Comparison Between Healthcare-Associated and Community-Acquired Infective Endocarditis at Tertiary Care Hospitals in Japan

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Background: Healthcare-associated infective endocarditis (HAIE) has become increasingly recognized worldwide because of the underlying patient conditions are completely different from those of community-acquired infective endocarditis (CIE). However, data on HAIE in the Japanese population is lacking. We sought to clarify the patient characteristics and prognosis of HAIE in a Japanese population.

Methods and Results: A retrospective study was conducted in 158 patients who were diagnosed with infective endocarditis, 53 of whom (33.5%) were classified as HAIE. Compared with patients with CIE, those with HAIE were older (median age 72 vs. 61 years; P=0.0002) and received surgical treatment less frequently (41.5% vs. 62.9%; P=0.01). Regarding causative microorganisms, staphylococci, including methicillin-resistant pathogens, were more common in patients with HAIE (32.1% vs. 14.3%; P=0.01). Patients with HAIE had higher in-hospital mortality (32.1% vs. 4.8%; P<0.0001) and Kaplan-Meier analysis showed worse prognosis for patients with HAIE than CIE (HR=0.0001, log-rank test). On multivariate Cox analysis, HAIE (hazard ratio 3.26; 95% confidence interval 1.49–7.14), age ≥60 years, surgical treatment, stroke, and heart failure were independently associated with mortality.

Conclusions: HAIE has different clinical characteristics and causative microorganisms, as well as worse prognosis, than CIE. Preventive strategies, and the prompt and appropriate identification of HAIE may improve the outcome of infective endocarditis.

Key Words: Community-acquired; Healthcare-associated; Infective endocarditis

Infective endocarditis (IE) is a rare, but lethal disease. The annual incidence of IE in developed countries is only approximately 3–10 per 100,000 people; however, in-hospital mortality is as high as 25%. The morbidity rates from systemic emboli, stroke, and organ failure are still high. The mortality rate has not improved at all in the past decade, despite significant diagnostic innovations through new imaging techniques, the design of new powerful antibiotics, and advances in surgical methods. This apparent paradox is due to a temporal change in the pattern of predisposing patient conditions (e.g., a decrease in rheumatic heart disease, an aging population, increased implantation of prosthetic valves and intracardiac devices, and an increased prevalence of hemodialysis) and a shift in causative pathogens.

Healthcare-associated IE (HAIE) is increasingly being recognized in the current era. Previously, common cases of IE occurred outside the healthcare setting, namely community-acquired IE (CIE), but IE acquired around the healthcare setting. HAIE has become more widespread as medical care has advanced. HAIE has quite a different clinical background and worse prognosis than CIE, and several studies indicate that underlying healthcare conditions should be considered in the management of IE. The 2015 European Society of Cardiology (ESC) guidelines for the management of IE recommended classification of the site of acquisition of infection (CIE or HAIE), particularly for the selection of antibiotic regimens for initial empirical treatment. The Japanese Circulation Society (JCS) guidelines for the prevention and treatment of IE, revised in 2017, highlight the need to be aware of underlying HAIE based on the 2015 ESC guidelines. However, this recommendation is based on research conducted in Western countries, because Japanese data on IE are lacking. Japan has unique characteristics, including the world’s most aging society, a high prevalence of hemodialysis, and few injecting...
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Methods

Study Population
This study was a retrospective study based on the medical records of patients diagnosed with IE who were admitted to The University of Tokyo Hospital from April 2007 to December 2017 or to Juntendo University Hospital from April 2014 to December 2018. All consecutive patients during the observation period were enrolled regardless of age, the type of valve (prosthetic or native valve), and the relapse of IE. Patients with definitive IE based on the modified Duke criteria were included in the study, whereas patients with possible IE were excluded. In all, the records of 158 patients (94 from the University of Tokyo Hospital and 64 from Juntendo University Hospital) were examined, and patients were divided into 2 groups (CIE and HAIE) according to the site of infection acquisition. The flowchart of patient enrollment is shown in Figure 1.

Ethical Considerations
The study was approved by the institutional review boards of The University of Tokyo Hospital and Juntendo University Hospital. This retrospective study was performed according to the ethics guidelines of each institution; the need for written informed consent was waived because the study was a retrospective study. The study was performed in accordance with the principles of the Declaration of Helsinki.

