ORIGINAL PAPER

Nagoya J. Med. Sci. **79**. 467 ~ 476, 2017
doi:10.18999/nagjms.79.4.467

Clinical features of patients with infective endocarditis presenting to the emergency department: a retrospective case series

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ABSTRACT

Infective endocarditis (IE) is an uncommon clinical problem with diverse, nonspecific presentations. Therefore, information on the clinical features of IE patients presenting to emergency departments (EDs) is scarce. To descriptively analyze the pertinent data, we performed a retrospective chart review. We reviewed 15 consecutive IE patients admitted directly from ED in a university hospital in Japan between 2013 and 2015. We compared their clinical features with those of 14 IE patients admitted during the same period without ED presentations. Patients admitted directly from ED were older than those without ED presentations (median, 78 vs. 52 years; adjusted $p = 0.036$) and were more likely to have come without referrals (referral rate, 21% vs. 86%; adjusted $p = 0.012$). These patients were less likely to have been treated with antibiotics before admission (antibiotic-exposure rate, 7% vs. 64%; adjusted $p = 0.013$) and had earlier blood-culture positivity (median, 2 vs. 5 days; adjusted $p = 0.012$), resulting in earlier diagnosis (median duration of symptoms before diagnosis, 5 vs. 30 days; adjusted $p = 0.012$). Other clinical features, including causative pathogens and IE-related comorbidities, were similar between the groups, consistent with previous a nationwide Japanese study. In conclusion, most IE patients admitted to the hospital from ED were elderly, were antibiotic-naïve, and had presented without a referral. Relatively few patients had classical presentations of IE. Given the limited data, more research is needed to confirm that IE patients presenting to EDs constitute a unique group of elderly patients with specific clinical features.

Keywords: blood culture, echocardiography, emergency service, endocarditis

INTRODUCTION

Infective endocarditis (IE) is an uncommon clinical problem with diverse and nonspecific presentations.[1-3] IE can present as classical fever of unknown origin (FUO)[4] or as unexplained stroke or systemic embolism, with risks of morbidity and mortality.[1-3] Despite improved culture techniques and modernized imaging technologies, and even with the introduction of the revised standard diagnostic criteria,[5] IE still remains a diagnostic challenge.[3]

Received: February 28, 2017; accepted: August 10, 2017

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In the emergency department (ED), IE can present as fever unexplained by basic laboratory tests, including urinalysis, chest X-rays, and thoracoabdominal computed tomography (CT) with or without contrast enhancement.[6,7] Therefore, diagnostic recommendations for emergency physicians who suspect IE have emphasized the recognition of classical features, such as a history of intravenous drug use or structural heart disease, or a heart murmur found by auscultation on physical examination.[6] However, these recommendations are based on the whole population of IE patients, and specific data on the clinical features of IE patients presenting to ED are scarce. In this study, we descriptively analyzed the clinical characteristics of adult IE patients who presented to, and were admitted from, ED in a tertiary-care university hospital (ED patients). We compared their clinical features with those of IE patients who were admitted to the hospital from clinical contexts other than ED (non-ED patients), with particular attention to characteristics of classical presentation.

MATERIALS AND METHODS

Study design

The institutional review board of Fujita Health University approved this case series based on retrospective chart review and granted a waiver of informed consent on the basis of its retrospective design (approval number HM-16-161). Our case series included 15 consecutive IE patients who visited ED at the Fujita Health University Hospital, a 1435-bed tertiary-care teaching hospital in Japan, and were directly hospitalized for treatment during a 2-year period from April 1, 2013, to March 31, 2015. We identified these patients from the hospital database with the use of the International Classification of Diseases 10 codes for IE. Another 14 consecutive IE patients admitted from non-ED contexts during the same period were identified as the reference cases. We diagnosed IE according to the modified Duke criteria[5] and judged patients who met the definite or the possible definite criteria for IE.

Assessment

We recorded the following data from each patient's medical chart. Patient characteristics were age; sex; nature and duration of symptoms at presentation; recent medical history, including dental procedures and use of antibiotics; and past medical history of IE, valvular heart disease, or congenital heart disease. Physical findings were the first vital signs recorded in ED or on admission, including blood pressure, heart rate, respiratory rate, body temperature, and peripheral capillary oxygen saturation (SpO_2); mental status according to the Japan Coma Scale; heart murmur; and petechiae. Laboratory findings were white-blood-cell count, C-reactive protein (CRP) level, erythrocyte sedimentation rate, vegetations detected by transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), and blood-culture results. Clinical outcomes were complications associated with IE, any surgical interventions, and in-hospital mortality. We diagnosed the systemic inflammatory response syndrome (SIRS) according to the ACCP/SCCM Consensus Conference Committee.[8] Any types of minor hemorrhagic lesions related to IE, such as splinter hemorrhages, Janeway's lesions, Roth's spots, or conjunctival hemorrhages, were considered petechiae.

