41238-71212)</b>	
<b>In-hospital death</b>	<b>9 (15.0)</b>	<b>22 (36.7)</b>	<b>0.012</b>

396 MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant

397 *Staphylococcus aureus*; LoS, length of stay.

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398 Values are shown as median (interquartile range) or an absolute number (percentage).

399 \*Length of stay after blood culture submission.

400 \*\*1 USD = 110 JPY.

401 †Mann-Whitney test for continuous variables and Fischer’s exact test for binary

402 variables.

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404 **Figure legends**

405 **Figure 1. Length of stay after blood culture submission by strain**

406 MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant

407 *Staphylococcus aureus*.

408

409 **Figure 2. Hospitalization cost per day by strain**

410 MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant

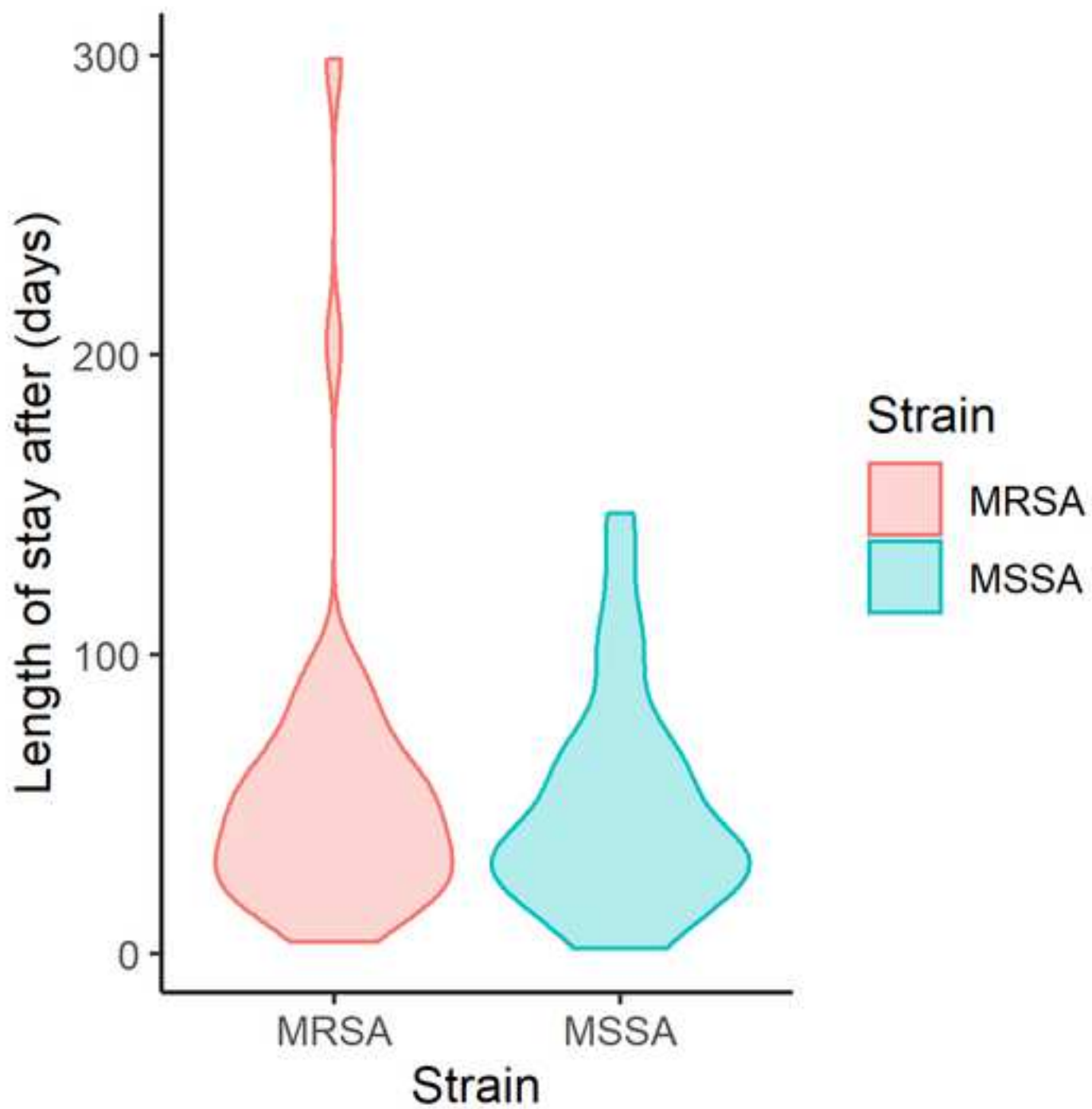
411 *Staphylococcus aureus*.

