Profile of infective endocarditis at a tertiary-care hospital in Japan over a 14-year period: characteristics, outcome and predictors for in-hospital mortality

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SUMMARY

Objectives: The aims of this study were to describe the epidemiological features and clinical characteristics of infective endocarditis (IE) at a tertiary-care hospital in Japan and to identify the factors associated with in-hospital mortality.

Methods: A retrospective observational study was conducted at a 925-bed tertiary-care teaching hospital in Japan. All adult patients diagnosed with definite IE between August 2000 and July 2014 according to the modified Duke criteria were included.

Results: A total of 180 patients (60.6% men; mean age, 69.1 years) with definite IE were included. The most common pathogen was Staphylococcus aureus (27.2%). Nine patients (5.0%) had culture-negative IE. Transthoracic and transoesophageal echocardiography were performed in 180 (100%) and 132 patients (73.3%), respectively, and vegetations were detected in 128 patients (71.1%). Surgical therapy was performed in 31 patients (17.2%). Overall, the in-hospital mortality rate was 26.1%. The independent predictors of in-hospital mortality were methicillin-resistant S. aureus (MRSA), vascular phenomena, health care-associated IE and heart failure.

Conclusions: MRSA, vascular phenomena, health care-associated IE and heart failure were independent predictors of in-hospital mortality. The unique characteristics in our cohort were the very high mean age, low rate of culture-negative IE, high rate of definite IE without detected vegetations and predominance of S. aureus.

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1. Background

Infective endocarditis (IE) has a high mortality rate.1–3 Its characteristics and causative pathogens differ by country and have changed over time.4–6 The increasing opportunities of contact with pathogens in the health care setting and the use of invasive procedures are important reasons for the variations in causative pathogens.7

To improve the outcome of this highly lethal disease, the early identification of patients who are at a high risk of mortality is important. Although several studies8–11 have evaluated possible predictors of mortality in patients with IE, reports from Japan are scarce.

We conducted this study to describe the epidemiological features and clinical characteristics of IE in a tertiary-care hospital in Japan and to identify the factors associated with in-hospital mortality.

2. Methods

2.1. Study design and setting

This retrospective cohort study was conducted at Kameda Medical Center, a large tertiary-care teaching hospital with 925 beds, in Japan. The study was approved by the Committee for Ethics of Kameda Medical Center under the condition that personal data be kept confidential. Because of the retrospective,
observational nature of the study, the requirement for informed consent was waived.

2.2. Participant selection

Patients diagnosed with IE between August 2000 and July 2014 were potentially eligible for study inclusion. We extracted information for these patients from the electronic medical record and our department database. The clinical information regarding these patients was retrospectively obtained from the electronic medical records. The modified Duke criteria were used to screen definite IE cases, and possible IE cases were excluded.

2.3. Definition of variables

The demographic data obtained were age, gender and comorbidities, such as diabetes, cancer, the use of glucocorticoids, haemodialysis and prosthetic valve involvement. Diabetes was considered present when it was listed in the patient record as a comorbid condition or if the patient’s HbA1c (Japan Diabetes Society) was >6.2%, which is equivalent to HbA1c (National Glycohemoglobin Standardization Program) >6.6%. Cancer was considered present when patients had any active disease or if they had received chemotherapy for cancer. Glucocorticoid users were defined as those receiving an equivalent of ≥10 mg of prednisolone for >1 month. Haemodialysis use was considered present if a patient had undergone maintenance haemodialysis.

Information regarding clinical characteristics, including the presence of shock, altered mental status, heart failure, persistent bacteraemia, vascular phenomena, immunological phenomena, vegetations and causative pathogens, was also obtained. Shock was defined as a systolic blood pressure <90 mmHg that did not recover after intravascular volume resuscitation. The Framingham criteria were used to diagnose chronic heart failure. Persistent bacteraemia was defined as at least two positive blood cultures obtained on different calendar days during the same infectious episodes. Vascular phenomena include major arterial emboli, septic pulmonary infarcts, myocitic aneurysms, intracranial haemorrhages, conjunctival haemorrhages and Janeway lesions. Immunological phenomena included glomerulonephritis, Osler’s nodes, Roth spots and rheumatoid factor positivity. Vascular and immunological phenomena were considered negative when no findings of these phenomena were documented. Vegetations were considered to be present when detected by either transthoracic echocardiography (TTE) or transoesophageal echocardiography (TEE). The location of the vegetations was documented when it was specified in the records.