A staff-level emergency physician performed bedside TTE in ED at the discretion of the attending physician or physicians. Board-certified ultrasound technicians with at least 3 years of experience performed a formal TTE within 3 days after admission, and the results were double-checked by board-certified cardiologists specializing in echocardiography. Board-certified cardiologists performed TEE when indicated. We defined a vegetation as an echocardiographi-

cally identified oscillating or nonoscillating intracardiac mass on the valves or other endocardial structures or on the implanted intracardiac devices, according to the recommendations of the European Association of Echocardiography.[9)]

Statistical analysis

We descriptively analyzed all categorical and continuous variables with the use of tables. We compared data from ED and non-ED patients by the chi-square test or the Fisher-Boschloo exact unconditional test (when one or more cells in a 2 × 2 table contain fewer than five events) for categorical data[10)] and the rank-based Brunner-Munzel test for continuous data, because the assessment of distribution symmetry and variances for the two groups was not straightforward because of the small sample size.[11,12)] We also performed Welch's modified *t*-test for sensitivity analysis of continuous data.[13,14)] For multiple comparisons, we determined statistical significance based on *q*-values, also known as adjusted *p*-values,[15)] using the Benjamini-Hochberg procedure.[16,17)]

We calculated the sensitivity of TTE performed in ED to detect vegetation and its exact binomial 95% confidence interval (CI) using the standard method, assuming that the formal TTE, followed by TEE if indicated, was the gold standard. We quantified inter-rater agreement between TTE performed in ED and the formal TTE performed after admission by estimating the kappa coefficient with its 95% CI, and assessed the strength of agreement according to the recommended criteria.[18)]

Missing data are common in any type of study, including retrospective chart reviews, which can bias the study findings.[19)] Of 35 data items, data on nine (26%) for ED patients (median proportion of missing data per item, 7%; range, 7%-60%) and 13 (37%) for non-ED patients (median, 36%; range, 7%-86%) were missing. We performed complete case analysis in the main analysis by disregarding cases with missing data.[19)] In sensitivity analysis, we excluded data items from statistical comparisons that included missing outcome data on -four (corresponding to ≥25%) items per group.

All analyses were performed with Stata SE, version 14.1 (Stata Corp, College Station, TX, USA) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). *P*-values for all comparisons were two-tailed, and *p*-values of <0.05 were considered to indicate statistical significance.

RESULTS

Patient characteristics

Of 15 eligible ED patients, 10 (67%) and 5 (33%), respectively. satisfied the definite and possible diagnosis criteria for IE (Table 1). Their age ranged from 21 to 90 years (median, 78 years), and the mode of arrival was by ambulance in 10 patients (67%) and walk-in in 5 patients (33%). With regard to the classical presentations of IE, no patient had used intravenous substances, and only five (33%) had a history of structural heart disease. Twelve patients (80%) were admitted to our general internal medicine department for further workup, while three patients (20%) were directly admitted to our cardiology department: Two patients were highly suspected of IE by TTE performed in ED and another patient was complicated with congestive heart failure.

The 14 non-ED patients in the reference group had various clinical courses before admission. Ten patients (71%) had undergone a workup in another hospital and were then transferred to our hospital; seven were transferred to the cardiology department (n = 5) or cardiovascular surgery department (n = 2) for treatment of diagnosed IE, and another three were transferred to cardiology department for further workup of FUO because of highly suspected IE. Two patients (14%) were

Table 1 Patient characteristics and diagnosis.

