ORIGINAL RESEARCH

Status Quo of Diagnostic Procedures and Treatment of Inpatients with Infective Endocarditis at the Department of General Medicine at a University Hospital in a Suburban City in Japan: A Single-Hospital-Based Retrospective Study

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Background: Our hospital's department of general medicine is often involved in the diagnosis and treatment of diseases that are considered by other hospitals or other departments in our hospital to be difficult to diagnose correctly.

Objective: The aim of this study was to clarify how patients with infective endocarditis (IE) being admitted to our hospital's department of general medicine were examined and treated and to elucidate their prognosis compared with patients admitted to other departments.

Materials and Methods: Inpatients of Saga University Hospital with definite IE from September 2007 to August 2017 were divided into 2 groups: those admitted to the general medicine department (the GM group) and those admitted to other departments (the non-GM group).

Results: Seventy-four patients were included; 17 (23%) were admitted to the general medicine department. In the GM group, the percentage of patients diagnosed with definite or suspected IE was lower (0% vs 32%, $p=0.008$), as was the rate of patients with echocardiographic findings that fulfilled the major modified Duke's criteria (71% vs 98%, $p \leq 0.001$), preadmission. The GM group had higher percentages of patients with back or joint pain (41% vs 9%, $p=0.001$) and complications, including pyogenic spondylitis (35% vs 2%, $p \leq 0.001$), deep-seated abscesses (24% vs 5%, $p=0.024$), pyogenic arthritis (18% vs 0%, $p=0.001$), and glomerulonephritis (77% vs 37%, $p=0.004$) than did the non-GM group. Mortality within 30 days of admission to our hospital (12% vs 14%, $p=0.753$) and overall in-hospital mortality (12% vs 18%, $p=0.570$) did not significantly differ.

Conclusion: The general medicine department could have accurately diagnosed IE, given appropriate treatments, and obtained similar prognoses to those of IE patients treated by other departments, including cardiology and cardiovascular surgery, even in patients for whom diagnosing IE was more difficult or who had less typical echocardiographic findings preadmission.

Keywords: infective endocarditis, echocardiographic findings of infective endocarditis, general medicine, cardiology, cardiovascular surgery

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Introduction

Infective endocarditis (IE) reportedly has an annual incidence that reaches 32.4 per 1,000,000 people.[1] Many clinical departments in addition to those specializing in cardiology or cardiovascular surgery can be involved in diagnosing and treating

patients with IE owing to its various nonspecific manifestations and findings on physical and laboratory examinations.[2] Regardless of which department the patient is admitted to, modified Duke's criteria are usually used to make the diagnosis.[3] Among these departments, the general medicine departments, especially at university hospitals in Japan, which are often in charge of diagnosing diagnostically challenging diseases, including fevers of unknown origin, are likely to see patients with IE.[4–7] Our previous research showed that the general medicine department of Saga University Hospital in Japan diagnosed and treated the third-highest number of inpatients with IE after the departments of cardiology and cardiovascular surgery.[4]

The department of cardiovascular surgery plays a clearly delineated role in treating IE in terms of when and how to operate and how to manage patients after surgery.[8] The roles of cardiology departments in Japan were depicted in a report showing the clinical features of IE in Japanese patients treated and registered only by cardiologists at multiple centers through the web-based registration system, Cardiac Disease Registration.[9] To our knowledge, however, the clinical characteristics of patients with IE who have been admitted to and treated by general medicine departments, especially in university hospitals in Japan, are unreported. The aim of this study was to clarify how patients with IE admitted to our hospital's department of general medicine were examined and treated and to elucidate their prognosis.

We herein report how the general medicine department of Saga University Hospital, located in a suburban city in Japan, is involved in diagnosing and treating IE by comparing the characteristics of patients treated by the general medicine department to those of patients treated by other departments, including cardiology and cardiovascular surgery.

Materials and Methods
Study Design and Patients
The present study was a single-hospital-based retrospective study, performed as a secondary analysis of our previous report of the clinical status quo of IE at a university hospital in Japan, especially regarding clinical manifestations, by investigating all patients diagnosed with IE admitted to any departments of Saga University Hospital, Japan, from 2007 to 2017.[4] As in our previous study, inpatients diagnosed with IE at Saga University Hospital were identified as per 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 modified Duke's clinical criteria or pathological criteria were enrolled in this retrospective study. Subjects were divided into 2 groups: patients who were admitted to the department of general medicine, including those only transiently before moving to another department (the GM group) and those admitted to any other departments without having been admitted to the general medicine department during this hospitalization (the non-GM group). The primary outcome of this study was to clarify the clinical manifestations of patients with IE in the GM group, by comparing the characteristics of patients in the non-GM group.

