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【 ORIGINAL ARTICLE 】

Clinical Status Quo of Infective Endocarditis in a University Hospital in Japan: A Single-hospital-based Retrospective Cohort Study

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Abstract:

Objective No research on infective endocarditis (IE) concerning populations of more than 40 patients from all departments of the hospitals they may have visited in Japan has been conducted since 2000. The present study clarified the status quo of IE in a university hospital in Japan.

Methods Data of inpatients of Saga University Hospital with definite IE from September 2007 to August 2017 were retrospectively analyzed.

Patients Records of inpatients with diagnosed IE admitted to any department were scrutinized; those with "definite IE" according to the modified Duke's criteria comprised the study cohort.

Results The study cohort was 74 patients with a median age 66.5 years old. Symptoms within 2 months before the first visit to our hospital included a fever (73.0%), general malaise (33.8%), disturbance of consciousness (24.3%), and dyspnea (24.3%). High-frequency causative microorganisms were *Staphylococcus aureus* (28.4%), followed by *Streptococcus viridans* (18.9%) and *Enterococcus* spp. (6.8%). The most frequently involved valves were the mitral valve (48.6%), followed by the aortic valve (25.7%) and multiple valves (14.9%). Patients without cardiac murmurs accounted for 37.8%, and those without or with only mild valvular disease accounted for 32.4%. The incidence of complications was 93.2%, and high-frequency complications were central nervous system disorder (60.8%), followed by glomerulonephritis (45.9%) and extracranial embolism (36.5%).

Conclusion The incidences of IE without cardiac murmurs and IE without or with only minor valvular disease were higher than those values previously reported in 2000 in Japan. When IE is suspected clinically, clinicians must check thoroughly for common complications, even in patients without cardiac murmurs or valvular disease.

Key words: infective endocarditis, clinical manifestation, cardiac murmur, valvular disease, complication, embolism

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Introduction

The annual incidence of infective endocarditis (IE) in Japan is as low as 32.4 per 1,000,000 people (1). Although the modified Duke's criteria are usually used to make the diagnosis (2), making a diagnosis can be challenging, as the manifestations and laboratory examination findings of IE are non-specific (3, 4). Therefore, knowing the precise clinical features of IE is extremely useful for making an accurate diagnosis.

In 2013, the clinical features of IE in Japanese patients were reported only by cardiologists at multiple centers registered on the web-based registration system, Cardiac Disease Registration (5); however, many patients with IE visit departments other than cardiovascular departments because of

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this disease's varied manifestations (6). It is therefore essential to investigate all patients with IE who visit any medical department to accurately determine all the clinical features of this condition. Because the last study targeting patients with IE visiting any department in Japan was reported approximately 20 years ago (7), further research is required, particularly because the clinical features may have changed with the marked aging of the Japanese population (8) and because there have been striking advances in medical modalities, especially imaging studies, including echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) (9).

We herein report the clinical status quo of IE in a university hospital in Japan, especially regarding clinical manifestations, as established by investigating all patients diagnosed with IE in any department of Saga University Hospital, Japan, from 2007 to 2017.

Materials and Methods

Study design and patients

The present investigation was a single-hospital-based retrospective cohort study. Inpatients diagnosed with IE in Saga University Hospital from September 2007 to August 2017 were identified from the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) (code number I-330). Patients who were subsequently diagnosed with "definite IE" according to the modified Duke's clinical criteria or pathological criteria were enrolled.

Setting

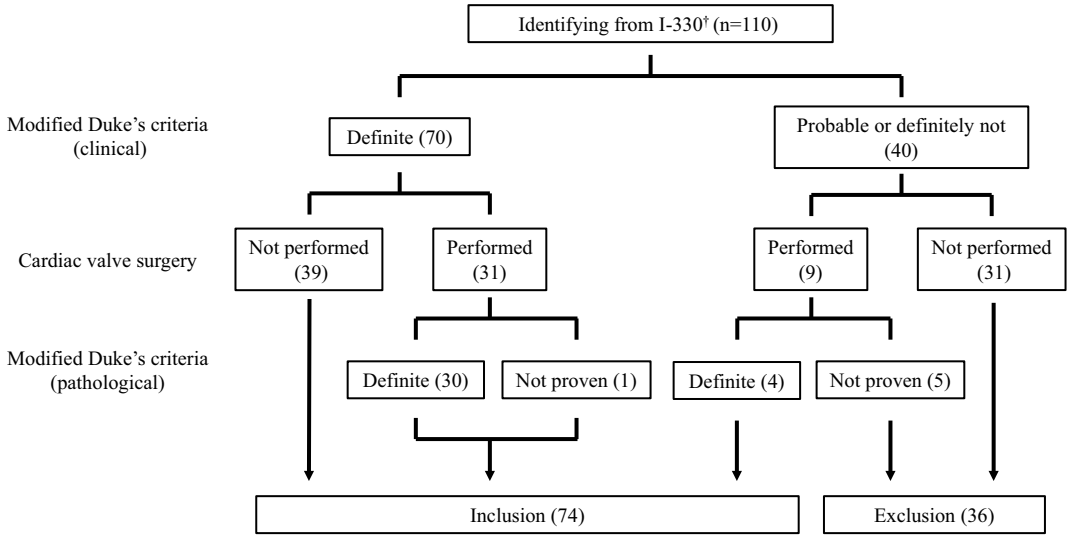
Saga University Hospital is situated in Saga Prefecture, which has a population of 800,000 and is located on the southern island of Kyushu, Japan. It is a university hospital with fully equipped outpatient clinics and 604 beds for inpatients in 29 clinical departments, including Departments of General Medicine, Cardiology, and Cardiovascular Surgery. The hospital provides high-level medical services mainly for patients in the acute phases of their diseases. The Division of Infectious Disease/Prevention and Control in our hospital usually supervises the process of making a diagnosis of IE and chooses appropriate antibiotics and durations of treatment for all patients with positive blood culture results as well as when consultations are requested from other departments. Furthermore, we preliminarily examine the frequency with which echocardiography is performed in cases with positive blood culture results revealing the presence of bacteria fulfilling the major modified Duke's criteria.