IE was classified according to the mode of acquisition on the basis of the definitions in a previous study. Community-acquired IE was that diagnosed at the time of admission or ≤48 h of admission in patients not fulfilling the criteria for health care-associated IE. Health care-associated IE was subclassified into nosocomial IE or non-nosocomial health care-associated IE. Nosocomial IE was that developing in patients hospitalized for >48 h before the onset of signs or symptoms of IE. Non-nosocomial health care-associated IE was that diagnosed ≤48 h of admission in outpatients with extensive health care contact, as evidenced by one of the following criteria: (1) if they received intravenous therapy, wound care or specialized nursing care at home ≤30 days before IE onset; (2) if they attended a hospital or haemodialysis clinic and/or had received intravenous chemotherapy ≤30 days before IE onset; (3) if they were hospitalized in an acute care hospital for ≥2 days in the 90 days before IE onset; or (4) if they resided in a nursing home or long-term care facility.

Appropriate empirical antimicrobial therapy was defined as the empirical administration of antimicrobials to which the subsequently isolated pathogens had in vitro susceptibility before the first report of microbiology cultures. If the causative pathogen was not detected, empirically administered antimicrobial agents that were recommended after consultation with the Infectious Diseases department were regarded as appropriate. These recommendations were usually based on either the American Heart Association guidelines or the European Society of Cardiology guidelines. Patients were considered to have undergone surgical therapy if it was performed during the course of antimicrobial treatment. In-hospital mortality was chosen as an outcome variable.

2.4. Statistical analysis

The odds ratio for in-hospital mortality was calculated with 95% confidence intervals for each variable of interest in univariate logistic regression. All variables with theoretical clinical importance and those that achieved a P value of <0.10 in the univariate analysis were included in the multivariate analysis. A backward stepwise method was used to select most useful predictors of the outcome. All analyses were performed using the R version 3.0.2 (http://www.r-project.org) with the EZR frontend.

3. Results

In total, 180 patients were diagnosed with definitive IE and were treated during the study period. A summary of the patients’ demographics, clinical characteristics, therapy and outcome is presented in Table 1. The mean age of the patients was 69.1 years, and 109 patients (60.6%) were men. The most common comorbidity

<table>
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<th>Table 1</th>
<th>Summary of patients’ demographics, clinical characteristics, therapy and outcomes (n = 180)</th>
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<tr>
<td>Variables</td>
<td>(n = 180)</td>
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<tr>
<td>Mean age, years (±SD)</td>
<td>69.1 (±14.0)</td>
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<tr>
<td>Sex, men, n (%)</td>
<td>109 (60.6)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>25 (13.8)</td>
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<tr>
<td>Cancer</td>
<td>15 (8.3)</td>
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<tr>
<td>Glucocorticoid use</td>
<td>11 (6.1)</td>
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<tr>
<td>Haemodialysis</td>
<td>19 (10.6)</td>
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<tr>
<td>Conditions, n (%)</td>
<td></td>
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<tr>
<td>Shock</td>
<td>21 (11.7)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>35 (19.4)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50 (27.8)</td>
</tr>
<tr>
<td>Vascular phenomena</td>
<td>107 (59.4)</td>
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<tr>
<td>Immunological phenomena</td>
<td>51 (28.3)</td>
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<tr>
<td>Persistent bacteraemia</td>
<td>107 (59.4)</td>
</tr>
<tr>
<td>Echocardiogram and vegetation findings, n (%)</td>
<td></td>
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<tr>
<td>Performance of TTE</td>
<td>180 (100)</td>
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<tr>
<td>Performance of both TTE and TEE</td>
<td>132 (73.3)</td>
</tr>
<tr>
<td>Vegetation detected by TTE</td>
<td>97 (53.9)</td>
</tr>
<tr>
<td>Vegetation detected either by TTE or TEE</td>
<td>128 (71.1)</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>58 (32.2)</td>
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<tr>
<td>Mitral valve</td>
<td>76 (42.2)</td>
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<tr>
<td>Pulmonic valve</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Multi</td>
<td>11 (6.1)</td>
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<td>Others</td>
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<tr>
<td>Type of IE, n (%)</td>
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<tr>
<td>Prosthetic valve involvement</td>
<td>35 (19.4)</td>
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<tr>
<td>Community acquired</td>
<td>106 (58.9)</td>
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<tr>
<td>Non-nosocomial health care associated</td>
<td>47 (26.1)</td>
</tr>
<tr>
<td>Nosocomial health care associated</td>
<td>27 (15.0)</td>
</tr>
<tr>
<td>Treatment and Outcome, n (%)</td>
<td></td>
</tr>
<tr>
<td>Appropriate empirical antimicrobial therapy</td>
<td>70 (38.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>31 (17.2)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>47 (26.1)</td>
</tr>
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SD: standard deviation; TTE: transthoracic echocardiogram, TEE: transoesophageal echocardiogram
was diabetes (13.8%). Heart failure, altered mental status and shock were observed in 50 (27.8%), 35 (19.4%) and 21 patients (11.7%), respectively. Vascular phenomena (59.4%) were more common than immunological phenomena (28.3%). Persistent bacteremia was observed in 107 patients (59.4%). TTE and TEE were performed in 180 (100%) and 132 patients (73.3%), respectively. Vegetations were detected by TTE in 97 patients (53.9%) and by either TTE or TEE in 128 patients (71.1%). The most commonly involved valve was the mitral valve (42.2%), followed by the aortic valve (32.2%). IE involving the prosthetic valves was observed in 35 patients (19.4%). Community-acquired IE was diagnosed in 106 patients (58.9%), non-nosocomial health care-associated IE was diagnosed in 47 (26.1%), and nosocomial health care-associated IE was diagnosed in 27 patients (15.0%).