Setting
Saga University Hospital is 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 inpatient beds in 29 clinical departments, including the departments of general medicine, cardiology, and cardiovascular surgery. The hospital provides high-level medical services mainly for patients in acute disease phases. The Division of Infectious Disease/Prevention and Control in our hospital usually supervises the diagnosing of infectious diseases, including IE, and chooses the appropriate antibiotics and treatment durations for all patients with positive blood culture results as well as when other departments request consultations. The general medicine department of this hospital manages the first-touch practice of outpatients without a reference from their primary doctors, in addition to treating both in- and outpatients with common diseases, fevers of unknown origin, diseases that are difficult to correctly diagnose, and complicated pathological situations requiring intensive care.[4–7] In this study, patients suspected of having, or diagnosed with IE before admission would, in principle, be seen by the endocarditis team of the department of cardiology and cardiovascular surgery. In comparison, patients with non-specific symptoms and signs such as fever of unknown origin, consciousness disorder, paralysis, or rash, who were not suspected of having, or were not diagnosed with IE prior to referral, would initially be seen by the department of general medicine, emergency medicine, neurology, or dermatology or whatever department seemed appropriate. When such patients are diagnosed with, or are suspected of

having, IE in our hospital, the Department of Cardiology or Cardiovascular Surgery is consulted to determine whether they should be treated by the specialist team or by each original department to which they were admitted. Thus, some patients are treated by the department of general medicine throughout their hospitalization and others by the department of cardiology or cardiovascular surgery later in the admission.

Data Sources

Three clinicians belonging to the department of general medicine in our hospital reviewed the medical charts and collected data on potentially eligible patients. Survey items are shown in Supplement 1. Nosocomial infection was defined as an infection acquired later than 48 hours after admission to our hospital caused by IE and manifesting new symptoms and signs. As for transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) findings, patients who fulfilled the major modified Duke's criteria were considered echocardiography-positive. Causative bacteria were determined from the results of blood cultures and cultures or polymerase chain reaction tests performed on the operated valves. Presence of acute heart failure (AHF), central nervous system (CNS) disorders, extracranial embolism, disseminated infection, glomerulonephritis, and disseminated intravascular coagulation (DIC) was 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 a low left ventricular ejection fraction (<50%). Embolic stroke and cerebral hemorrhaging were defined as CNS disorders. Disseminated infections included pyogenic spondylitis, pyogenic arthritis, spinal epidural abscesses, deep-seated abscesses, and mycotic aneurysms. Complicated glomerulonephritis was defined as the following abnormal findings on urinalysis: ≥1+ blood and ≥1+ protein on the 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]

Data Analysis

Continuous variables are expressed as the median and interquartile range, and were compared with the Mann–Whitney U-test. Categorical variables are expressed as percentages and were compared with χ^2 tests. Missing values were classified as "no abnormal findings" in each

analysis. Statistical significance was set at $p<0.05$. IBM SPSS Statistics (version 25, IBM, Armonk, New York, USA) and Microsoft Excel 2016 software were used for the statistical analyses.

Ethical Consideration

All subjects provided consent as per the comprehensive agreement method of our hospital, and patients' anonymity was protected. The Ethics Committee of Saga University Hospital (file number 2019–01-07) approved the study, which was conducted in accordance with the guidelines of the 1975 Declaration of Helsinki.

Results
Enrollment and Allocation of Study Patients

Of 110 patients identified as having IE using the ICD-10, 70 were diagnosed with "definite IE" according to the modified Duke's clinical criteria after reviewing their medical charts. Nine of 40 patients initially diagnosed with "probable IE" or "not IE" underwent valvular operations; four of these were initially diagnosed with "definite IE" according to the modified Duke's pathological criteria. Thus, 74 patients were diagnosed with "definite IE" according to either clinical or pathological criteria and accordingly enrolled and analyzed in our previous study[4] (Figure 1). Seventy-four patients were admitted to 15 clinical departments: cardiology (23 cases, 31%), general medicine (14, 19%), cardiovascular surgery (9, 12%), emergency medicine (6, 8%), nephrology (5, 7%), neurology (4, 5%), gastroenterology (3, 4%), hepatology (3, 4%), and other departments (7, 10%). Three of 60 patients initially admitted to the departments of urology, orthopedics, and cardiology were subsequently moved to the department of general medicine. Consequently, 17 patients (23%) were allocated to the GM group, and the remaining 57 patients (77%) were allocated to the non-GM group (Figure 2).

