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Factors associated with delayed diagnosis of infective endocarditis

A retrospective cohort study in a teaching hospital in Japan

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Abstract

Patients with infective endocarditis (IE), have high mortality and morbidity, however, its early diagnosis is difficult. Few studies have examined the delayed diagnosis of IE. We aimed to investigate the factors associated with the diagnostic delay of IE.

A retrospective cohort study was conducted for consecutive patients diagnosed with IE in an acute care teaching hospital in Japan from April 2006 to March 2018. Time-to-diagnosis was analyzed using a multivariate Cox hazard model for determining factors associated with days required for IE diagnosis. Factors analyzed in the model included age, gender, activities of daily living, Charlson comorbidity index, presence of internal device, chief complaint, inappropriate antibiotics use, shaking chill, fever >38°C, hypoxemia, serum C-reactive protein (CRP) < 10 mg/dL, *Staphylococcus aureus* as causative pathogen, findings on first echocardiography, resident as a first contact physician, primary care physician as a first contact doctor, and transport measures to the clinic/hospital.

There were 145 IE patients with a mean age of 70 years and 90 were male (62.1%). The median time to the diagnosis of definite IE was 13 days and median time to consider the diagnosis of IE from first clinic/hospital visit was 6 days. The time to consider IE diagnosis was significantly delayed in patients who had inappropriate prior antibiotic use (hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.01 to 2.57; $P = .045$), in patients without fever >38°C (HR, 1.80; 95% CI, 1.11 to 2.90; $P = .016$), in patients with serum CRP level < 10 mg/dL (HR, 1.53; 95% CI, 1.01 to 2.33; $P = .046$), and in patients who did not use an ambulance for hospital arrival (HR, 3.18; 95% CI, 1.72 to 5.85; $P < .001$).

Delay in considering IE diagnosis is associated with inappropriate prior antibiotics use, absence of high fever, absence of high CRP level, and use of a hospital arrival vehicle other than an ambulance. For earlier IE diagnosis, inappropriate use of antibiotics should be avoided and IE should not be excluded by relatively low level of temperature or serum CRP.

Abbreviations: ADL = activities of daily living, CI = confidence interval, CRP = C-reactive protein, ER = emergency room, HR = hazard ratio, IE = infective endocarditis, qSOFA = quick Sequential (Sepsis-related) Organ Failure Assessment, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

Keywords: C-reactive protein, delay, diagnosis, fever, inappropriate antibiotics, Infective endocarditis

1. Introduction

Infective endocarditis (IE) is not a common disease, but when it occurs, it is associated with significant mortality and morbidity. A substantial rate of mortality, 9% to 22%, was reported among the patients who received antibiotics for IE.[1–6]

Early diagnosis of IE is essential through investigations including blood culture and echocardiography.[7,8] Early high-dosage antibiotic administration, and surgical intervention, are strongly associated with a reduced risk of in-hospital mortality and morbidity in IE.[9,10]

On the other hand, delay in diagnosis and initiation of therapy lead to complications and unfavorable outcomes.[11] Therefore, delayed diagnosis of IE is a critical issue that needs to be resolved, to save lives and avoid disability. Several studies conducted in IE patients revealed a significant delay in their diagnosis.[2,12] However, to the best of our knowledge, no study has been conducted before that focused on the factors causing delayed IE diagnosis.

Therefore, this study was performed to investigate factors that may have a role in the delayed diagnosis of IE from the day of patients visit to recall diagnosis. We also evaluated the delayed factors of day to definite IE diagnosis from the day of positive blood cultures.

Editor: Abdelouahab Bellou.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Nishiguchi S, Nishino K, Kitagawa I, Tokuda Y. Factors associated with delayed diagnosis of infective endocarditis: a retrospective cohort study in a teaching hospital in Japan. Medicine 2020;99:30(e21418).