Variable	ED (n = 15)	Non-ED (n = 14)	Unadjusted p-value	Adjusted p-value
Demographic characteristics				
Median age (range), years	78 (21–90)	52 (27–86)	0.006	0.036
Male sex, no. (%)	9 (60)	9 (64)	0.81	0.84
Past medical history				
Infectious endocarditis, no. (%)	0 (0)	1 (7)	0.46	0.62
Valvular heart disease, no. (%)	5 (33)*	2 (14)†	0.31	0.50
Congenital heart disease, no. (%)	0 (0)	3 (21)	0.062	0.18
Recent history				
Dental treatment, no. (%)	4 (33)	2 (15)	0.30	0.50
Outpatient visits within previous week, no. (%)	6 (42)	12 (86)	0.021	0.083
Referral from another clinic or hospital, no. (%)	3 (21)	12 (86)	<0.001	0.012
Use of antibiotics, no. (%)	1 (7)	9 (64)	0.002	0.013
Symptoms				
Fever, no. (%)	11 (73)	13 (93)	0.26	0.46
Pain, no. (%)	6 (40)	2 (14)	0.14	0.32
Median symptomatic days before admission, no. (range)	3 (1–30)	7 (2–90)	0.030	0.11
Median symptomatic days before diagnosis, no. (range)	5 (1–45)	30 (2–180)	0.001	0.012
Diagnosis by modified Duke criteria			0.89	0.89
Definite, no. (%)	10 (67)	9 (64)		
Possible, no. (%)	5 (33)	5 (36)		

ED, emergency department.

* Two cases with mitral valve prolapse; two cases with previous history of aortic valve replacement for aortic stenosis; and one case with mitral regurgitation.

† One case with mitral valve prolapse and one case with aortic regurgitation.

directly referred to the cardiology department by local cardiology clinics for clinically suspected IE. Two other patients (14%) directly visited the outpatient clinic of the general internal medicine department: one for persistent low-grade fever and the other for posterior cervical pain, both of who were admitted to the general internal medicine department for further workup.

Compared with non-ED patients, ED patients were older (median, 78 vs. 52 years; adjusted p = 0.036) and were more likely to have come to the hospital without a referral (referral rate, 21% vs. 86%; adjusted p = 0.012). Fewer ED patients than non-ED patients had a recent history of antimicrobial treatment (1 of 15 [7%] vs. 9 of 14 [64%]; adjusted p = 0.013; Table 1).

Physical findings

Six of 15 ED patients (40%) had a temperature of 38°C or higher at presentation, and 11 (73%) met the SIRS criteria. Overall, vital signs were similar in the two groups (Table 2). Heart murmur, a classical presentation of IE, was detected by auscultation in fewer ED than non-ED

patients (5 of 15 [33%] vs. 11 of 14 [85%]; adjusted p = 0.036). Petechiae were observed in fewer than a third of patients in both groups (Table 2).

Laboratory findings

The typical initial workup for ED patients at presentation included urinalysis, chest X-ray, and thoracoabdominal CT. These tests failed to detect diagnostic clues of the presenting symptoms, including fever or pains, or elevated CRP levels. Fourteen of the 15 ED patients underwent the gold standard tests of formal TTE and TEE, which detected vegetation in 10 patients (67%; Table 3). Only one patient with a negative TTE performed in ED did not receive the gold standard combination of tests. Twelve patients underwent TTE performed in ED at the discretion of the attending emergency physicians, and all results were verified by the gold standard. TTE performed in ED detected vegetation in only three of 12 patients (25%), 10 of whom were eventually confirmed to have vegetations, for a sensitivity of 30% (95% CI, 7%–65%). Agreement between TTE performed in ED and the formal TTE was moderate (kappa = 0.50; 95% CI, 0.01–0.99). Of seven cases in whom TTE performed in ED failed to detect vegetations, coexistent vegetation and calcification in the aortic valve was later confirmed in the TEE in one case. No patient had a detectable valve perforation or abscess. Vegetation was most frequently found on the mitral valve, followed by the aortic valve (Table 3). There were no significant differences between ED and non-ED patients in the location of the vegetation.

Blood cultures were positive in 14 of 15 ED patients (93%). The most frequent organisms were streptococci, and the second-most frequent was methicillin-sensitive *Staphylococcus aureus*

Table 2 Vital signs and physical findings on admission.

Variable	ED (n = 15)	Non-ED (n = 14)	Unadjusted p-value	Adjusted p-value
Vital signs				
Median systolic blood pressure (range), mm Hg	126 (99–202)	118 (90–135)	0.15	0.32
Median diastolic blood pressure (range), mm Hg	71 (50–93)	59 (42–80)	0.017	0.083
Median heart rate (range)	100 (69–132)	90 (72–122)	0.16	0.32
Median respiratory rate (range)	28 (16–40)	22 (20–24)	0.27	0.46
Median body temperature (range), °C	37.6 (36.4–39.1)	37.3 (36.1–40.0)	0.45	0.62
Median peripheral capillary oxygen saturation (range), %	97 (89–100)	97 (94–97)	0.14	0.32
Mental status by Japan Coma Scale, no. (%)			0.065	0.18
Grade 0, alert	10 (67)	13 (93)		
Grade 1, eye-opening, not lucid	1 (7)	1 (7)		
Grade 2, eye-opening upon stimulation	2 (13)			
Grade 3, no eye-opening and coma	2 (13)			
Physical findings				
Murmur, no. (%)	5 (33)	11 (85)	0.006	0.036
Purpura, no. (%)	4 (27)	2 (15)	0.56	0.67

ED, emergency department.