Patient Characteristics

Table 1 shows the patients' characteristics. The GM group had no patients diagnosed with definite or suspected IE before hospitalization to our hospital (0 [0%] vs 18 [32%], $p=0.008$). In addition, more patients in the GM group had back or joint pain within 2 months before the first visit to our hospital than did the non-GM group (41% vs 9%, $p=0.001$). Although more patients had chronic dermatological disorders as comorbidities in the GM
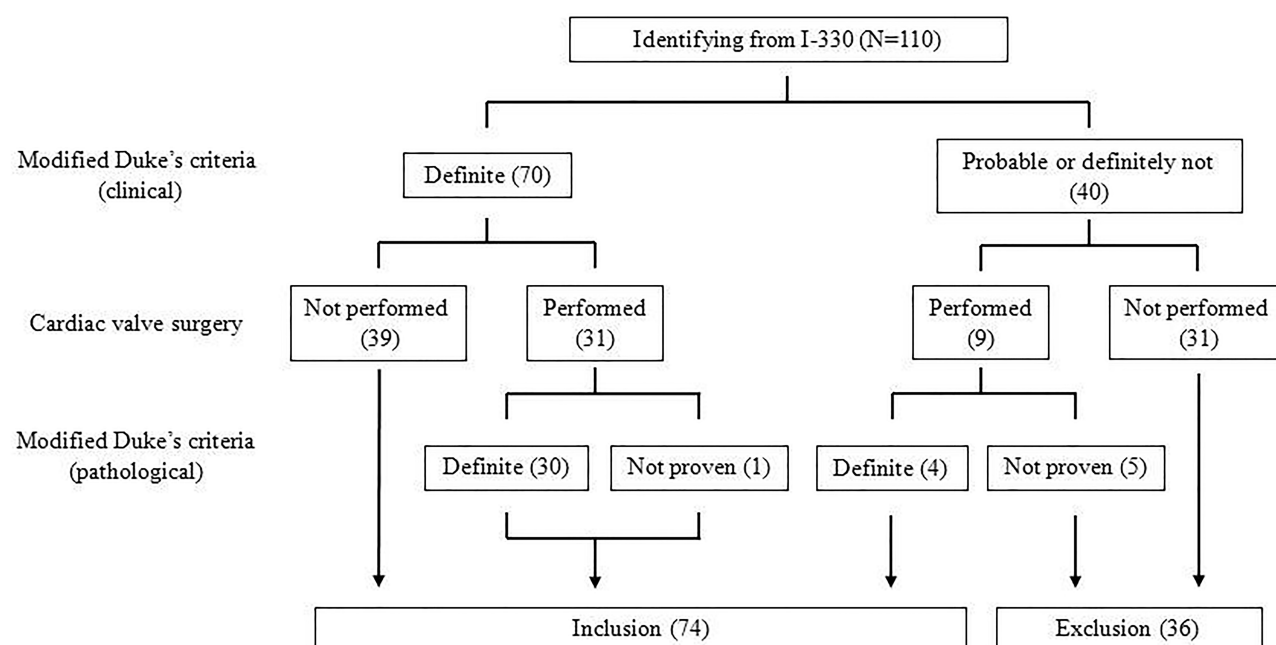
Figure 1 Inclusion criteria. Inpatients diagnosed with IE at Saga University Hospital from September 2007 to August 2017 were identified as per the International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10, code number I-330). Of 110 inpatients, 70 had "definite IE", and 40 had "probable IE" or "no IE". Cardiac valvular surgeries were performed on nine of 40 patients with "probable IE" or "no IE", after which, 4 were diagnosed with "definite IE" according to the modified Duke's pathological criteria. All 74 patients diagnosed with "definite IE" according to either the modified Duke's clinical criteria or pathological criteria were enrolled and analyzed in the present study.
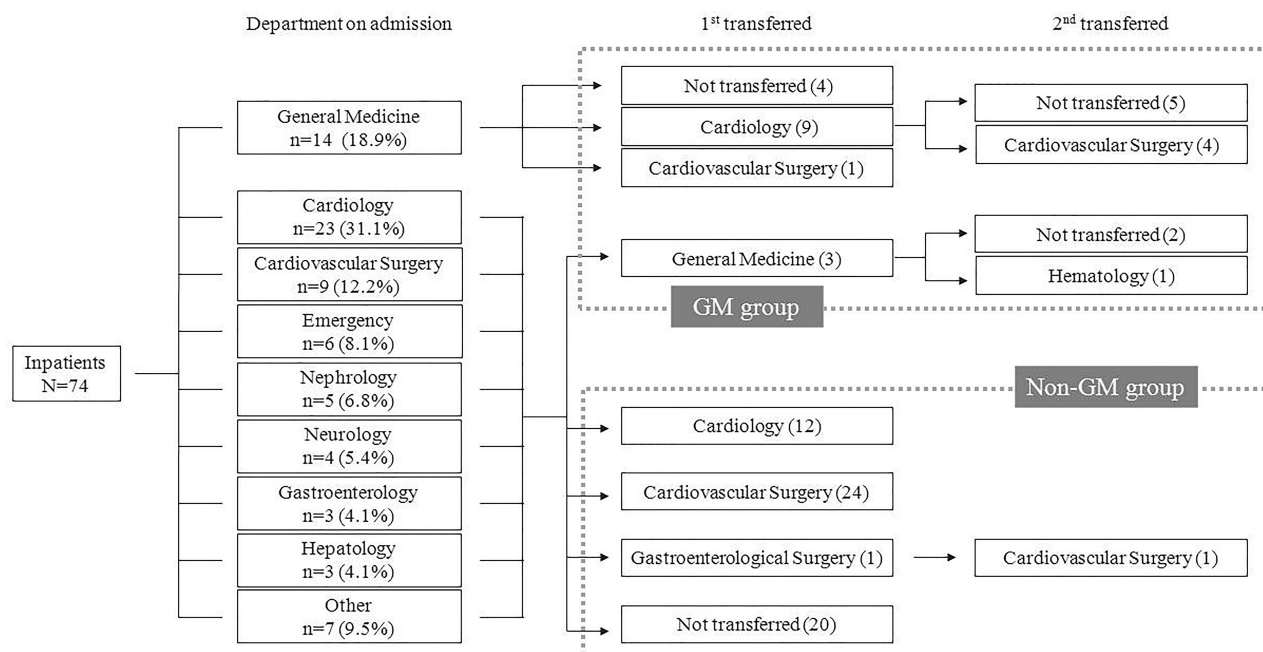
Figure 2 Allocation to the general medicine or non-general medicine group. Seventy-four enrolled patients were admitted to 15 different clinical departments; 14 of these patients were admitted to the department of general medicine. Three patients of 60 who were initially admitted to the departments of urology, orthopedics, and cardiology were subsequently moved to the department of general medicine. Seventeen patients (23%) were allocated to the group that had a "history of being admitted to the department of general medicine (GM group)." The remaining 57 patients (77%) were allocated to the group "without a history of being admitted to the department of general medicine (non-GM group)". Hematology, Pediatrics, Orthopedics, Neurosurgery, Dermatology, Plastic Surgery, and Urology were included in "Other departments".