Definition and Classification of IE
IE was diagnosed by the modified Duke criteria according to clinical, echocardiographic, and microbiological findings. IE was classified as either HAIE or CIE, and HAIE was further divided into 2 categories, nosocomial and non-nosocomial IE (Figure 1). Nosocomial IE was defined as that developing more than 48 h after hospital admission before the onset of signs or symptoms consistent with IE. In contrast, non-nosocomial IE was defined as that occurring before or within 48 h of hospital admission in patients with extensive out-of-hospital exposure to healthcare interventions or systems, including the following: (1) receipt of intravenous therapy, wound care, specialized nursing care, hemodialysis, or intravenous chemotherapy within 30 days prior to the onset of IE; (2) hospitalization for ≥2 days within 90 days before the onset of IE; and (3) residence in a nursing home or long-term care facility before hospital admission. CIE was defined as the signs and symptoms of IE before or within 48 h of hospital admission that did not fulfill the criteria for non-nosocomial IE.

Definitions of Other Variables
All information was retrieved from each hospital’s electronic medical records. The variables recorded included patient information, predisposing cardiac conditions, comorbid conditions, clinical findings, echocardiographic findings, causative microorganisms, complications, and outcomes. Predisposing cardiac conditions were defined as a history of the following: cardiac valve replacement (bioprosthetic or mechanical valve); valvular disease, including rheumatic and other acquired valve dysfunction; congenital heart disease; a prior IE episode; and implantation of cardiac devices, including pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy systems. Previous valvular disease was defined as significant (moderate or severe) native valve regurgitation or stenosis diagnosed before a diagnosis of IE.

Blood cultures were taken and transthoracic echocardiography (TTE) was performed routinely once IE was suspected. The HACEK group included Haemophilus spp., Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae. Valvular disease at admission was judged as significant when the degree of severity was moderate or more than moderate based on TTE.

Complications of IE included acute heart failure, ischemic stroke, and other embolic conditions, defined as an arterial embolus causing organ dysfunction such as renal or spleen infarction and limb ischemia. Surgical treatment was defined as operations performed to eliminate infected drug users (IDUs); therefore, research in this field in the Japanese population is required. The aim of this study was to describe the patient characteristics, causative organisms, and prognosis of HAIE compared with CIE and to clarify the risk factors for mortality in a Japanese population.
Statistical Analysis
Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean ± SD and discrete variables are presented as the median and interquartile range (IQR). Categorical variables were compared using the Chi-squared test. Continuous variables were compared using Student’s t-test, and discrete variables were compared using the Kruskal-Wallis test. Survival analysis was performed using the Kaplan-Meier method, with the day of admission as the starting point and up to 5 years of follow-up. Survival curves were compared using the log-rank test. A Cox proportional hazards regression model was used to calculate hazards ratios (HRs) to determine the effect of different variables on mortality. Multivariate analysis was performed using covariates that had P-values of <0.20 in univariate analysis.

Two-sided <0.05 were considered to indicate statistically significant differences. Statistical analyses were performed using JMP Pro 14.2.0 (SAS Institute, Cary, NC, USA).

Results
Baseline Characteristics, Causative Microorganisms, and Echocardiographic Findings
In all, 158 cases of IE were recorded during the study period, and 53 were diagnosed as HAIE. The baseline clinical characteristics of the study population are given in Table 1. Patients with HAIE were significantly older than those with CIE, and there was a tendency for more females in the HAIE group. The proportion of patients with previous valvular disease was significantly lower among patients with HAIE than CIE. Congenital heart disease was seen only in 6 patients with CIE. Cardiac devices were implanted...
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Cardiovascular Outcomes

Table 4 summarizes the complications and outcomes in the CIE and HAIE groups. All complications, such as heart failure, ischemic stroke, and other embolic complications, were comparable between the 2 groups (60.4% vs. 54.3%; P=0.47), although mortality was significantly higher among patients with HAIE than CIE (32.1% vs 4.8%; P<0.0001). In addition, patients with HAIE underwent surgical treatment less frequently and had a longer hospital stay than those with CIE.

In univariate analysis, age ≥ 60 years, surgical treatment, S. aureus, heart failure, and HAIE were associated with mortality. Multivariate analysis demonstrated that HAIE (HR 3.26, P=0.003), age ≥ 60 years, surgical treatment, stroke, and heart failure were independently associated with mortality (Table 5).

Survival curves are shown in Figure 2. The event-free survival rate was significantly lower for patients with HAIE than CIE (P<0.0001, log-rank test).

Discussion

The aim of this study was to clarify the characteristics and prognosis of HAIE compared with CIE at tertiary care hospitals in Japan. There are 3 key findings of this study.