In our hospital from January to December 2018, 82 patients showed positive results, including 35 patients with *Staphylococcus aureus* infection (42.7%), 11 with *Streptococcus* spp. infection (13.4%), and 36 with *Enterococcus* spp. infection (43.9%). We found that echocardiography was performed in 45 (54.9%) of these patients.

Data sources

Two doctors from the Department of General Medicine in our hospital checked the medical charts and collected data on potentially eligible patients. Survey items included the age, sex, duration of hospitalization in our hospital, outcome on discharge, department to which the patient was admitted (in the case of patients who changed departments during their hospitalization, all departments in which the patient was treated were analyzed separately), transportation by ambulance or not, nosocomial infection or not, presence or absence of comorbidities and their nature (including hemodialysis, chronic dermatological disorders, and diabetes mellitus), administration of steroids or immunosuppressants, presence or absence of antibiotics treatment prior to blood culture, presence or absence of dental disease on admission, history of a dental clinic visit within the past 6 months, history of invasive dental treatments within the past 6 months, valvular surgery for IE during this hospital stay or not, death within 30 days of admission to our hospital or not, presence or absence of in-hospital mortality at any time during hospitalization, symptoms that were present within 2 months before the first visit to our hospital, presence or absence of cardiac murmurs on admission, presence or absence of valvular disease on admission, type and grade of valvular disease on admission, causative microorganisms, the valve or valves infected, presence or absence of any complications and their nature, and the number of complications.

Regarding complications, the presence of acute heart failure (AHF), central nervous system (CNS) disorders, extracranial embolism, disseminated infection, glomerulonephritis, and disseminated intravascular coagulation (DIC) were investigated, and the sum of the numbers of these complications was calculated (range 0-6). AHF was defined according to the European Society of Cardiology and American College of Cardiology Foundation/American Heart Association guidelines (10, 11) as low a left ventricular ejection fraction (EF) (EF <50.0%). Embolic stroke and cerebral hemorrhaging were defined as CNS disorders. Disseminated infections included pyogenic spondylitis, pyogenic arthritis, spinal epidural abscess, deep-seated abscess, and mycotic aneurysm. Complicated glomerulonephritis was defined as the following abnormal findings on urinalysis: ≥1+ blood and ≥1+ protein in dipstick, or urinary blood cell casts, or dysmorphic hematuria. DIC was diagnosed according to the DIC scoring system of the Japanese Association for Acute Medicine (12). Furthermore, laboratory and imaging investigations that were performed from the first visit to the previous doctors to the end of hospitalization in our hospital were checked, including complete blood count, blood chemistry tests, urinalysis, blood culture, culture and polymerase chain reaction (PCR) on operated valves to determine the causative bacteria, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), cranial CT, thoracic CT with contrast enhancement, abdominal CT with contrast enhancement, coronary CT angiography, and cranial



†International Statistical Classification of Diseases and Related Health Problems-10 code number

Figure 1. Inclusion criteria. One hundred and 10 inpatients diagnosed with IE in Saga University Hospital from September 2007 to August 2017 were identified from the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) (code number I-330). Two doctors of the Department of General Medicine in our hospital re-checked these patients' data according to the modified Duke's clinical criteria and found that 70 of them had "definite IE" and 40 "probable IE" or "not IE". Cardiac valve surgery was performed in 31 patients in the "definite IE" group and 9 in the "probable IE" or "not IE" groups, after which 30 patients were diagnosed with "definite IE" group and 4 with "probable IE" or "not IE" according to the modified Duke's pathological criteria. All 74 patients diagnosed with "definite IE" according to either the modified Duke's clinical or pathological criteria were enrolled and analyzed in the present study.

and spinal MRI with or without contrast enhancement. Concerning the findings of TTE or TEE, patients who fulfilled the major modified Duke's criteria were defined as echocardiography-positive.

Data analyses

The results are expressed as the median values for quantitative data and as percentages for categorical data. The IBM SPSS (version 25, IBM, Armork, USA) and Microsoft Excel 2016 software programs were used for the statistical analyses.

Ethical considerations

We obtained consent from all of the subjects by the comprehensive agreement method of the hospital, and the anonymity of the patients was protected. The study was approved by the Ethics Committee of Saga University Hospital and conducted in accordance with the guidelines of the 1975 Declaration of Helsinki.