Table 1 Patient Characters

Characteristic	Total (N = 74)	GM (N=17)	Non-GM (N=57)	*p* value
Age, year[†]	67 (54–76)	71 (53–79)	66 (54–75)	0.643
Aged over 60 years	51 (69)	11 (65)	40 (70)	0.669
Male	42 (57)	8 (47)	34 (60)	0.358
Transferred by ambulance	36 (49)	6 (35)	30 (53)	0.209
Nosocomial onset	4 (5)	N/A	4 (7)	0.261
Duration of hospital stay[†]	41 (29–61)	40 (30–61)	40 (31–61)	0.857
Cause of referral				
IE diagnosed and/or IE suspected	18 (24)	N/A	18 (32)	0.008
IE operation	4 (5)	N/A	4 (7)	0.261
Used antibiotics prior to blood culture	32 (43)	7 (41)	25 (44)	0.845
Past medical history				
Diabetes	15 (20)	2 (12)	13 (23)	0.320
Prosthetic replacement	11 (15)	2 (12)	9 (16)	0.682
Intravascular device	11 (15)	1 (6)	10 (18)	0.236
Using immunosuppressant	9 (12)	2 (12)	7 (12)	0.954
Chronic dermatological disorder	8 (11)	4 (24)	4 (7)	0.054
Hemodialysis	6 (8)	N/A	6 (11)	0.163
Dental problem				
Dental disease	29 (39)	7 (41)	22 (39)	0.848
Dentistry going to hospital[††]	15 (35)	2 (12)	13 (23)	0.320
Invasive dental treatment history[††]	13 (18)	1 (6)	12 (21)	0.149
Symptoms within 2 months				
Fever (over 37°C)	54 (73)	13 (77)	41 (72)	0.711
Malaise	25 (34)	7 (41)	18 (32)	0.463
Consciousness disorder	18 (24)	3 (18)	15 (26)	0.465
Dyspnea	18 (24)	4 (24)	14 (25)	0.931
Decreased appetite	16 (22)	6 (35)	10 (18)	0.119
Arthralgia/Back pain	12 (16)	7 (41)	5 (9)	0.001
Nausea/Vomiting	12 (16)	4 (24)	8 (14)	0.351
Paralysis/Weakness	12 (16)	2 (12)	10 (18)	0.570
Symptoms of a common cold[†††]	5 (7)	2 (12)	3 (5)	0.349
Difficulty in body movement	4 (5)	1 (6)	3 (5)	0.921
Weight loss more than 10%	4 (5)	1 (6)	3 (5)	0.921
Surgical therapy	35 (47)	6 (35)	29 (51)	0.259
Mortality				
30 days mortality	10 (14)	2 (12)	8 (14)	0.753
In-hospital mortality	12 (16)	2 (12)	10 (18)	0.570