Table 3. Echocardiographic Findings in Patients With HAIE or CIE

| Valvular disease at admission | CIE (n=105) | HAIE (n=53) | P-value |
|------------------------------|-------------|-------------|---------|
| Aortic stenosis              | 10 (9.5)    | 4 (7.5)    | 0.68    |
| Aortic regurgitation         | 25 (23.8)   | 11 (20.8)  | 0.66    |
| Mitral stenosis              | 1 (1.0)     | 0 (0)      | 0.01†   |
| Mitral regurgitation         | 46 (43.8)   | 17 (32.1)  | 0.15    |
| Tricuspid regurgitation      | 11 (10.5)   | 5 (9.4)    | 0.84    |
| MAC                          | 9 (8.6)     | 9 (17.0)   | 0.13    |

| Vegetation                   |             |             |         |
|------------------------------|-------------|-------------|---------|
| Aortic valve                 | 39 (37.1)   | 21 (39.6)   | 0.76    |
| Mitral valve                 | 62 (59.0)   | 22 (41.5)   | 0.04    |
| Tricuspid valve              | 4 (3.8)     | 3 (5.7)     | 0.60    |
| Pulmonary valve              | 1 (1.0)     | 0 (0)       | 0.01†   |
| Device lead or other         | 4 (3.8)     | 5 (9.4)     | 0.16    |

| Size of vegetation (mm)      |             |             |         |
|------------------------------|-------------|-------------|---------|
| Aortic valve                 | 7.8±6.3     | 8.5±7.3     | 0.54    |
| Mitral valve                 | 7.6±8.4     | 6.9±6.9     | 0.98†   |
| Tricuspid valve              | 6.5±5.5     | 4.8±4.8     | 0.01†   |
| Pulmonary valve              | 1.0±0.7     | 0±0        | 0.01†   |

Data are expressed as the mean±SD or number (percentage). MAC, mitral annular calcification. Other abbreviations as in Table 1.

Table 4. Complications and Outcomes in Patients With HAIE or CIE

| Complications                   | CIE (n=105) | HAIE (n=53) | P-value |
|---------------------------------|-------------|-------------|---------|
| Heart failure                   | 27 (25.7)   | 18 (34.0)   | 0.28    |
| Ischemic stroke                 | 29 (27.6)   | 16 (30.2)   | 0.74    |
| Other embolization              | 22 (21.0)   | 10 (18.9)   | 0.76    |
| Surgical treatment              | 66 (62.9)   | 22 (41.5)   | 0.01†   |
| Duration of hospital stay (days)| 49 [39–71.8]| 60 [33–95.5]| 0.04†   |

In-hospital death

Data are expressed as the number (percentage) or median [interquartile range]. †P values are significant. Other abbreviations as in Table 1.

Table 5. Treatment and Prognosis in Patients With HAIE or CIE

| Treatment                      | CIE (n=105) | HAIE (n=53) | P-value |
|--------------------------------|-------------|-------------|---------|
| Surgery                        | 66 (62.9)   | 22 (41.5)   | 0.01†   |
| Duration of hospital stay (days)| 49 [39–71.8]| 60 [33–95.5]| 0.04†   |

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investigated the risk factors for poor prognosis in nosocomial IE in 560 patients with IE in Korea and recommended paying attention to the early diagnosis and active management of IE, especially in older patients and those receiving chemotherapy.

Wu et al also recommended the early recognition of non-nosocomial IE based on the high mortality rate from the Taiwan single-center experience in 192 patients with IE.

To the best of our knowledge, the present study is the first to describe the clinical characteristics and prognosis of HAIE in Japan.

In the present study, approximately one-third of patients with IE acquired it as a complication of healthcare. The proportion of HAIE in this cohort was similar to that reported in observational studies in other countries. However, it is of note that the median disease age seems higher in the present study than in previous studies. This reflects the unique Japanese surroundings. Japan leads other developed countries in terms of aging, which may contribute to an increased number of patients with HAIE. Conversely, fewer IDUs or patients with implanted cardiac devices in Japan may decrease the number of patients with HAIE. The combination of these different backgrounds led to the epidemiological results reported herein. The

First, HAIE was present in 33.5% of all patients with IE. Second, the characteristics of HAIE patients were completely different to those of CIE patients: patients with HAIE were older and received surgical treatment less frequently than those with CIE, and staphylococci, including methicillin-resistant pathogens, were more common in patients with HAIE than CIE. Finally, patients with HAIE had a significantly worse prognosis than those with CIE.