Received: 21 December 2019 / Received in final form: 19 June 2020 / Accepted: 24 June 2020

http://dx.doi.org/10.1097/MD.0000000000021418

2. Methods

2.1. Study population

Our retrospective cohort study was performed on patients who were diagnosed with IE in Shonan Kamakura General Hospital, Japan from April 2006 to March 2018. The private acute-care teaching hospital provides primary and tertiary care in Kanagawa prefecture, with about 9 million inhabitants. This 619 bedded hospital has departments in Cardiothoracic Surgery, Cardiovascular Medicine, Emergency Medicine, and General Internal Medicine. The hospital receives patients from all quarters, namely, primary care clinics, other hospitals, and directly from the adjoining areas for free access to physicians of various specialties. Our study included hospitalized patients with definite IE according to modified Duke criteria.[13] The consecutive IE patients with nosocomial infections were excluded.

2.2. Data collection

Data on the following patient-related factors were collected: age, gender, alcoholism, activities of daily living (ADL), living place, history of IE, history of cardiac surgery, heart valve disease, valve, device insertion, Charlson comorbidity index,[14] recent history of dental care or dental caries, inappropriate antibiotic use, complaint of fever, complaint related heart failure, complaint related stroke, complaint related osteomyelitis, complaint related other septic embolism, fever >38°C, shaking chill, hypoxemia, quick sequential [Sepsis-related] organ failure assessment (qSOFA) score,[15,16] cardiac murmur, serum C-reactive protein (CRP) level (mg/dL), rhythm on electrocardiogram, ejection fraction >60% on echocardiography, negative finding on first echocardiography, microbiological finding (*Staphylococcus aureus* and *Streptococcus species*), impaired valve, and vegetation size. We also collected data on medical facility and physician-related factors like hospital resident on the hospital as a first contact doctor, primary care physician as a first contact doctor, General Internal Medicine physician as a first contact doctor, and whether the patient was transferred to the hospital by ambulance. Moreover, we evaluated data on the following outcome and complications: heart failure, infectious cerebral aneurysm, stroke, osteomyelitis, other septic embolism, surgery, length of stay (day), in-hospital mortality (%), and 90-day mortality (%). For appropriateness of previous antibiotic use, we assessed the chart information. We defined any antibiotics use before obtaining blood cultures as "inappropriate."

2.3. Statistical analysis

We aimed to evaluate factors associated with delayed recall diagnosis of IE patients. The primary outcome measure was the duration from the visit to the clinic or hospital and to the recall of the IE diagnosis (Fig. 1). For the day of visit-to-the day of diagnosis, we used the Cox proportional hazard model to analyze factors associated with delaying the diagnosis of IE. In a univariate model, the "patient-related factors" and "medical facility and physician-related factors" were evaluated as possible reasons for the delayed diagnosis of IE, based on log-rank test. Multivariable model was developed using the age, gender, ADL, Charlson comorbidity index, non-device insertion, non-chief complaint related fever, non-chief complaint related heart failure, inappropriate antibiotics use, absence of shaking chill, absence of fever >38°C, hypoxemia, serum CRP level <10 mg/dL, another bacteria of *S aureus*, negative finding on first echocardiography, resident on the hospital as a first contact physician, primary care physician as a first contact doctor, and transferred by a vehicle other than non-ambulance.

Additionally, we assessed factors associated with the delayed definite diagnosis from reported positive blood cultures among IE patients (Fig. 1). The multivariable model analysis was developed using the multivariate Cox proportional hazard model. We selected the explanatory factors for the age, gender, device insertion, department, only 1 set positive blood culture, negative finding on first echocardiography, negative finding on first echocardiography after reported positive blood cultures, vegetation < 10 mm, *S aureus*, no complication of stroke, no complication of osteomyelitis, and no complication of septic embolism.

A two-tailed p-value <.05 was considered statistically significant. All statistical tests were undertaken using the SPSS Statistics version 21J (IBM, Tokyo, Japan). This research was approved by the Institutional Review Board of the Shonan Kamakura General Hospital (No. TGE01079-024).