Results

Process of enrollment of study patients

Of the 110 patients identified as having been diagnosed with IE using ICD-10, 70 were diagnosed with "definite IE" according to modified Duke's clinical criteria on review of their charts. In addition, 9 of 40 patients who had initially been diagnosed with "probable IE" or "not IE" underwent valvular operations, and 4 of these 9 were diagnosed with "definite IE" according to the modified Duke's pathological criteria. Thus, a total of 74 patients were diagnosed with "definite IE" according to either clinical or pathological criteria and accordingly enrolled and analyzed in the present study (Fig. 1).

Patients' characteristics

The characteristics of the study participants are shown in Table 1. The median age was 66.5 (53.8-76.0) years old, with a high proportion being ≥60 years old (68.9%), and 56.8% of patients were men. Patients transported by ambulance and those with nosocomial infection accounted for 48.6% and 5.4%, respectively. The mean duration of hospitalization was 41.0 days, ranging from 28.8 to 60.5 days. Valvular surgery was performed on 47.3% of patients. Antibiotics had been administered prior to blood culture in 43.2% of patients. The prevalence of comorbidities was as follows: diabetes mellitus, 20.3%; history of prosthetic valve replacement, 14.9%; presence of intravascular device such as pacemaker or central intravenous catheter, 14.9%; administration of steroids or immunosuppressants, 12.2%; chronic dermatological disorder such as atopic dermatitis, 10.8%;

Table 1. Patients' Characteristics.

Characteristic	n=74
Age (inter-quartile range), years†	66.5 (53.8-76.0)
Aged over 60 years	51 (68.9%)
Male	42 (56.8%)
Transportation by ambulance	36 (48.6%)
Nosocomial infection	4 (5.4%)
Use of antibiotics prior to blood culture	32 (43.2%)
Comorbidities	
Diabetes	15 (20.3%)
History prosthetic valve replacement	11 (14.9%)
Intravascular device	11 (14.9%)
Administration of steroids or immunosuppressants	9 (12.2%)
Chronic dermatological disorder	8 (10.8%)
Hemodialysis	6 (8.1%)
Dental problem	
Dental disease	29 (39.2%)
Visited a dental clinic within previous 6 months	15 (34.9%)
Invasive dental care within previous 6 months	13 (17.6%)
Undergoing valvular surgery	35 (47.3%)
Mortality	
Mortality within 30 days from admission to our hospital	10 (13.5%)
In-hospital mortality	12 (16.2%)

†: median (range).

Table 2. Laboratory Findings on Admission to Our Hospital.

	Total (n=74)	Antimicrobial agent not administered on admission (n=36)
White blood cell count ($\times10^3$/μL)	12.6 (2.3-49.0)	14.1 (6.7-49.0)
Neutrophil count (%)	86.5 (51.7-98.5)	90.3 (51.7-98.5)
Platelet count ($\times10^4$/μL)	12.7 (0.4-51.5)	12.3 (0.4-51.5)
FDP (μg/mL)	17.7 (2.2-104.8)	22.6 (3.9-90.4)
D-dimer (μg/mL)	6.7 (0.6-75.8)	8.1 (1.4-75.8)
PT-INR	1.2 (0.9-7.8)	1.2 (0.9-7.8)
Albumin (g/dL)	2.6 (1.0-4.0)	2.5 (1.0-3.9)
Total bilirubin (mg/dL)	0.9 (0.3-6.4)	1.0 (0.4-6.4)
AST (IU/L)	34.0 (12-363)	34.5 (12-363)
ALT (IU/L)	22.0 (4.0-213)	22.5 (4.0-213)
LDH (IU/L)	316 (111-2,216)	327 (111-1,088)
BUN (mg/dL)	23.3 (4.4-170.7)	24.4 (8.3-171)
Creatinine (mg/dL)	1.0 (0.4-10.8)	1.1 (0.6-9.2)
Sodium (mEq/L)	136 (120-152)	136 (120-152)
Potassium (mEq/L)	4.1 (2.8-6.1)	4.3 (3.1-5.9)
Chloride (mEq/L)	100 (85-117)	101 (85-117)
C-reactive protein (mg/dL)	7.5 (0.1-33.4)	9.3 (0.4-30.5)

Values are presented as median (range).

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen FDP: fibrin/fibrinogen degradation products, LDH: lactate dehydrogenase, PT-INR: prothrombin time-international normalized ratio

and hemodialysis, 8.1%. Concerning the dental history, 34.9% of patients had visited a dental clinic, and 17.6% had received invasive dental care within the past 6 months before admission. On admission to our hospital, 39.2% of patients had dental diseases, including periodontitis (14.9%), poor oral sanitation (12.2%), dental caries (10.8%), and loss of teeth (4.1%).

The laboratory findings on admission to our hospital are shown in Table 2. The median white blood cell count and C-reactive protein concentration were 12.6×10^3/μL and 7.5

Table 3. Symptoms and Signs within 2 Months before the First Visit to Our Hospital.