Notes: All values are n (%). [†]This value is a median level (inter-quartile range). [††]Within a half year. [†††]Symptoms of a common cold means cough, sputum, and sore throat.

group than in the non-GM group, the difference was not significant (24% vs 7%, *p*=0.054). Age, sex, transportation by ambulance, antibiotic treatment prior to blood culturing, dental disease on admission to our hospital, having visited a dental clinic within 6 months, invasive dental treatments within 6 months, valvular surgery for IE during the hospital stay, mortality within 30 days from admission to our hospital, and overall in-hospital

mortality did not significantly differ between the two groups. Table 2 shows the laboratory findings on admission to our hospital, none of which differed significantly between the groups.

Microbiology

Table 3 shows the microbiological characteristics. Blood cultures were performed on all 74 patients (100%), including

Table 2 Laboratory Findings at the First Visit in Our Hospital

	Total (N=74)	GM (N=17)	Non-GM (N=57)	*p* value
White blood cell (×10³/μL)	12.6 (8.7–17.1)	16.8 (8.8–20.0)	11.9 (8.7–15.8)	0.237
Neutrophil (%)	86.5 (77.2–92.8)	91.8 (81.7–95.6)	85.3 (75.5–92.5)	0.093
Platelet (×10⁴/μL)	12.7 (8.6–22.5)	16.0 (9.5–27.9)	12.6 (0.8–21.5)	0.206
FDP (μg/mL)	17.7 (8.2–39.6)	18.6 (11.7–34.1)	16.9 (7.0–42.1)	0.856
D-dimer (μg/mL)	6.7 (2.4–19.0)	6.8 (2.3–10.6)	6.5 (2.4–20.1)	0.738
PT-INR	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.4)	0.378
Albumin (g/dL)	2.6 (2.2–3.1)	3.0 (1.8–3.6)	2.6 (2.2–3.0)	0.459
Total bilirubin (mg/dL)	0.9 (0.6–1.3)	0.9 (0.7–1.3)	0.8 (0.6–1.3)	0.540
AST (IU/L)	34.0 (22.8–56.2)	41.0 (18.0–62.0)	33.0 (23.5–56.5)	0.705
ALT (IU/L)	22.0 (14.8–41.3)	23.0 (14.0–45.5)	22.0 (14.5–40.5)	0.842
LDH (IU/L)	326.0 (250.0–428.0)	336.0 (240.0–400.0)	309.0 (251.0–443.0)	0.817
BUN (mg/dL)	23.3 (14.4–34.0)	24.1 (18.0–30.8)	21.2 (14.2–39.2)	0.594
Creatinine (mg/dL)	1.0 (0.7–1.6)	0.9 (0.7–1.3)	1.0 (0.7–1.7)	0.729
Sodium (mEq/L)	136.0 (132.0–139.0)	133.0 (126.5–138.0)	137.0 (132.5–139.0)	0.099
Potassium (mEq/L)	4.1 (3.7–4.5)	3.9 (3.6–4.7)	4.2 (3.8–4.5)	0.827
Chlorine (mEq/L)	100.0 (95.8–104.0)	97.0 (90.0–102.5)	101.0 (96.0–104.0)	0.153
C-reactive protein (mg/dL)	7.5 (3.4–15.1)	11.4 (4.3–24.4)	7.2 (2.8–14.2)	0.152

Note: Values are median level (interquartile range).
Abbreviations: 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.

Table 3 Microbiological Findings

Microbiological Findings	Total (N = 74)	GM (N=17)	Non-GM (N=57)	*p* value
Negative blood culture	10 (14)	2 (12)	8 (14)	0.810
Staphylococcus. aureus	21 (28)	4 (24)	17 (30)	0.613
Methicillin sensitive *Staphylococcus aureus*	13 (18)	4 (24)	9 (16)	0.462
Methicillin resistant *Staphylococcus aureus*	8 (11)	N/A	8 (14)	0.102
Viridans-group *Streptococci*	14 (19)	2 (12)	12 (21)	0.391
Streptococcus. gallolyticus	1 (1)	N/A	1 (2)	0.582
Enterococcus spp.	5 (7)	1 (6)	4 (7)	0.870
Polymicrobial	5 (7)	2 (12)	3 (5)	0.349
Others†	18 (24)	6 (35)	12 (21)	0.230

Notes: All values are n (%). †*Staphylococcus* spp. 7 (10), *Streptococcus* spp. 6 (8), *Corynebacterium* spp. 2 (3), *Escherichia coli* 1 (1), *Lactococcus graviae* 1 (1), *Aerococcus urinae* 1 (1).

those performed at the patients' previous hospitals. Sixty-four patients (87%) were positive; 10 patients (14%) were negative. The rates of positive blood cultures did not significantly differ between the GM and non-GM groups (88% vs 86%, *p*=0.810), nor did they significantly differ in causative bacteria, ie, *Staphylococcus aureus* (24% vs 30%, *p*=0.613), viridans-group *Streptococci* (12% vs 21%, *p*=0.391), *Streptococcus gallolyticus* (0% vs 2%, *p*=0.582), and

Enterococcus spp. (6% vs 7%, *p*=0.870), which fulfilled the major modified Duke's criteria.