Causative pathogens are listed in Table 2. The most common causative pathogen was *S. aureus* in 49 patients (27.2%), followed by viridans streptococci in 40 patients (22.2%), coagulase-negative staphylococci in 21 patients (11.7%), *Enterococcus faecalis* in 14 patients (7.8%), β-haemolytic streptococci in 11 patients (6.1%), *Enterobacteriaceae* in 11 patients (6.1%), *Streptococcus anginosus* group in 10 patients (5.6%) and other pathogens, including *Pseudomonas* spp., *Corynebacterium* spp., *Granulicatella adiacens*, *Streptococcus bovis*, *Abiotrophia* spp., *Gemella morbillorum*, *Propionibacterium acnes*, *Actinobacillus actinomycetemcomitans* and *Weissella confusa*, in 15 patients (8.3%). Nine patients (5.0%) had culture-negative IE, including two patients with *Bartonella henselae* infection, as detected by the polymerase chain reaction on DNA isolated from a surgically removed valve. Sixty-eight patients (37.8%) received appropriate empirical antimicrobial therapy as per our definition. Surgical therapy was performed in 31 patients (17.2%). Overall, 47 patients died before discharge, and the in-hospital mortality rate was 26.1%.

Variables identified as significant predictors of in-hospital mortality in the univariate analyses were age ≥70 years, diabetes, haemodialysis, shock, altered mental status, heart failure, vascular phenomena, methicillin-resistant *S. aureus* (MRSA), viridans streptococci, prosthetic valve involvement and health care-associated IE. These eleven variables were included in the final multivariable logistic regression model. As presented in Table 3, heart failure, vascular phenomena, MRSA and health care-associated IE were independently associated with in-hospital mortality.

### 4. Discussion

We conducted a retrospective cohort study to describe the epidemiological and clinical features of IE and to identify factors associated with in-hospital mortality in patients admitted to a tertiary-care hospital in Japan. The study demonstrated that the mean age of the patients was 69.1 years, *S. aureus* was the most common causative pathogen, surgical therapy was performed in 17.2% patients and the in-hospital mortality rate was 26.1%. We also found that MRSA, vascular phenomena, health care-associated IE and heart failure were independent predictors of in-hospital mortality.

Routine consultation for all patients with positive blood culture with regular inpatient and outpatient infectious diseases consultation services was implemented in 2005 at our institution. As a result of this proactive intervention, improved IE detection rate and a decreased IE relapse rate within 6 months were achieved. At our institution, a total of 180 patients have been diagnosed with IE and treated in the past 14 years. Although a web-based survey involving 118 hospitals [Cardiac Disease Registration Infective Endocarditis (CADRE-IE)] has reported the details of 513 cases, to date, our study is the largest single-centre study of definite IE conducted in Japan.

The mean age of patients in our cohort was 69.1 years. IE appears to affect the elderly population in developed countries. The mean patient age in our cohort was higher than that in the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) (57.9 years), the largest cohort study of IE worldwide, and CADRE-IE (61 years), the largest cohort study of IE in Japan. This very high mean age in our cohort reflects the typical demographics in rural areas in Japan.