Symptoms and signs	n=74
Fever over 37°C	54 (73.0%)
General malaise	25 (33.8%)
Disturbance of consciousness	18 (24.3%)
Dyspnea	18 (24.3%)
Loss of appetite	16 (21.6%)
Back/joint pain	12 (16.2%)
Nausea/vomiting	12 (16.2%)
Paralysis/weakness in any extremity	12 (16.2%)
Symptoms of a common cold†	5 (6.8%)
Difficulty with body movement	4 (5.4%)
Weight loss††	4 (5.4%)
Other†††	14 (18.9%)

†: Symptoms of a common cold comprised cough, sputum, and sore throat.
††: More than 10% weight loss.
†††: Other includes muscle pain 3 (4.1%), thirst 2 (2.7%), unsteadiness 2 (2.7%), difficulty walking 1 (1.4%), vertigo 1 (1.4%), aphasia 1(1.4%), aphasia 1 (1.4%), tightness in chest 1 (1.4%), headache 1 (1.4%), and anuresis 1 (1.4%).

mg/dL, respectively. The mean concentrations of fibrin/fibrinogen degradation products and D-dimer were 17.7 μg/mL and 6.7 μg/mL, respectively, indicating a high prevalence of coagulopathy. Furthermore, the clinical status of IE patients according to the presence or absence of a history of being treated by the departments of Cardiology or Cardiovascular Surgery or other departments during hospitalizations are shown in Supplementary material 1; the clinical status included symptoms and signs, causative bacteria, infected valves, and complications, as described below.

Symptoms and signs

The symptoms and signs experienced within the 2 months before the first visit to our hospital were a fever over 37℃ (73.0%), general malaise (33.8%), disturbance of consciousness (24.3%), dyspnea (24.3%), loss of appetite (21.6%), nausea or vomiting (16.2%), back or joint pain (16.2%), and paralysis or weakness in any extremity (16.2%) (Table 3).

Departments in which patients were treated

Patients who were referred to any department of our hospital after being diagnosed by their previous doctors with IE or who were referred to the department of Cardiovascular Surgery for surgical operation accounted for 24.3% and 5.4%, respectively. Patients were initially admitted to 15 different clinical departments in our hospital. The most common departments admitting them were Cardiology (23, 31.1%), General Medicine (14, 18.9%), and Cardiovascular Surgery (9, 12.2%) (Supplementary material 2). Forty patients were moved to other departments (54.1%), including 29 moved to Cardiovascular Surgery (72.5%), 12 moved to Cardiology (30.0%), and 3 moved to General Medicine (7.5%). In addition, the department of Gastroenterological Surgery treated 1 patient only after a department change, resulting in the involvement of 16 total departments.

Throughout the duration of the patients' hospitalizations, the department of Cardiovascular Surgery treated 38 patients (51.4%), and the Cardiology department treated 35 patients (47.3%), with 53 patients (71.6%) being treated by the department of Cardiovascular Surgery or Cardiology. The Division of Infectious Disease/Prevention and Control was involved in the planning and implementation of antibiotics treatment for 73 patients (98.6%). All 5 patients admitted to the departments of Orthopedics, Neurosurgery, Dermatology, Plastic Surgery, and Urology were treated under the supervision of the Division of Infectious Disease/Prevention and Control. Three of these patients changed departments during their hospitalizations. Two patients admitted to the departments of Orthopedics and Urology were moved to the department of General Medicine, and 1 patient admitted to the department of Neurosurgery was moved to the department of Cardiovascular Surgery.

Microbiology

Blood cultures had been performed in all 74 patients, some after being admitted to our hospital and some at the hospitals that had been treating them prior to admission to our hospital. They were positive in 64 patients (86.5%) and negative in the remaining 10 (13.5%). Fifty-seven of the patients with positive blood cultures fulfilled the major modified Duke's criteria. The causative bacteria in order of frequency of detection by blood culture or culture or PCR performed on the operated valve were as follows: *Staphylococcus aureus,* 28.4%, including methicillin-sensitive *Staphylococcus aureus* (MSSA; 17.6%) and methicillin-resistant *Staphylococcus aureus* (MRSA; 10.8%); *Streptococcus viridans,* 18.9%; and *Enterococcus* spp., 6.8% (Table 4). One case was definitely diagnosed as IE based only on culture of the operated valve, because negative results of 8 blood cultures bottles and twice TEEs failed to fulfill the modified Duke's clinical criteria (4). *Streptococcus viridans* was detected most often in patients with cardiac murmurs. Among the 8 patients with chronic dermatological disorders as comorbidities, the causative bacteria were MSSA in 5 patients (62.5%), unknown in 2 patients (25.0%), and *Streptococcus agalactiae* in 1 patient (12.5%). The type and frequency of antimicrobial agents administered for IE are shown in Supplementary material 3.

Findings concerning infected valves

On admission, no cardiac murmurs were audible in 28 patients (37.8%). There was no apparent connection between the presence of cardiac murmur and the presence of intravascular devices. TTE was performed on all 74 patients (100%) and was positive in 56 (75.7%). TEE was performed on 26 patients (35.1%) and was positive in 24 (92.3%), including 12 patients with negative TTE (16.2%). No valvular disease was detected by either TTE or TEE in 13 patients (17.6%). A total of 24 patients (32.4%) only had mild valvular diseases (below grade I) or no valvular diseases. The

Table 4. Causative Bacteria.