(Table 3). There were no significant differences between ED and non-ED patients in the positivity rates and frequencies of detected organisms, although blood cultures became positive an earlier in ED patients (median, 2 vs. 5 days; adjusted $p = 0.012$).

Clinical outcomes

For ED patients, physicians from the general internal medicine department treated 5 patients and cardiologists treated 10 patients. In contrast, all non-ED patients were treated by either cardiologists or cardiovascular surgeons. Complications developed in 10 of 15 ED patients (66%). The most frequent complication was embolic events, and the second-most frequent was acute kidney injury (Table 4). Four patients (27%) underwent surgical intervention, and one patient

Table 3 Laboratory, echocardiographic, and blood-culture findings.

Variable	ED ($n = 15$)	Non-ED ($n = 14$)	Unadjusted p-value	Adjusted p-value
Basic laboratory tests				
Median white blood cells (range), /μL	10,300 (6,200–19,400)	10,150 (5,900–21,300)	0.82	0.84
Median C-reactive protein (range), mg/dL	9.7 (2.9–31.3)	5.1 (0.5–22.6)	0.021	0.083
Median erythrocyte sedimentation rate (range), mm	58 (36–82)	43 (18–88)	0.76	0.84
Echocardiography*				
Detection of vegetation, no. (%)	10 (65)	11 (79)	0.58	0.70
Mitral valve	6 (60)	9 (75)		
Aortic valve	3 (30)	2 (17)		
Tricuspid valve	1 (10)	1 (8)		
Blood-culture results				
Positive blood culture, no. (%)	14 (93)	11 (92)	0.74	0.84
Median days until positive results, no. (range)	2 (1–6)	5 (2–14)	<0.001	0.012
Organisms, no. (%)			0.34	0.52
Streptococci	8 (57)	10 (67)		
Viridans group streptococci	2 (14)	6 (55)		
Streptococcus bovis	3 (21)	0 (0)		
Others	4 (24)	4 (30)		
Methicillin-sensitive *Staphylococcus aureus*	4 (29)	1 (8)		
Enterococci	2 (14)	1 (8)		
Anaerobic gram-positive cocci	0 (0)	1 (8)		

ED, emergency department.

*Aortic valve calcification was detected in three cases in ED group (20%) and two in non-ED group (14%), of which coexistence of calcification and vegetation in the aortic calve was confirmed by either trans-thoracic echocardiography or trans-esophageal echocardiography performed after admission in one case (33%) and two cases (100%), respectively.

(7%) died from congestive heart failure. Similarly, seven of 14 non-ED patients (50%) had any complications, six of which were embolic events. Surgery was performed in seven patients (50%). Overall, there were no significant differences between ED and non-ED patients with regard to complications and clinical outcomes (Table 4).

Sensitivity analysis

In sensitivity analysis, unadjusted results based on Welch's modified *t*-test were similar to those in the main analysis (data not shown). However, the Benjamini-Hochberg correction left only two factors that were significantly different between two groups: referral from other institutions (adjusted $p = 0.026$) and prior antibiotic use (adjusted $p = 0.026$). In addition, the results were not different from those in the main analysis when seven data items, from which data on ≥four items per group were missing (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, SpO_2, and ESR), were excluded (data not shown).

DISCUSSION

We report a retrospective case series in which we surveyed the clinical characteristics and outcomes of adult IE patients who presented to ED at an academic referral hospital in Japan. ED patients were older than non-ED patients and were more likely to have visited ED directly without referral from other institutions. ED patients were typically not previously treated with antibiotics, and their blood cultures became positive an average of 3 days earlier, resulting in an earlier diagnosis. Other clinical features, including causative pathogens and IE-related comorbidities, were similar in ED and non-ED patients. It is uncertain whether recognition of the classical presentations helped expedite the diagnosis, because relatively few ED patients showed such clinical features.

These findings, although noteworthy, are not surprising, because it is well recognized in Japan that frail, elderly patients are more likely to visit EDs than patients who are younger with fewer comorbidities.[20,21] Our elderly ED patients presented directly to ED in the tertiary-care setting, typically within 1 week after symptom onset, without referral, and therefore they had few

Table 4 Complications and clinical outcomes.