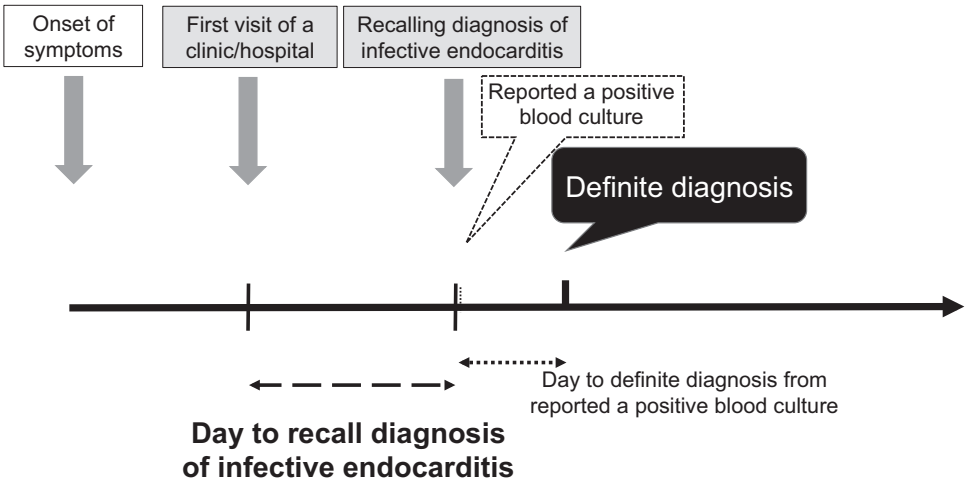

Figure 1. Schematic representation of the diagnosis flow from onset of patient symptoms.

Table 1

Patients characteristics and univariate analysis associated with delayed recall diagnosis of infective endocarditis.