Bacteria	Total n=74	With murmur n=45	Without murmur n=29
Negative blood culture	10 (13.5%)	5 (11.1%)	5 (17.2%)
Staphylococcus aureus	21 (28.4%)	11 (24.4%)	10 (34.5%)
Methicillin sensitive *Staphylococcus aureus*	13 (17.6%)	5 (11.1%)	8 (27.6%)
Methicillin resistant *Staphylococcus aureus*	8 (10.8%)	6 (13.3%)	2 (6.9%)
Streptococcus viridans	14 (18.9%)	12 (26.7%)	2 (6.9%)
Streptococcus bovis	1 (1.4%)	1 (2.2%)	N/A
Enterococcus spp.	5 (6.8%)	3 (6.7%)	2 (6.9%)
Polymicrobial	5 (6.8%)	2 (4.4%)	3 (10.3%)
Other†	18 (24.3%)	11 (24.4%)	7 (24.1%)

†: *Staphylococcus* spp. 7 (9.5%), *Streptococcus* spp. 6 (8.1%), *Corynebacterium* spp. 2 (2.7%), *Escherichia coli* 1 (1.4%), *Lactococcus garvieae* 1 (1.4%), *Aerococcus urinae* 1 (1.4%).

Table 5. Infected Valves.

Sites of infected valves	Total n=74	With murmur n=45	Without murmur n=29
Mitral valve	36 (48.6%)	21 (46.7%)	15 (51.7%)
Aortic valve	19 (25.7%)	14 (31.1%)	5 (17.2%)
Multiple valves	11 (14.9%)	9 (20.0%)	2 (6.9%)
Mitral and aortic valves	10 (13.9%)	8 (17.8%)	2 (6.9%)
Tricuspid valve	2 (2.7%)	1 (4.4%)	1 (3.4%)
Pulmonary valve	1 (1.4%)	N/A	1 (3.4%)
Unknown	5 (6.8%)	N/A	5 (17.2%)
Prosthetic valve†	11 (14.9%)	6 (13.3%)	5 (17.2%)

†: Prosthetic aortic or mitral valves were doubly analyzed as both prosthetic valves and aortic or mitral valves.

types of infected valves were as follows: mitral valve, 48.6%; aortic valve, 25.7%; multiple valves, 14.9%; tricuspid valve, 2.7%; and pulmonary valve, (1.4%) (Table 5). Prosthetic valves were infected in 14.9% of cases. Representative valvular diseases detected during the clinical course in order of prevalence were mitral regurgitation (63.5%), aortic regurgitation (37.8%), tricuspid regurgitation (28.4%), and pulmonary regurgitation (5.4%) (Fig. 2). A comparison of the incidence of valvular diseases in patients with and without cardiac murmur is presented in Supplementary material 4.

Rate of using imaging studies other than echocardiography

Cranial CT was performed on 67 patients (90.5%), cranial MRI with or without contrast enhancement on 49 (66.2%), thoracic CT with contrast enhancement on 60 (81.1%), abdominal CT with contrast enhancement on 52 (70.3%), simultaneous thoracic and abdominal CT with contrast enhancement on 51 (68.9%), coronary CT angiography on 14 (18.9%), and spinal MRI with or without contrast enhancement on 12 (16.2%). Concerning the detection of intracranial complications, neither cranial CT nor cranial MRI was performed on 7 patients (9.5%). Furthermore, concerning the detection of vertebral complications, 21 patients (28.4%) did not undergo thoracic CT, abdominal CT, simultaneous thoracic and abdominal CT, or spinal MRI.

Complications

The patients developed various complications, such as CNS disorders (60.8%); glomerulonephritis (45.9%); extracranial embolism (36.5%), including splenic infarction (23.0%), renal infarction (12.2%), pulmonary embolism (10.8%), hepatic infarction (2.7%), and superior mesenteric artery embolism (1.4%); DIC (32.4%); disseminated infections (18.9%), including pyogenic spondylitis (9.5%), deep-seated abscess (9.5%), mycotic aneurysm (5.4%), pyogenic arthritis (4.1%), and spinal epidural abscess (1.4%); and AHF (14.9%). CNS disorders consisted of embolic stroke (52.7%) and cerebral hemorrhaging (31.1%). Cerebral hemorrhaging was detected by cranial CT in 23.0% of patients and by cranial MRI in 31.1%; the latter included asymptomatic microhemorrhaging. Valvular surgery was performed in 30.4% of 23 patients with relatively slight cerebral hemorrhaging, resulting in the survival of all patients. On a urinalysis, occult blood was detected in 43 patients (58.1%) and proteinuria in 35 (47.3%). The total number of complications per patient were as follows: 0 in 5 patients (6.8%), 1 in 20 (27.0%), 2 in 20 (27.0%), 3 in 19 (25.7%), and 4 in 10 (13.5%). No patient had 5 or more complications (Ta-