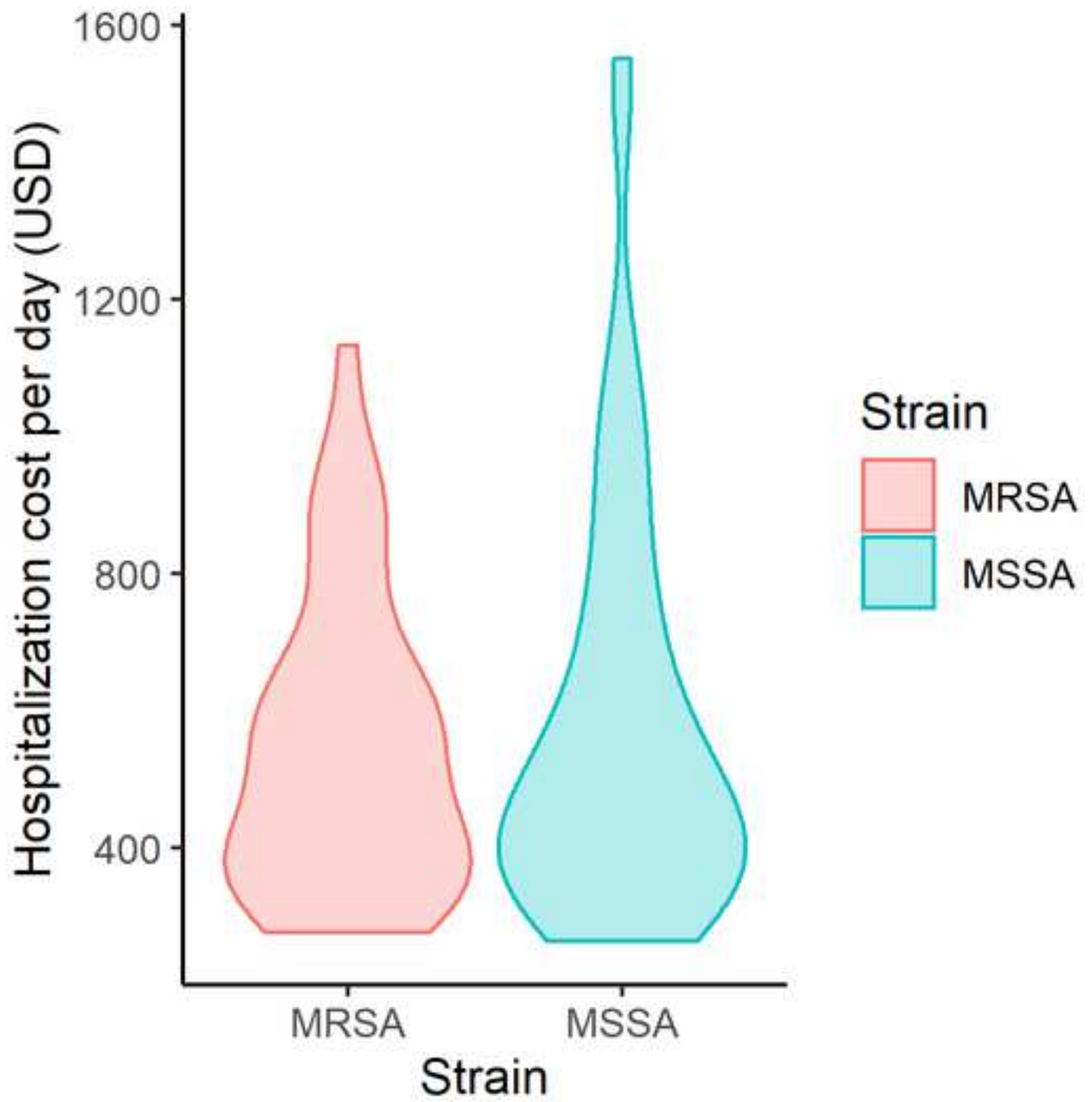
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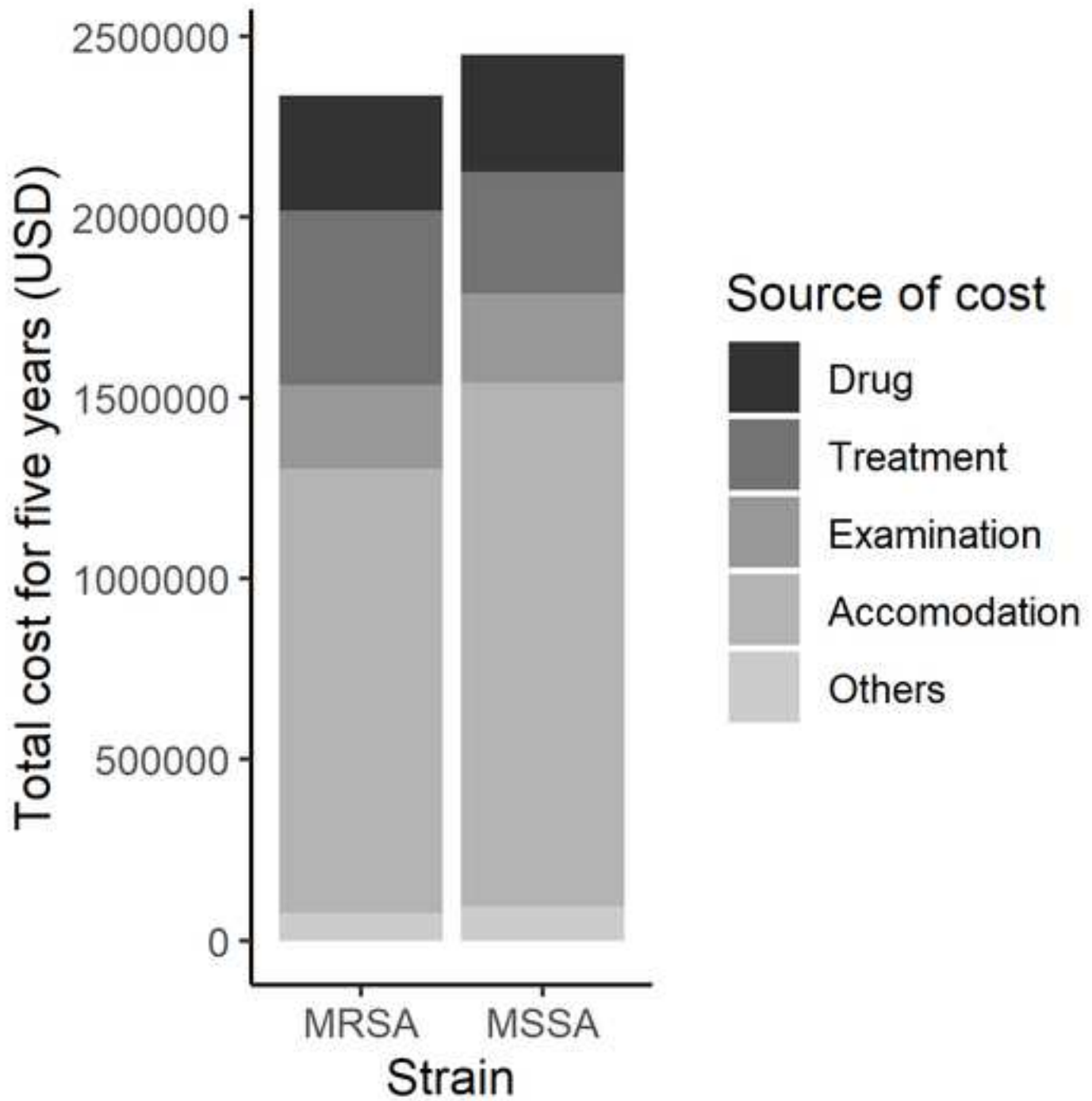
413 **Figure 3. Breakdown of the total hospitalization cost from 2016 to 2020**


414 The horizontal axis represents the accumulated hospitalization cost during the study

415 period.









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**RDM Data Profile XML**  
LoS.R