Echocardiologic Data

In the present study, TTE was performed on all 74 patients (100%). TEE was performed on 26 patients (35%): 6/17 patients (35%) in the GM group and 20/57 (35%) in the non-GM group. TEE was not performed in 48 patients (65%), 43 of whom were diagnosed only by TTE without requiring TEE, and 2 of them died before TEE had been performed. The reasons for the remaining 3 patients not undergoing TEE could not be identified. The GM group had more negative results that did not fulfill the major modified Duke's criteria than did the non-GM group via TTE or TEE (29% vs 2%, *p*<0.001), especially on the TTE (53% vs 2%, *p*<0.001). The infected valve type, presence or absence of a prosthetic valve, and presence or absence of valvular diseases more severe than grade I did not significantly differ between the groups (Table 4).

Imaging Studies Other Than Echocardiography

Table 5 shows the rates for which imaging studies other than echocardiography were performed. Spinal magnetic resonance imaging (MRI) (47% vs 7%, *p*<0.001), especially lumbar MRIs (41% vs 4%, *p*<0.001) were

Table 4 The Findings of Microbiology and Echocardiology

Echocardiologic Findings	Total (N = 74)	GM (N=17)	Non-GM (N=57)	*p* value
Site of infected valves				
Mitral valve	36 (49)	6 (35)	30 (53)	0.209
Aortic valve	19 (26)	5 (29)	14 (25)	0.688
Multiple valves	11 (15)	1 (6)	10 (18)	0.236
Tricuspid valve	2 (3)	1 (6)	1 (2)	0.357
Pulmonic valve	1 (1)	N/A	1 (2)	0.582
Unknown	5 (7)	4 (24)	1 (2)	0.002
Prosthetic valve	11 (15)	2 (12)	9 (16)	0.682
Valvular disease over grade II				
Mitral regurgitation	33 (45)	6 (35)	27 (47)	0.379
Aortic regurgitation	23 (31)	4 (24)	19 (33)	0.443
Tricuspid regurgitation	18 (24)	5 (29)	13 (23)	0.577
Pulmonic regurgitation	2 (3)	N/A	2 (4)	0.434

Note: All values are n (%).

Table 5 Performing of Imaging Tests Excluding Echocardiology

Imaging Tests	Total (N = 74)	GM (N=17)	Non-GM (N=57)	*p* value
Head CT[†]	67 (91)	16 (94)	51 (90)	0.566
Head MRI[††]	49 (66)	13 (77)	36 (63)	0.308
Chest enhanced CT	60 (81)	14 (82)	46 (81)	0.879
Abdominal enhanced CT	52 (70)	13 (77)	39 (68)	0.524
Chest and abdominal CT	51 (69)	13 (77)	38 (67)	0.443
Coronary CT	14 (19)	1 (6)	13 (23)	0.118
Spinal MRI	12 (16)	8 (47)	4 (7)	<0.001
Lumbar spinal MRI	9 (12)	7 (41)	2 (4)	<0.001

Notes: All values are n (%). †Computed tomography. ††Magnetic resonance imaging.

performed more often in the GM group than in the non-GM group. The rates at which other imaging studies were performed did not significantly differ between the groups.

Complications

Table 6 shows the complications in the present study. More patients in the GM group than in the non-GM group had glomerulonephritis (77% vs 37%, *p*=0.004), pyogenic spondylitis (35% vs 2%, *p*<0.001), pyogenic arthritis (18% vs 0%, *p*=0.001), and deep-seated abscesses (24% vs 5%, *p*=0.024). A higher frequency of urinalyses was performed in the GM group than in the non-GM group (94% vs 63%, *p*=0.014). CNS disorders including embolic stroke and cerebral hemorrhaging; extracranial embolism including splenic infarction, renal infarction, pulmonary embolism, pulmonary infarction, hepatic infarction and superior mesenteric artery embolism; DIC; and AHF did not significantly differ between the groups, nor did the total number of complications and embolisms per patient.