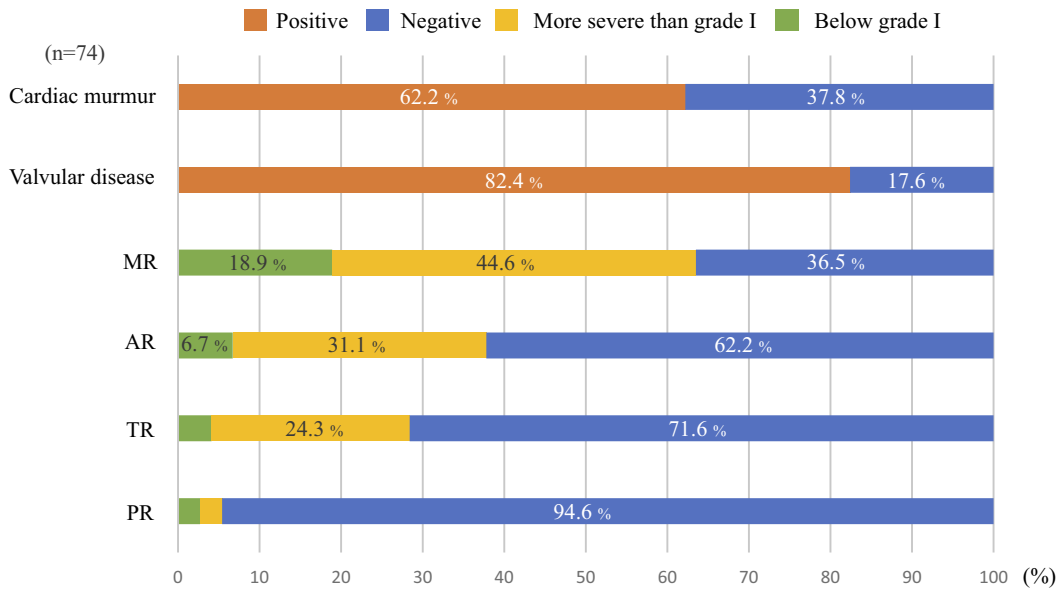


Figure 2. Cardiac murmurs and valvular disease. Findings of cardiac auscultation were recorded in the medical charts of 73/74 patients, and findings of echocardiography were recorded for all study patients. No cardiac murmurs were detected in 28 patients (37.8%), and no valvular disease was detected in 13 (17.6%) by either TTE or TEE, resulting in 24 patients (32.4%) being classified as having no or only grade I valvular disease. Detected valvular diseases consisted of mitral regurgitation (47, 63.5%), aortic regurgitation (28, 37.8%), tricuspid regurgitation (21, 28.4%), and pulmonary regurgitation (4, 5.4%), and valvular diseases more severe than grade I were found in 33 (44.6%), 23 (31.1%), 18 (24.3%), and 2 (2.7%) of these patients, respectively.

ble 6).

The associations between complications, causative bacteria, and infected valves are shown in Tables 7 and 8. Cerebral hemorrhaging (61.9%), deep-seated abscess (23.8%), pyogenic arthritis (9.5%), and DIC (61.9%) were detected more frequently in patients with IE caused by *Staphylococcus aureus* than IE caused by *Streptococcus viridans* and *Enterococcus* spp. Deep-seated abscess and pyogenic arthritis were detected more frequently in patients with IE caused by MSSA than in those by MRSA, and cerebral hemorrhaging was detected more frequently in patients with IE caused by MRSA than in those by MSSA. Renal infarction was detected more frequently in patients with IE caused by *Streptococcus viridans* than in those by *Staphylococcus aureus* and *Enterococcus* spp. There were no apparent connections between infected valves and any complications.

Mortality

The rate of mortality within 30 days from admission to our hospital was 13.5%, and the total in-hospital mortality rate was 16.2% (Table 1). The rate of mortality within 30 days from admission to our hospital and the in-hospital mortality rate of patients treated by any departments except for Cardiology or Cardiovascular Surgery (Non-Specialist) were 28.6% and 33.3%, respectively, which were higher than those of patients treated only by the Cardiology or Cardiovascular Surgery departments (only specialists) (6.5%) (Supplementary material 1). Patients treated by non-specialists were older with higher incidences of diabetes, administration of steroids or immunosuppressants, *Staphylococcus aureus* infection, pyogenic spondylitis, deep-seated abscess, pyogenic arthritis, cerebral hemorrhaging, and DIC than those treated by only specialists.

Discussion

A multi-center study on the clinical manifestations of IE in Japan was reported in 2013 (5); however, it only included patients attending departments of cardiology and therefore could not comprehensively determine the features of IE in Japanese patients, as patients with IE typically have non-specific symptoms and signs and therefore visit not only cardiology departments but other departments as well, including the general internal medicine department. Indeed, in the present study, patients were treated in 16 different departments of our hospital. Given that the most recent research on clinical features of patients with IE who were treated in various hospital departments in Japan was reported in 2000, we considered it essential to study current trends in patients with IE, particularly because these trends would certainly have changed since 2000 as a result of the aging of Japan's population, which is the most marked in the world (8), and progress in medical technologies that has resulted in marked advances in and refinement of imaging modalities, such as TTE, TEE, CT, and MRI (9).

Indeed, the present study showed remarkable changes since the publication of the studies cited above, such as increased numbers of aged patients, an increased incidence of

Table 6. Complications.

Complications	n=74
Central nerve system disorder	45 (60.8%)
Embolic stroke	39 (52.7%)
Cerebral hemorrhage	17 (23.0%)
Cerebral hemorrhage including microhemorrhage†	23 (31.1%)
Glomerulonephritis	34 (45.9%)
Hematuria	43 (58.1%)
Proteinuria	35 (47.3%)
Extracranial embolism	27 (36.5%)
Spleen	17 (23.0%)
Kidney	9 (12.2%)
Pulmonary	8 (10.8%)
Liver	2 (2.7%)
Superior mesenteric artery	1 (1.4%)
Disseminated intravascular coagulation	24 (32.4%)
Disseminated infection	14 (18.9%)
Pyogenic spondylitis	7 (9.5%)
Deep-seated abscess	7 (9.5%)
Mycotic aneurysm	4 (5.4%)
Pyogenic arthritis	3 (4.1%)
Spinal epidural abscess	1 (1.4%)
Acute heart failure	11 (14.9%)
Total complications per patient	
None	5 (6.8%)
One	20 (27.0%)
Two	20 (27.0%)
Three	19 (25.7%)
Four	10 (13.5%)
Over five	N/A

†: microhemorrhage: an asymptomatic cerebral hemorrhage that can be diagnosed only by cranial MRI.