(N = 145) Characteristic	No.(%) or mean ± SD	Day-to-recall (95% CI)	*P* value
Patient-related factors			
Age (yr)	69.6 ± 16.1		.635
<65	47 (32.4%)	7.00 (4.328–9.672)	
>65	98 (67.6%)	4.00 (1.921–6.079)	
Male gender	90 (62.1%)	5.00 (3.010–6.990)	.727
Female gender	55 (37.9%)	6.00 (2.697–9.303)	
Alcoholism	40 (27.6%)	6.00 (0.000–12.190)	.514
Non-alcoholism	98 (67.6%)	4.00 (2.060–5.940)	
Dependent ADL	108 (74.5%)	6.00 (3.651–8.349)	.151
Partially dependent ADL	29 (20.0%)	4.00 (2.862–5.138)	
Independent ADL	8 (5.5%)	8.00 (0.000–16.316)	
House	129 (89.0%)	6.00 (4.148–7.852)	.175
Elderly facility	16 (11.0%)	3.00 (1.693–4.307)	
Past history of IE	4 (2.8%)	4.00 (0.000–38.300)	.626
No past history of IE	141 (97.2%)	5.00 (3.210–6.790)	
Past history of cardiac surgery	21 (14.5%)	3.00 (0.009–5.991)	.294
No past history of cardiac surgery	124 (85.5%)	6.00 (4.327–7.673)	
Heart valve disease	72 (49.7%)	6.00 (2.535–9.465)	.745
Non-heart valve disease	73 (50.3%)	5.00 (3.072–6.928)	
Valve			.789
Native valve	128 (88.3%)	5.00 (3.416–6.584)	
Bioprosthetic valve	3 (2.1%)	10.00 (0.000–24.403)	
Mechanical valve	14 (9.7%)	3.00 (0.000–17.667)	
Device insertion	32 (22.1%)	3.00 (0.783–5.217)	.080
No device insertion	113 (77.9%)	6.00 (4.267–7.733)	
Charlson comorbidity index			.252
rank:0 (score:0)	43 (29.7%)	6.00 (2.145–9.855)	
rank:1 (score:1–2)	44 (30.3%)	7.00 (0.499–13.501)	
rank:2 (score:3–4)	27 (18.6%)	4.00 (2.313–5.687)	
rank:3 (score>4)	31 (21.4%)	3.00 (1.190–4.810)	
Recent history of dental care or dental caries	15 (10.3%)	17.00 (0.000–35.935)	.398
No recent history of dental care or dental caries	123 (84.8%)	5.00 (3.189–6.811)	
Inappropriate antibiotics use	36 (24.8%)	16.00 (4.258–27.742)	.001*
Complaint of fever	76 (52.4%)	5.00 (3.169–6.831)	.396
Complaint of non-fever	69 (47.6%)	5.00 (1.744–8.256)	
Complaint related heart failure	7 (4.8%)	9.00 (0.000–21.831)	.199
Complaint related non-heart failure	138 (95.2%)	5.00 (3.273–6.727)	
Complaint related stroke	27 (18.6%)	3.00 (1.554–4.446)	.329
Complaint related non-stroke	118 (81.4%)	6.00 (3.719–8.281)	
Complaint related osteomyelitis	5 (3.4%)	6.00 (0.000–14.588)	.279
Complaint related non-osteomyelitis	140 (96.6%)	5.00 (3.145–6.855)	
Complaint related other septic embolism	7 (4.8%)	13.00 (10.434–15.566)	.283
Complaint related non-other septic embolism	138 (95.2%)	5.00 (3.252–6.748)	
Fever>38°C	99 (68.3%)	5.00 (3.172–6.828)	.044*
Fever<38°C	46 (31.7%)	5.00 (0.846–9.154)	
Shaking chill	18 (12.4%)	2.00 (0.000–4.066)	.035*
No shaking chill	127 (87.6%)	6.00 (3.452–8.548)	
Hypoxemia	25 (17.2%)	3.00 (1.368–4.632)	.016*
Non-hypoxemia	120 (82.8%)	6.00 (3.700–8.300)	
qSOFA			.004*
Score:0	64 (44.1%)	23.80 (10.798–36.796)	
Score:1	54 (37.2%)	19.80 (10.919–28.673)	
Score:2	25 (17.2%)	5.24 (2.224–8.256)	
Score:3	2 (1.3%)	3.00 (1.040–4.960)	
Cardiac murmur	70 (48.3%)	4.00 (1.268–6.732)	.947
No cardiac murmur	75 (51.7%)	6.00 (3.687–8.313)	
CRP level (mg/dL)	11.3 ± 8.5		
CRP<10	77 (53.1%)	13.00 (7.539–18.461)	<.001*
CRP>10	68 (46.9%)	4.00 (2.776–5.224)	
AF rhythm on electrocardiogram	28 (19.3%)	4.00 (1.783–6.217)	.428
Sinus rhythm on electrocardiogram	117 (80.7%)	6.00 (3.882–8.118)	
Ejection fraction>60% on echocardiography	93 (64.1%)	6.00 (2.367–9.633)	.618
Ejection fraction<60% on echocardiography	52 (35.9%)	5.00 (3.374–6.626)	
Negative finding on first echocardiography	73 (50.3%)	4.00 (1.916–6.084)	.030*
Positive finding on first echocardiography	72 (49.7%)	7.00 (1.803–12.197)	
Microbiological finding			
Staphylococcus aureus	37 (25.6%)	4.00 (2.844–5.156)	.011*
Streptococcus species	72 (49.7%)	7.00 (3.306–10.694)	.321
Impaired valve			
Mitral valve	89 (61.4%)	6.00 (3.956–8.044)	.628
Aortic valve	52 (35.9%)	6.00 (0.000–12.057)	.712
Vegetation>10 mm	69 (47.6%)	4.00 (1.676–6.324)	.577
Medical facility and physician-related factors			
Resident on the hospital as a first contact doctor	27 (18.6%)	2.00 (1.297–2.703)	<.001*
Non-resident on the hospital as a first contact doctor	118 (81.4%)	7.00 (4.339–9.661)	
Primary care physician as a first contact doctor	38 (26.2%)	12.00 (3.542–20.458)	.022*
Non-primary care physician as a first contact doctor	107 (73.8%)	4.00 (2.656–5.344)	
GIM physician as a first contact doctor	12 (8.3%)	11.00 (0.000–33.066)	.095
Non-GIM physician as a first contact doctor	133 (91.7%)	5.00 (3.305–6.695)	
Transferred to the hospital by ambulance	52 (35.9%)	3.56 (1.415–5.701)	<.001*
Transferred to the hospital by non-ambulance	93 (64.1%)	27.36 (17.367–37.342)	
Medical care provided at ER walk-in	17 (11.7%)	6.00 (0.622–11.378)	.409