Although our cohort did not include a confirmed case of IE in intravenous drug users, the most common causative pathogen was *S. aureus*. The predominance of *S. aureus* was consistent with the recent trend observed in developed countries. However, viridans streptococci were the most common pathogens in the CADRE-IE cohort. This discrepancy may be explained by our proactive infectious diseases consultation service, which improved the detection of IE among patients with positive blood culture. Many IE cases in our cohort were diagnosed under this service in patients with *S. aureus* bacteraemia, and the same result was reported from another hospital in the US.

Culture-negative IE accounted only for 5.0% patients in our cohort, even though culture-negative IE has accounted for a mean of 10% patients in ICE-PCS and 20% patients in CADRE-IE. Although we experienced two cases of *B. henselae* infection, fastidious microorganisms, such as *Bartonella* spp., *Brucella* spp. and *Coxiella burnetii*, are rarely reported in Japan. Although clear data were not collected, the high rate of blood culture performance and low rate of antimicrobial use before diagnosis also contributed to this low rate of culture-negative endocarditis. In addition, our proactive infectious diseases consultation service for patients with bacteraemia was considered to affect the rate of culture-negative IE by improving the detection of IE among patients with bacteraemia.

Vegetations were detected in only 71.1% patients in our cohort. This incidence was lower than the rates of 87.0% and 90.2% reported in ICE-PCS and CADRE-IE, respectively. Low performance rate of TEE could be a reason for low detection of vegetations; however, 73.3% patients in our cohort underwent TEE, which was higher than the rate of 59.0% reported in ICE-PCS.
One possible explanation for this result is that our proactive consultation service for positive blood culture actively identified patients meeting other Duke criteria to facilitate a diagnosis even when vegetations were not detected by TEE. In fact, patients without detected vegetations were diagnosed with definite IE on the basis of one major criterion (positive blood culture for infective endocarditis) and three minor criteria of the modified Duke criteria.

Surgical therapy was performed in 17.2% patients in our cohort, which was significantly lower than the rates of 48.2% and 61% reported in ICE-PCS and CADRE-IE, respectively. This low percentage of surgical therapy may be explained by several factors. First, the relatively large number of patients without detected vegetations in our cohort limited the number of patients indicated for surgical therapy. As discussed above, vegetations were not detected in 28.9% patients in our cohort. Second, none of the patients in our cohort was transferred for the purpose of surgical therapy. This lack of referral patients with surgical indication may have decreased the percentage of patients requiring surgical therapy. Most patients with IE were diagnosed in our hospital; therefore, our cohort included many patients who did not fulfill the indication for surgical therapy. On the other hand, other large multi-centre cohorts included many patients who were referred for surgical therapy. Third, elderly patients in our cohort may have been relatively less likely considered for surgical therapy.

The overall in-hospital mortality rate was 26.1%, which was higher than the rates of 18% reported in ICE-PCS and 16% reported in CADRE-IE. Because early surgery is believed to be an effective treatment option to decrease mortality in stable patients with IE and large vegetations, it is possible that this discrepancy is explained by the low rate of surgical treatment in our cohort. However, as noted above, the small number of referral patients suitable for surgical therapy, age of the population and the predominance of S. aureus may explain the higher mortality rate.

Multivariate analysis in our study identified MRSA, vascular phenomena, health care-associated IE and heart failure as independent predictors of in-hospital mortality. Among these four factors, MRSA had the highest odds ratio. Some studies have also confirmed that these factors were associated with in-hospital mortality. However, other studies identified other significant factors associated with in-hospital mortality, such as increasing age, prosthetic valve involvement, coagulase-negative staphylococcal infection, mitral valve vegetations, paravalvular complications and diabetes mellitus. These discrepancies may be because of the lack of uniformity of variables and differences in study design.

Our study has some limitations. First, this study is single-centre study; therefore, our patient population does not precisely reflect the general demographics in Japan. Second, the small number of events resulted in relatively wide, albeit statistically significant, confidence intervals. Thus, another study with a larger number of patients is required to confirm the predictors for in-hospital mortality.

In conclusion, our study demonstrated that IE remains a highly lethal disease in the elderly population in Japan, and that it is associated with high in-hospital mortality rates. MRSA, vascular phenomena, health care-associated IE and heart failure were independent predictors of in-hospital mortality. The low rate of culture-negative IE, high rate of definite IE without detected vegetations and the predominance of S. aureus were unique findings in our cohort; these characteristics were influenced by our proactive infectious diseases consultation service for patients with bacteremia.

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