Staphylococcus aureus as the most common causative bacteria, diabetes mellitus and chronic dermatological disorders as comorbidities, CNS disorders and embolisms as complications, and patients without cardiac murmurs. In addition, the incidence of complicated AHF and the number of patients undergoing valvular surgery were significantly higher in the report from only cardiology departments in 2013 than in the present study (5). These differences emphasize the importance of studying patients from all departments in which patients with IE may have been treated in order to accurately determine their clinical features, making the present study quite valuable.

One of the remarkable findings of the present study was the relatively large number of patients with IE without cardiac murmurs. Although cardiac murmurs are a clue to a possible diagnosis of IE, 2.0-20.0% of patients with IE reportedly do not have cardiac murmurs (7, 13-15). Furthermore, apparently structurally normal valves were reportedly observed in 26.0% of patients with IE with no underlying cardiac disease recognized before the onset of IE (16). In the present study, there was an even higher rate of patients without cardiac murmurs on admission (37.8%), together with 17.6% of patients without any valvular disease and 14.8% with only minor valvular disease below grade I. These apparent discrepancies may be attributable to the marked advances in and/or much wider availability of imaging modalities, such as echocardiography, CT, and MRI, in Japan than in other countries (9, 17) and/or clinicians' increased recognition of IE following the release of the modified Duke's criteria in 2000 (2). These factors may account for the more frequent diagnosis of IE in patients without

Table 7. Frequency of Complications by Main Causative Bacteria of IE.

Complications	Negatives n=10	*Staphylococcus aureus* n=21	*Streptococcus viridans* n=14	*Enterococcus* n=5	Polymicrobial n=5
Central nerve system disorder	7 (70.0%)	16 (76.2%)	8 (57.1%)	2 (40.0%)	2 (40.0%)
Embolic stroke	6 (60.0%)	13 (61.9%)	7 (50.0%)	2 (40.0%)	2 (40.0%)
Cerebral hemorrhage†	3 (30.0%)	13 (61.9%)	3 (14.3%)	N/A	1 (20.0%)
Glomerulonephritis	5 (50.0%)	12 (57.1%)	5 (23.8%)	2 (40.0%)	2 (40.0%)
Extracranial embolism	3 (30.0%)	7 (33.3%)	6 (28.6%)	2 (40.0%)	1 (20.0%)
Spleen	2 (20.0%)	5 (23.8%)	3 (14.3%)	2 (40.0%)	N/A
Kidney	2 (20.0%)	1 (4.8%)	5 (23.8%)	N/A	N/A
Pulmonary	N/A	3 (14.3%)	N/A	N/A	1 (20.0%)
Liver	2 (20.0%)	1 (4.8%)	N/A	N/A	N/A
Superior mesenteric artery	N/A	N/A	N/A	N/A	N/A
DIC	1 (10.0%)	13 (61.9%)	1 (7.1%)	N/A	1 (20.0%)
Disseminated infection	N/A	5 (23.8%)	2 (9.5%)	N/A	2 (40.0%)
Pyogenic spondylitis	N/A	3 (14.3%)	2 (9.5%)	N/A	1 (20.0%)
Deep-seated abscess	N/A	5 (23.8%)	N/A	N/A	1 (20.0%)
Mycotic aneurysm	N/A	N/A	1 (7.1%)	N/A	N/A
Pyogenic arthritis	N/A	2 (9.5%)	N/A	N/A	1 (20.0%)
Spinal epidural abscess	N/A	1 (4.8%)	N/A	N/A	N/A
Acute heart failure	1 (10.0%)	2 (9.5%)	N/A	2 (40.0%)	2 (40.0%)

All data are expressed as N (%).

†: including an asymptomatic cerebral hemorrhage that can be diagnosed only by cranial MRI.

IE: infective endocarditis, DIC: disseminated intravascular coagulation

Table 8. Frequency of Complications by Main Infected Valve.

Complications	Mitral valve n=36	Aortic valve n=19	Multiple valve n=11	Prosthetic valve n=11
Central nerve system disorder	22 (61.1%)	13 (68.4%)	8 (72.7%)	6 (54.5%)
Embolic stroke	18 (50.0%)	11 (57.9%)	8 (72.7%)	5 (45.5%)
Cerebral hemorrhage†	11 (30.6%)	8 (42.1%)	3 (27.3%)	4 (36.4%)
Glomerulonephritis	12 (33.3%)	12 (57.1%)	5 (45.5%)	6 (54.5%)
Extracranial embolism	12 (33.3%)	8 (42.1%)	5 (45.5%)	5 (45.5%)
Spleen	9 (25.0%)	5 (26.3%)	3 (27.3%)	4 (36.4%)
Kidney	3 (8.3%)	3 (15.8%)	3 (27.3%)	2 (18.2%)
Pulmonary	3 (8.3%)	3 (15.8%)	N/A	1 (9.1%)
Liver	2 (5.6%)	N/A	N/A	N/A
Superior mesenteric artery	N/A	N/A	1 (9.1%)	N/A
DIC	13 (36.1%)	5 (26.3%)	2 (18.2%)	4 (36.4%)
Disseminated infection	6 (16.7%)	1 (5.3%)	3 (27.3%)	N/A
Pyogenic spondylitis	3 (8.3%)	1 (5.3%)	2 (18.2%)	N/A
Deep-seated abscess	3 (8.3%)	1 (5.3%)	N/A	N/A
Mycotic aneurysm	2 (5.6%)	N/A	1 (9.1%)	N/A
Pyogenic arthritis	1 (2.8%)	1 (5.3%)	N/A	N/A
Spinal epidural abscess	N/A	N/A	N/A	N/A
Acute heart failure	5 (13.9%)	3 (15.8%)	2 (18.2%)	1 (9.1%)