ADL = activities of daily living, AF = atrial fibrillation, Resident indicate physician who was graduated within 2 years, CI = confidence interval, CRP = C-reactive protein, ER = emergency room, GIM = general Internal Medicine, IE = infective endocarditis, N = numbers, No. = number, qSOFA = quick sequential organ failure assessment, SD = standard deviation.

Based on logrank test or cox hazard crude model, where appropriate.

* $P < .05$.

3. Results

Of the 145 patients diagnosed with definite IE during the study period, the mean age was 69.6 ± 16.1 years with 90 (62.1%) male and 55 (37.9%) female patients (Table 1). The various characteristics and univariate analysis in Table 1 shows: the median time from first contact doctor to recall the diagnosis was 6 days (quartile, 2–16 day) (Fig. 2), from reported positive blood culture to definite diagnosis, it took 4 days (quartile, 2–9 day), eighty-one (55.9%) patients obtained blood cultures at the first visit, etiological organism was identified in 138 (95.2%) cases. The organisms associated with IE are seen in Table 1 with

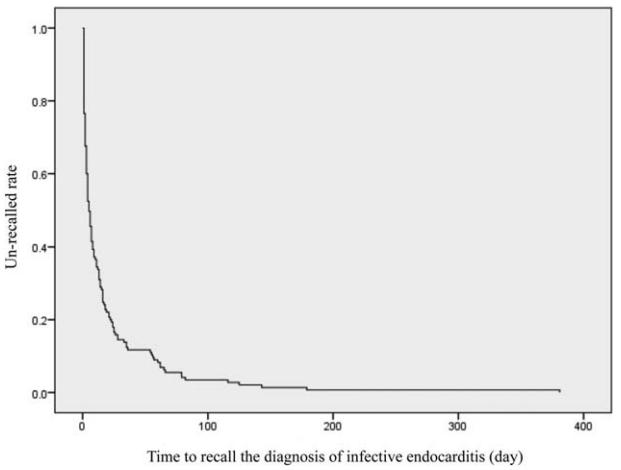

Figure 2. Kaplan-Meier curve of the time to recall the diagnosis of infective endocarditis (day).

Streptococcal species, being the most common (72 cases [49.7%]), followed by *Staphylococcal species* (44 cases [30.3%]) including *S aureus* (37 cases [25.5%]). During the hospital stay, 26 (17.9%) patients died in the hospital. Three month and in-hospital morality were 17.9% each. Sixty-eight (46.9%) patients received cardiac surgery for IE treatment. As a complication of IE, 45 (31.0%) patients had heart failure, 2 (1.4%) patients had an infectious cerebral mycotic aneurysm, 63 (43.4%) patients had a stroke, 18 (12.4%) patients had vertebral osteomyelitis, and 59 (40.7%) patients had another septic embolism. The mean length of hospital stay was 46 ± 26 days.

The median days for various events as shown in Figure 3 include, patient symptoms to the first visit to a clinic/hospital was 3 days, to obtain blood cultures was 6 days, to admit in the hospital was 7 days, to report a positive blood culture was 7 days, to recall diagnosis of IE was 9 days, and to diagnose definite IE was 13 days, respectively.

Univariate analysis description revealed, inappropriate antibiotics use ($P = .001$), fever ($P = .044$), no-shaking chill ($P = .035$), non-hypoxemia ($P = .016$), qSOFA score ($P = .004$), serum CRP <10 mg/dL ($P < .001$), negative-finding on first echocardiography ($P = .03$), *S aureus* (p = .011), resident in the hospital as a first contact doctor ($P < .001$), primary care physician as a first contact doctor ($P = .022$), and transfer to the hospital by ambulance ($P < .001$) were significant factors associated with a delayed diagnosis of IE (Table 1).