Discussion

This is the first report to compare the clinical characteristics of patients with IE admitted to and treated in the general medicine department at a university hospital in Japan to those of patients admitted to other departments without a history of admission to the general medicine department. Cardiology and cardiovascular surgery are two representative departments involved in diagnosing and treating IE. The roles of the cardiovascular surgery department in treating IE are defined in the consensus guidelines for IE published by the American Association for Thoracic Surgery in 2016, which describe when and how to operate and how to manage patients after surgery.[8] Furthermore, the roles of the cardiology department in Japan were described in a report of a multicenter study of cardiologists in 2013, which described the clinical features of IE treated by the cardiology department, such as the predisposing background, causative microorganisms, appropriate antibiotics, echocardiographic findings, and complications.[9] However, as we previously reported, the general medicine

Table 6 Complications

Complications	Total (N = 74)	GM (N=17)	Non-GM (N=57)	*p* value
Neurologic complications	45 (61)	9 (53)	36 (63)	0.449
Embolic stroke	39 (53)	8 (47)	31 (54)	0.595
Cerebral hemorrhage	17 (23)	1 (6)	16 (28)	0.056
Cerebral hemorrhage including micro hemorrhage[†]	23 (31)	3 (18)	20 (35)	0.173
Glomerulonephritis	34 (46)	13 (77)	21 (37)	0.004
Hematuria[††]	43 (58)	14 (82)	29 (51)	0.021
Proteinuria[†††]	39 (53)	14 (82)	25 (44)	0.005
Embolism except embolic stroke	27 (37)	4 (24)	23 (40)	0.206
Spleen	17 (23)	1 (6)	16 (28)	0.056
Kidney	9 (12)	1 (6)	8 (14)	0.367
Pulmonary	8 (11)	4 (24)	4 (7)	0.054
Liver	2 (3)	N/A	2 (4)	0.434
Mesentery artery	1 (1)	N/A	1 (2)	0.582
Disseminated intravascular coagulation	24 (32)	6 (35)	18 (32)	0.774
Metastatic infection	14 (19)	8 (47)	6 (11)	0.001
Pyogenic spondylitis	7 (10)	6 (35)	1 (2)	<0.001
Deep seated abscess	7 (10)	4 (24)	3 (5)	0.024
Mycotic aneurysm	4 (5)	2 (12)	2 (4)	0.186
Pyogenic arthritis	3 (4)	3 (18)	N/A	0.001
Spinal epidural abscess	1 (1)	1 (6)	N/A	0.065
Acute heart failure	11 (15)	2 (12)	9 (16)	0.682
Counts of coexistence complications				
0 count	5 (7)	N/A	5 (9)	0.206
1 count	20 (27)	3 (18)	17 (30)	0.321
2 count	20 (27)	5 (29)	15 (26)	0.801
3 count	19 (26)	6 (35)	13 (23)	0.301
4 count	10 (14)	3 (18)	7 (12)	0.570
over 5 count	N/A	N/A	N/A	NA

Notes: All values are n (%). [†]Micro hemorrhage is an asymptomatic cerebral hemorrhage which can be diagnosed only with head MRI. [††]≥1+ blood. [†††]≥1+ protein.

department of our hospital treated the third-highest number of inpatients with IE,[4] thus emphasizing the significance of the present study.

The nonspecific features, manifestations, and laboratory examination findings make suspecting and diagnosing IE itself challenging.[2] Modified Duke's criteria, whose two major criteria include consecutive positive blood cultures and presence of vegetation usually detected by echocardiography, are used worldwide to diagnose IE.[3] Therefore, failure to detect the presence of vegetation by echocardiography could make IE more complicated to diagnose.[3] The present study showed that many patients in the GM group were not suspected to IE or diagnosed with definite IE because of negative echocardiography results obtained before admission to our hospital. Surprisingly, in the present study, we even found a patient with IE who had

negative results on eight consecutive blood cultures and two TEEs. The IE was conclusively diagnosed only via valvular surgery, showing the extreme difficulties in correctly diagnosing IE in the GM group.[5] Accordingly, we conclude that our hospital's department of general medicine correctly diagnosed inpatients with IE who were difficult to diagnose and treat and who had not been suspected of having, or been diagnosed with, IE on admission because of their atypical clinical manifestations. The combination of ^{18}F-FDG positron emission tomography and computed tomographic imaging (^{18}F-FDG PET/CT) could be useful tools for making diagnoses in patients in whom the diagnosis was obscure, such as IE complicating a prosthetic valve or intracardiac device, or detection of embolic complications, metastatic infections, or underlying cancers.[13] However, the Japanese Health Insurance

system reimburses the cost of ^{18}F-FDG PET/CT only when this procedure is performed to detect a primary lesion of metastatic cancer of unknown origin, which may explain why many patients did not undergo ^{18}F-FDG PET/CT in the present retrospective study.