There is an infinite variety of characteristics of IE in different countries because of the different underlying surroundings. Information on IE has been primarily accumulated in regional population-based cohorts. HAIE has been recognized as an increasingly frequent pathology, and several regional studies in non-Asian populations have investigated the clinical characteristics and outcomes of HAIE. These studies stated the importance of awareness of HAIE because of the completely different backgrounds and worse outcomes of HAIE. Some studies focusing on Asian countries have investigated HAIE. For example, Yang et al investigated the epidemiology and prognosis of HAIE in 154 patients, including 28 (18.2%) with HAIE, in China and suggested that HAIE, including non-nosocomial IE, had a poor outcome. Hwang et al investigated the risk factors for poor prognosis in nosocomial IE in 560 patients with IE in Korea and recommended paying attention to the early diagnosis and active management of IE, especially in older patients and those receiving chemotherapy. Wu et al also recommended the early recognition of non-nosocomial IE based on the high mortality rate from the Taiwan single-center experience in 192 patients with IE. To the best of our knowledge, the present study is the first to describe the clinical characteristics and prognosis of HAIE in Japan.

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| Table 5. Risk Factors for Mortality in Patients With HAIE or CIE |
|---------------------------------------------------------------|
| **Univariate analysis**                                       | **Multivariable analysis** |
|---------------------------------------------------------------|
|                  | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age ≥60 years    | 8.06 (2.46–26.42) | 0.0006 | 4.40 (1.24–15.67) | 0.02 |
| Male sex         | 0.69 (0.35–1.36) | 0.29 |                   |        |
| Diabetes         | 1.23 (0.54–2.83) | 0.62 |                   |        |
| Surgical treatment | 0.23 (0.11–0.48) | <0.0001 | 0.26 (0.12–0.58) | 0.001 |
| Staphylococcus aureus | 2.16 (1.04–4.51) | 0.04 | 1.53 (0.66–3.52) | 0.32 |
| Stroke           | 1.91 (0.97–3.76) | 0.06 | 2.83 (1.31–6.12) | 0.008 |
| Heart failure    | 2.77 (1.43–5.38) | 0.003 | 2.04 (1.01–4.10) | 0.046 |

**IE type**

| CIE             | Reference |
|-----------------|-----------|
| HAIE            | 5.18 (2.53–10.58) | <0.0001 |

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

**Figure 2.** Kaplan-Meier survival curves for patients with healthcare-associated infective endocarditis (HAIE) and community-acquired infective endocarditis (CIE). Patients with HAIE had a worse prognosis than those with CIE.
prevalence of hemodialysis, which has been recognized as an independent risk factor for IE.\textsuperscript{22} was 18.9\% among patients with HAIE in the present study, which does not differ from that reported in other studies, despite the fact that hemodialysis is more widespread in Japan than in other countries.\textsuperscript{5,10,19} Further studies with a larger sample size are needed, but we assume that our data represent a snapshot of the epidemiology of HAIE in Japan.

In the present study, the clinical features of HAIE were quite different from those of CIE. Patients with HAIE had more severe debilitating conditions than those with CIE. In addition to advanced age, patients with HAIE had a tendency for a higher rate of underlying diabetes mellitus, the use of more immunosuppressive therapies, and a higher rate of malignancy than those with CIE. These findings are compatible with those of previous studies.\textsuperscript{8,10,19} In contrast with the similar clinical features, the unique Japanese results are due, in part, to different causative microorganisms. Streptococci were the most frequent pathogens, and were isolated in half of all the patients with IE in this study. The International Collaboration on Endocarditis – Prospective Cohort Study, a worldwide prospective registry, suggested \textit{S. aureus} was the most common pathogen in IE patients,\textsuperscript{8} whereas the CArdiac Disease REgistration–Infective Endocarditis (CADRE-IE) registry, a nationwide registry in Japan, found streptococci in more than half of all IE patients.\textsuperscript{22} A systematic review also noted that the frequency of microbes identified in non-Asian countries did not follow the same pattern as in Asian countries and emphasized that a global “one-size-fits-all” approach to the management of IE is not appropriate.\textsuperscript{24} The results of the present study prove that streptococci are the common pathogens responsible for IE in Japan, which is concordant with the CADRE-IE registry.\textsuperscript{23} Possible explanations for the differences in causative microbes compared with non-Asian countries is that prosthetic valves or intracardiac devices, which can be breeding grounds for staphylococci, are implanted less frequently in Japan and IDU, which typically causes staphylococci infection, is less frequent in Japan than in other countries. However, even under such unique circumstances in Japan, this study showed that \textit{S. aureus} was the most common microbial cause in patients with HAIE, and we confirmed the findings from other countries that HAIE is most commonly caused by staphylococci.