On multivariate analysis using Cox hazard model, inappropriate antibiotics use (HR, 1.61; 95% CI, 1.01 to 2.57; $P = .045$), absence of fever >38°C (HR, 1.80; 95% CI, 1.11 to 2.90; $P = .016$), serum CRP level <10 mg/dL (HR, 1.53; 95% CI, 1.01 to 2.33; $P = .046$), and transfer to hospital by a vehicle other than an ambulance (HR, 3.18; 95% CI, 1.72 to 5.85; $P < .001$) were significantly associated with delayed recall diagnosis of IE (Table 2)

Out of the 126 patients evaluated for the delayed definite diagnosis from reported positive blood cultures among IE patients, 19 patients were excluded. The 7 among excluded, were negative for blood culture and the 12 were diagnosed with IE before reported positive blood culture. On additional multivariate analysis, Cox hazard model revealed, device insertion (HR, 2.01; 95% CI, 1.17 to 3.48; $P = .012$), negative finding on first echocardiography after report of positive blood culture (HR, 1.85; 95% CI, 1.10 to 3.11; $P = .020$), no complication of stroke (HR, 1.51; 95% CI, 1.03 to 2.22; $P = .037$); all these factors were significantly associated with delayed definite diagnosis of IE after a reported positive blood culture (Table 3).

4. Discussion

In present retrospective cohort study, we found that inappropriate antibiotic use, non-ambulance transfer to a hospital, absence

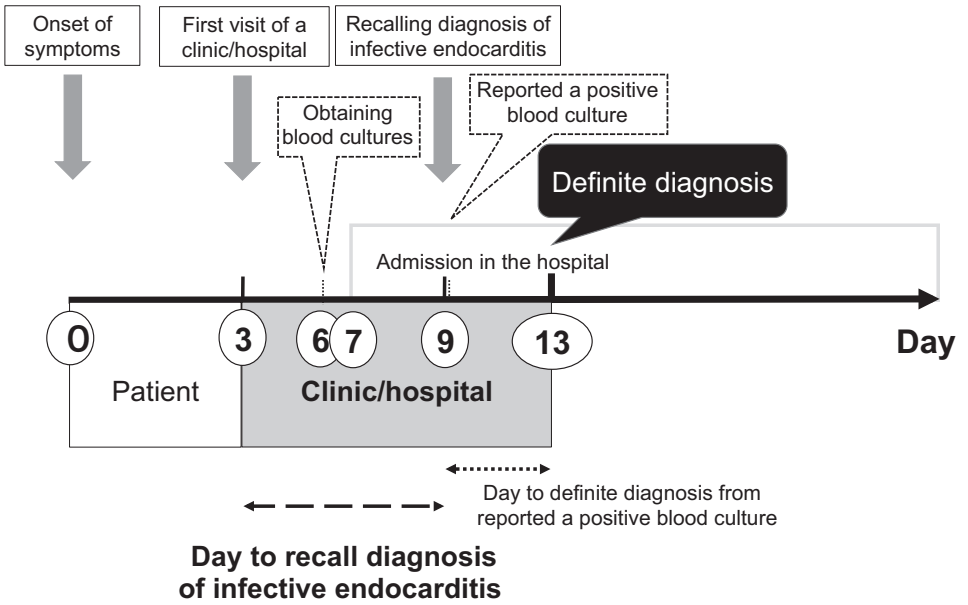

Figure 3. Day until definite diagnosis of infective endocarditis from appearance of patient symptoms.

Table 2

Factors associated with delayed recall diagnosis of infective endocarditis.