While 27% of known pyogenic spondylitis patients were reported to be complicated with IE,[14] 5% and 21% of IE patients were conversely complicated with pyogenic spondylitis and pyogenic arthritis, respectively,[15,16] indicating the importance of suspecting the complications of pyogenic spondylitis or pyogenic arthritis with IE and vice versa. We found more cases of complicated pyogenic spondylitis and pyogenic arthritis in the GM group than in the non-GM group in the present study. However, the risks of complicating pyogenic spondylitis or pyogenic arthritis with IE were considered equal between both groups because no significant differences were found in the incidences of diabetes mellitus or the administration of steroids or immunosuppressants, which were reported as risk factors of pyogenic spondylitis and pyogenic arthritis.[17,18] In addition, the incidences of predisposing cardiac disease, presence of bacteremia by Gram-positive cocci including *Staphylococcus aureus* and *Enterococcus* spp., and complications of irreversible CNS disorders, which are often reported in patients with both IE and pyogenic spondylitis,[14] were equal between both groups. Two reasons for the high incidences of complicating pyogenic spondylitis or pyogenic arthritis in the GM group despite these issues were considered: the larger number of patients admitted due to pyogenic spondylitis or pyogenic arthritis with undiagnosed baseline IE in the GM group and the carefulness of the physicians in the general medicine department when seeing patients with IE. These physicians actively detected the presence of back or joint pain, took patients' histories, and conducted physical examinations, which enabled determination of complicating pyogenic spondylitis and pyogenic arthritis, regardless of the presence or absence of risk factors. Significantly more patients in the GM group had back or joint pain starting within 2 months before the first visit to our hospital; thus, spinal MRIs were performed more often. This could suggest that physicians actively suspected IE when patients had pyogenic spondylitis or pyogenic arthritis; thus, the general medicine department aggressively investigated the pyogenic spondylitis or pyogenic arthritis.

Although glomerulonephritis is a minor item on the modified Duke's criteria,[3] the reported incidence varied from almost null to approximately 26%.[19,20] In the present study, the GM group had a higher incidence of glomerulonephritis. Although the rates of patients with diabetes mellitus, patients on hemodialysis, patients taking antibiotic treatment prior to

blood culturing, and serum creatinine concentrations did not significantly differ between the groups, the GM group was given more urinalyses, indicating that clinicians in the general medicine department were actively testing for glomerulonephritis in patients with IE, which may have increased the rate of detecting glomerulonephritis in the GM group.

Even in this era of modernized antibiotics, mortality from IE and the rate of valvular surgery in patients with IE have commonly been reported to be 15%–30% and 25%–60%, respectively.[9,21–25] It has even been reported that in-hospital mortality from IE is 11% in Japan.[9] Various risk factors adversely influence the IE prognosis, including disadvantageous patient backgrounds (eg, old age, prosthetic valve infection, diabetes mellitus, administration of steroids or immunosuppressants, chronic hepatic disorder, and chronic kidney disease), serious complications of IE (eg, AHF, acute kidney injury, embolic stroke, cerebral hemorrhage, and septic shock), vicious causative microorganisms (eg, *Staphylococcus aureus*, multidrug-resistant organisms, and fungi), and undesirable echocardiographic findings (eg, vegetation on the left side of the heart, vegetation size >10 mm, annular abscesses, massive valve destruction, and decreased left ventricular function).[26] However, these factors did not significantly differ, nor did the mortality rate within 30 days from admission to our hospital, the rate of overall in-hospital mortality, or the rate of performing valvar surgery between both groups. Thus, the general medicine department at our hospital treated patients with IE with equivalent seriousness and mortality rates, achieving similar prognoses to those of the other departments, including cardiology and cardiovascular surgery.

Limitations

The present study was a single-hospital based retrospective study at a university hospital, performed as a secondary analysis of a previous study with relatively few subjects. Therefore, the study setting could have introduced some selection bias. Some patients might have been inappropriately excluded because inpatients with IE in the present study were identified via ICD-10. Furthermore, a multicenter prospective study is needed to clarify the roles of general medicine departments throughout Japan when treating diagnostically challenging diseases or fevers of unknown origin on a daily basis and in diagnosing and treating IE.

Conclusion

The department of general medicine at our university hospital in Japan could have correctly diagnosed inpatients with IE who were not suspected to have IE or showed no typical findings on

echocardiography before admission, especially with similar prognostic factors, and achieved similar prognoses as those of other departments, including cardiology and cardiovascular surgery. Clinicians in the department of general medicine actively suspected and diagnosed IE from the presence of pyogenic spondylitis, pyogenic arthritis, or glomerulonephritis.

Acknowledgment

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors state that they have no conflicts of interest.

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