Previous valvular disease was significantly less frequent in patients with HAIE in the present study. Because it was often challenging to determine whether the valvular disease observed at the time of IE diagnosis was pre-existing or caused by IE, the findings may be due to undiagnosed valvular diseases in this population. Alternatively, it may be associated with susceptibility to IE in this group without pre-existing significant valvular disease.

In addition to increased age, surgical treatment, and endocarditis complications such as stroke and heart failure, we identified the site of IE acquisition as an independent risk factor for mortality in a Cox proportional hazards regression model. All these factors have been reported as independent predictors of mortality in other studies, and the present study confirmed those previous findings.\textsuperscript{17,25,26} In particular, surgical treatment had a strong inverse correlation with increased mortality. Some pivotal studies recommend aggressive cardiac surgery in IE patients to improve heart failure and prevent embolic sequelae.\textsuperscript{27,28} A possible cause of the poor prognosis in HAIE patients is that many underlying comorbid conditions and complications are contraindications to surgical treatment, leading to a high mortality rate. However, we performed subgroup analysis among the patients who received surgical treatment and found that those with HAIE tended to have a worse prognosis than those with CIE, although the difference did not reach statistical significance (P=0.084, log-rank test; \textsuperscript{Supplementary Figure}). Surgery for IE clearly improves prognosis, although higher mortality has been reported in elderly patients with IE who underwent surgery.\textsuperscript{29} Patients with HAIE are often elderly, and it is contentious as to whether surgical treatment is useful in these patients. Once patients acquire IE as a complication of healthcare, the prognosis is worse than for those with CIE, even if surgical treatment is performed. Efforts should be made to prevent healthcare-associated acquisition, and an early diagnosis of HAIE should be obtained.

The JCS guideline for the prevention and treatment of IE (revised in 2017)\textsuperscript{30} recommended an awareness of HAIE and selection of antibiotic regimens for initial empirical treatment to target staphylococci, based on the 2015 ESC guidelines. We confirm the completely different characteristics, causative microorganisms, and poor prognosis of HAIE in Japan, and support the rationale of antibiotic regimens for initial empirical treatment recommended in the JCS guideline.

We acknowledge several limitations in this study. First, this study had a small sample size and the statistical power was insufficient to draw any conclusions based on non-associated data. Nevertheless, variables such as age, sex, and the causative microorganisms were comparable to those in CADRE-IE, a nationwide survey in Japan. Second, the study was conducted at 2 tertiary medical hospitals in Japan. Patients may be transferred to these hospitals from other hospitals for intensive treatment, including surgical treatment, which could have led to a selection bias in the present study. Furthermore, there was a difference in observation periods between the 2 institutions, although consecutive patients with IE were enrolled at each institution. This was due to a difference in periods when both medical records and echocardiographic images were available for the study at each institution. In preliminary comparisons of the long-term survival between HAIE and CIE patients at each hospital, Kaplan-Meier analysis revealed that HAIE had a significantly worse prognosis than CIE at both institutions. We also confirmed similar clinical backgrounds, including causative microorganisms, between the 2 phases (i.e., April 2007–March 2014 and April 2014–December 2018; \textsuperscript{Supplementary Table 1}). However, there is a possibility that the prognosis was different between the 2 institutions due to differences in clinical background, including the observation periods and the postoperative outcomes, and this may affect selection bias in the present study. Third, we defined HAIE as 2 entities, nosocomial and non-nosocomial IE. As noted earlier, nosocomial acquisition is considered when IE occurs within the hospital, whereas non-nosocomial IE develops outside the hospital in patients with extensive healthcare system contact. Some previous studies analyzed nosocomial and non-nosocomial IE separately.\textsuperscript{5,8,9,10,19,20} In the present study we investigated patients with HAIE, integrating the 2 entities because of the small sample size. However, our preliminary analysis showed that both categories have almost similar clinical characteristics and poor prognosis (\textsuperscript{Supplementary Table 2}). Further studies investigating nosocomial and non-nosocomial IE separately with a larger sample size are needed.
Conclusions

HAIE accounts for one-third of all cases of IE in Japan. HAIE had different clinical characteristics and causative microorganisms (with staphylococci the leading cause of HAIE) from those of CIE. Moreover, HAIE has a worse prognosis than CIE. The increasing frequency and high mortality of HAIE imply that preventive strategies should be considered, and that prompt and appropriate identification of HAIE may improve the outcome of IE.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Supplementary Files

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-19-0887