(N = 145) Factor	Adjusted HR	95% CI for HR	*P* value
Age < 65 years-old	1.10	(0.680–1.786)	.692
Female gender	0.94	(0.617–1.420)	.755
ADL			.482
Partial dependent	0.90	(0.528–1.441)	
Dependent	1.54	(0.658–3.597)	
Charlson comorbidity index			.948
rank:1 (score:1–2)	1.11	(0.630–1.946)	
rank:2 (score:3–4)	0.95	(0.498–1.818)	
rank:3 (score>4)	1.10	(0.600–2.000)	
Non-device insertion	1.22	(0.724–2.037)	.462
Non-chief complaint related fever	1.04	(0.653–1.658)	.868
Non-chief complaint related heart failure	0.58	(0.214–1.585)	.289
Inappropriate antibiotics use	1.61	(1.011–2.571)	.045*
Absence of shaking chill	1.00	(0.548–1.821)	.997
Absence of fever>38°C	1.80	(1.114–2.899)	.016*
Hypoxemia	0.98	(0.571–1.695)	.955
Serum CRP level <10 mg/dL	1.53	(1.008–2.326)	.046*
Another bacteria of *staphylococcus aureus*	0.98	(0.617–1.567)	.944
Negative finding on first echocardiography	0.97	(0.630–1.493)	.889
Resident on the hospital as a first contact doctor	0.73	(0.406–1.305)	.287
Primary care physician as a first contact doctor	0.97	(0.596–1.595)	.919
Transferred by non-ambulance	3.18	(1.724–5.848)	<.001*

ADL = activity of daily life, CI = confidence interval, CRP = C-reactive protein, HR = hazard ratio, N = number.
* $P < .05$. Multivariable Cox proportional hazards model was used.

of fever >38°C, and serum CRP level <10 mg/dL were associated with delayed diagnosis of IE. Device insertion; negative echocardiography finding after reporting a positive blood culture, and no complication of stroke were factors related to a delayed definite diagnosis, after a reported positive blood culture.

The duration between the first visit to a clinic/hospital and the definite diagnosis of IE (10 days), was more than the duration between the development of patient symptoms to the first visit of a clinic/hospital (3 days) (Fig. 3). The result show that diagnosing IE as early as possible is more important than the duration taken for the first visit to a clinic/hospital, to improve its mortality and morbidity. It is, therefore, important to promote medical education and improve the diagnostic methods for IE, to shorten the duration for its diagnosis.

Table 3

Factors related with delayed definite diagnosis of infective endocarditis after a reported positive blood culture.

Variable (n = 126)	Adjusted HR	95% CI for HR	*P* value
Age < 65 years-old	0.83	(0.542 to 1.258)	.372
Female gender	0.76	(0.500 to 1.149)	.192
Device insertion	2.01	(1.165 to 3.482)	.012*
Non-General Internal Medicine department	1.22	(0.801 to 1.869)	.350
Only 1 set positive blood culture	1.23	(0.461 to 3.268)	.682
Negative finding on first echocardiography	0.74	(0.432 to 1.267)	.273
Negative finding on first echocardiography after report of positive blood culture	1.85	(1.100 to 3.106)	.020*
Vegetation <10 mm	1.07	(0.722 to 1.595)	.729
Staphylococcus aureus	0.81	(0.525 to 1.235)	.320
No complication of stroke	1.51	(1.026 to 2.215)	.037*
No complication of osteomyelitis	0.91	(0.501 to 1.651)	.756
No complication of septic embolism	0.78	(0.492 to 1.248)	.305

CI = confidence interval, HR = hazard ratio, n = number.
* $P < .05$.