Variable	ED ($n = 15$)	Non-ED ($n = 14$)	Unadjusted *p*-value	Adjusted *p*-value
Embolization, no. (%)	5 (33)	7 (50)	0.36	0.53
Brain, no.	2	4		
Kidney, no.	1	1		
Spleen, no.	1	1		
Others, no.	1	1		
Acute kidney injury, no. (%)	4 (27)	0 (0)	0.067	0.18
Congestive heart failure, no. (%)	3 (20)	1 (7)	0.49	0.63
Psoas abscess, no. (%)	1 (7)	0 (0)		
Spondylitis, no. (%)	0 (0)	1 (7)		
Surgical interventions, no. (%)	4 (27)	7 (50)	0.21	0.41
In-hospital mortality, no. (%)	1 (7)	0 (0)	0.75	0.84

ED, emergency department.

opportunities to visit their primary or secondary-care facilities to receive medical interventions, including antimicrobial therapy. Because prior antibiotic use can decrease the sensitivity of blood culture, which can delay or even hinder the diagnosis of IE,[3,22] visiting ED directly can in theory result in an earlier diagnosis. Except for these features, the clinical features of our ED patients were generally in agreement with reports from the CADRE-IR, a nationwide survey of IE in Japan. These features include the low numbers of intravenous drug abusers, streptococci and *Staphylococcus aureus* as the two most common causative microorganisms, and the location of vegetations.[23] Thus, our ED patients can be speculated to represent a subgroup of typical IE patients in Japan who seek acute medical care earlier in the disease course, with no or minimal preceding interventions.

Only a few case reports have described the usefulness of echocardiography specifically performed by emergency physicians for expeditious diagnosis of IE in EDs.[24-27] In our case series, TTE performed in ED by emergency physicians had a sensitivity of 30%, which is lower than the generally reported sensitivity of approximately 75%.[28] The low sensitivity found in our study is based on retrospective observations of selected cases from an ED where emergency physicians who were not certified as ultrasonologists performed TTE as part of their clinical practice. This situation is different from that in protocol-driven prospective studies in which echocardiography is standardized and routinely performed by certified cardiologists or ultrasonography technicians for all patients with suspected IE. Furthermore, echocardiographic diagnosis can be particularly challenging at early stages of IE when vegetations may be smaller or in the case of severe valvular or perivalvular calcifications.[9]

Our study has several limitations. First, it is based on a retrospective chart review of only 15 cases of interest and 14 reference cases from a hospital database, which precludes definitive conclusions. We performed complete case analysis excluding patients with missing data, which further decreased the sample size and decreased statistical power. It is uncertain whether data were missing at random or in a systematic way. If data were systematically missing, our complete case analysis could have introduced bias. Therefore, interpretation of the presented findings needs to be made with care. Second, we performed exploratory statistical comparison of 35 variables of potential interest. Although we adjusted the crude *p*-values by performing a false-discovery-rate control procedure,[16] aiming at "screening" potentially important variables, these corrections may have led to some factors being incorrectly eliminated. In addition, we did not assess interactions between variables of interest, because the sample size was only 29. Multivariable analyses modeling two or more variables would be unrealistic in a study with such a small sample size. Third, although a significant difference between ED and non-ED patients was observed only for heart murmur, information on vital signs and findings of physical examination was collected from non-ED patients at a later stage of IE than it was collected from ED patients. To improve the comparability of the timing of examinations between the two groups, data obtained in the prior institutions from most non-ED patients should have been used. Fourth, we cannot completely exclude the possibility that data from some eligible IE patients who visited our ED are missing because they were discharged and never returned to the hospital. This is unlikely, because our institution is the only tertiary-care hospital in the area.

In summary, the results of a small, retrospective observational study in a university hospital suggest that IE patients who are admitted directly from ED may form a unique patient group who are elderly, were not previously treated with antibiotics, and visited tertiary-care centers without a referral earlier in the course of the disease. Furthermore, blood cultures obtained in EDs may yield positive results earlier. These findings from very limited evidence are only hypothetical and should be validated. External validation in similar patient populations is needed to prospectively assess whether the current findings also apply to EDs in general in Japan. Potentially feasible

approaches might include a retrospective analysis of existing IE cohorts, such CADRE-IR.[23)]

ACKNOWLEDGMENTS

We thank Dr. Masaya Hibino for assistance in identifying earlier cases. The authors declare that they have no competing interests.

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