All data are expressed as N (%).

†: including an asymptomatic cerebral hemorrhage that could be diagnosed only by cranial MRI.

DIC: disseminated intravascular coagulation

cardiac murmurs or underlying valvular disease in Japan than in other countries.

The detection of common complications of IE, such as AHF, CNS disorders, kidney injuries, extracranial embolism, or pyogenic spondylitis, can also be a clue to a correct diagnosis of IE in patients without definite cardiac murmurs or any underlying valvular disease (6, 18, 19). In the present study, the average number of complications per patient was 2.1, with 66.2% of patients having ≥2 complications (Table 6), which is far higher than the 17.0% reported in a previous study in 1992 (18). This increase is considered to be attributable to rapid and marked advances in diagnostic technologies, including imaging modalities, such as CT or MRI, facilitating the detection of complications and potentially an accurate diagnosis of IE (9). Physicians should bear in mind that there is a high probability that a patient with IE will have 2 or more complications.

Embolism is a major and characteristic complication of IE (20-22). Reports from Sweden, the USA, and France from 1999 to 2008 have shown that the most frequent consequence of embolism is embolic stroke, including asymptomatic stroke (15.2% to 65.0%) (20, 23), followed by splenic infarction (7.9% to 40.0%) (21-23). In our study, there was a considerably higher incidence of embolism as a complication than in the study reported in 2000 from Japan (7). Specifically, in our study, embolism occurred in 68.9% of patients overall, comprising embolic stroke in 52.7%, splenic infarction in 23.0%, renal infarction in 12.2%, and septic pulmonary embolism in 10.8%, whereas in the 2000 study in Japan, embolism occurred in 24.0% of patients overall, comprising embolic stroke in 11.0%, splenic infarction in 7.0%, renal infarction in 4.0%, and septic pulmonary embolism in 2.0% (7). Of note, in the present study, 90.5% of patients had undergone cranial CT, 66.2% cranial MRI, and 68.9% simultaneous thoracic and abdominal CT with contrast enhancement. The present and 2000 study (7) both enrolled patients from all departments; the difference in the incidence of diagnosed embolism may thus be due to advances in imaging modalities (9). Because of its high incidence, it is essential to thoroughly investigate the presence of embolism as a complication, especially embolic stroke and splenic infarction, with cranial CT or MRI and thoracic and abdominal CT with contrast enhancement, even in patients with no clinical evidence of embolism.

Renal disorders are also reportedly a major complication of IE; these mainly consist of renal infarction, renal abscess, glomerulonephritis (such as focal and diffuse glomerulonephritis caused by immune complex deposition), and acute interstitial nephritis as a complication of medications, such as antibiotic agents (24). Interestingly, there is great variation in the reported incidence of glomerulonephritis, ranging from almost null to approximately 26.0% (7, 24). In the present study, there was a much higher incidence of glomerulonephritis than reported previously; indeed, 34 cases (45.9%) were detected from the first visit to a doctor to the end of the first week of admission to our hospital. The hematuria or proteinuria detected in our study may have been attributable to factors other than glomerulonephritis, such as underlying renal diseases present before the onset of IE or medications to treat IE, as it is difficult to distinguish between these possibilities without performing a renal biopsy. However, the complication of glomerulonephritis was

the likely diagnosis in the 60.9% of patients with hematuria and proteinuria who did not have underlying kidney diseases or diabetes mellitus, had not received antibiotics before admission to our hospital, and had no evidence of renal infarction or renal abscess. In this context, it is necessary to perform a urinalysis when IE is suspected, as the presence of hematuria and proteinuria can be vital clues to detecting the complication of glomerulonephritis without performing a renal biopsy.

Because the present study was a single-hospital-based retrospective study, it is necessary to interpret the incidence of complications with care, bearing in mind that most previous studies failed to mention the rates of performing various investigations, including imaging studies. Some patients might have been excluded inappropriately because the IE patients in the present study were identified by ICD-10.

In conclusion, while about 40% and 30% of our patients with IE did not have cardiac murmurs or underlying valvular disease or only minor valvular disease (below grade I), respectively, more than 60% had ≥2 complications. When IE is suspected clinically, especially in patients without cardiac murmurs, clinically significant valvular disease, or symptoms suggesting the presence of complications, it is essential to thoroughly investigate the possible common complications of IE, particularly both intracranial and extracranial embolism and glomerulonephritis, in order to facilitate a timely and correct diagnosis.

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The authors state that they have no Conflict of Interest (COI).

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