In one of the earlier studies, univariate analysis has shown the tendency of the relationship about inappropriate antibiotics use as an associate factor for the delayed diagnosis of IE, but the multivariate analysis did not show any relationship, probably due to small sample size used.[2] Although high body temperature predicts bacteremia,[17,18] patients without fever >38°C may be overlooked bacteremia such as for a diagnosis of IE. Fever may be absent in 20% to 30% of elderly patients being affected with a serious infection.[19] Therefore, physicians can't exclude the diagnosis of IE even in the absence of a fever. We speculate, physicians may delay obtaining blood cultures in patients with lower CRP level, similar to delay in diagnosis of vertebral osteomyelitis related to lower CRP level.[20] Physicians may attribute either viral infections or some other non-bacterial causes in patients with the lower CRP level. Moreover, our research (data not shown in the part of Results) showed that patients with IE attributed to *streptococcus species* had lower CRP levels. In patients with serum CRP level <10 mg/dL (n = 77), *S aureus* were involved in 13.0% (n = 10) and *Streptococcus species* were involved in 54.5% (n = 42). On the other hand, in patients with serum CRP level >10 mg/dL (n = 68), *S aureus* were involved in 39.7% (n = 27) and *Streptococcus species* were involved in 44.1% (n = 30). Therefore, physicians should take care of delay diagnosis of *Streptococcal* IE patients with lower CRP level. It is easy to obtain blood cultures in emergency room (ER), especially patients using ambulance are obtained due to available access. While the diagnosis of IE was delayed in patients using non-ambulance services for hospital visit due to difficulty access to obtain blood cultures. Therefore, delayed recall diagnosis of IE, due to inappropriate antibiotics use, in patients transferred by non-ambulance vehicular services, in patients without high fever, and in patients with lower CRP level can be improved significantly through educating physicians and improving the diagnostic methods.

As device insertions, including cardiac pacemaker and implantable cardioverter-defibrillator were increased worldwide,[21] device-related infective endocarditis also increased.[22] The diagnosis of cardiac device infections, particularly device-related endocarditis, is challenging.[23] Thus, patients with device insertion may be taken longer days from reported a positive blood culture to definite IE diagnosis, consistent with the results of our additional analysis. After reporting a positive blood culture, transthoracic echocardiography (TTE) is usually performed. Most guidelines recommend transesophageal echocardiography (TEE) in cases of suspected IE, particularly when an initial TTE is negative.[24,25] Thus, those patients with false negative TTE will have their diagnosis delayed. False negative TTE may confer a more benign prognosis among patients ultimately diagnosed with IE.[8,26,27] In the hospital, there is a department of neuro-endovascular surgery. After diagnosed the stroke in the department of ER, the neuro-endovascular surgeon is referred as soon as possible and assesses the etiology of stroke. Therefore, IE complicated stroke may be early diagnosed after reporting a positive blood culture. The factors of device insertion, negative echocardiography, and no complication of stroke

depend on the IE patients, does not depend on steps taken for diagnostic improvement.

To the best of our knowledge, our research is the first study that focuses on factors associated with delayed diagnosis of IE. The noteworthy strength of this study is that the data were collected from a relatively large-scale sample. Moreover, we followed real data from patient symptoms through clinic/hospital visit to definite diagnosis of IE (Fig. 3). The results show that the duration between the patient's clinic/hospital visit and the day of obtaining blood cultures or the day recalling diagnosis of IE needs a lot to improve, during the period to a definite diagnosis.

This study has several limitations. Our research was based on a single-center cohort design. The clinical ability of physicians was variable, depending on their level of training and experience, which may have led to selection bias. Also, we are unable to establish a causal relationship in this retrospective observational study.

Future research needs to be directed at understanding the factors associated with a delayed diagnosis of IE; this information may help with earlier diagnosis of IE patients and improve patient outcomes. Therefore, multi-center, prospective studies, by using a multi-level analysis are required, across different population groups to support the evidence of our findings.

5. Conclusions

We revealed the process for a definite diagnosis of IE, from a time of its initial symptoms. Physicians can improve the diagnostic delay of IE, by shortening the duration to obtain blood cultures or recalling the IE diagnosis. Diagnosis of IE was delayed in patients with inappropriate antibiotics use, patients transferred by non-ambulance vehicular services, patients without high fever, and patients with lower CRP level. Therefore, physicians need to take care of appropriate antibiotic use and consider obtaining blood cultures in patients who are transferred by other means of transportation than in ambulances, patients without fever $>38°C$, and patients with lower CRP levels for earlier IE diagnosis.

Author contributions

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