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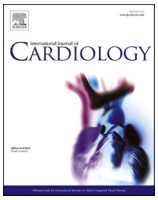

Variables associated with diagnostic delay and mortality in infective endocarditis: an observational retrospective study

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ABSTRACT

Background: In infective endocarditis (IE), a prompt diagnosis and therapy lead to better outcomes. Diagnostic delay seems common, but causing factors are still under-investigated, limiting actions to improve outcomes. This study examines variables associated with IE delayed diagnosis and mortality.
Methods: This single-centre retrospective observational study included adults diagnosed with IE according to Duke's criteria from 2009 to 2022. IE diagnoses within 5 days from hospital admission (<5d) were compared to those from day 5 onwards (≥5d). Logistic regression and Cox analyses identified factors associated with ≥5d diagnosis and in-hospital mortality. Sensitivity analyses excluding recurrent endocarditis or diagnoses before 2016, and a post-hoc analysis focused on fever at admission were performed.
Results: This study included 349 episodes of IE that occurred in 331 patients (females:31.2%; median age:72 years). Median time to diagnosis was 3 days (IQR:1–8), 196 (56.2%) patients received a diagnosis before and 153 (43.8%) after 5 days. Absence of fever at presentation was associated with ≥5d diagnosis (OR:2.09; 95%CI [1.23–3.56]; $p = 0.011$). Although mortality was not associated to a ≥ 5d diagnosis (HR:0.96; 95%CI [0.49–1.87] $p = 0.905$), a higher risk of mortality was found in patients with absence of fever (HR:2.03; 95%CI [1.06–3.90]; $p = 0.033$) and embolic events (HR:2.15; 95%CI [1.11–4.16]; $p = 0.023$), which were more frequent in patients without fever (46/120, 38.3%) than with fever (54/227, 23.8%, $p = 0.007$).
Conclusions: IE patients presenting without fever have higher risk of delayed diagnosis and mortality, possibly due to a higher incidence of embolic events. In these patients, efforts to improve early diagnosis are required.

1. Introduction

Infective Endocarditis (IE) is a major health challenge, characterized by high mortality, morbidity and complications [1]. IE mortality has not improved in two decades [2], despite advances in treatment and technology. Among factors that might influence patients' outcomes, a prompt diagnosis has probably the potentiality of affecting the natural history of the disease [3,4]. Indeed, a timely diagnosis is essential for a quick beginning of correct treatments: an early start of antibiotic therapy leads to a rapid fall of the risk of embolic events [5], which is associated with a lower mortality, as well as to an early surgical intervention [6]. On the opposite, a consistent delay in the diagnosis leads to a higher number of complications [7] and a worse prognosis. Therefore, time to diagnosis and diagnostic delay seem to be critical issues to be

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addressed in this field [8].

Despite the importance of a rapid diagnosis for IE patients, diagnostic delay in IE is known to be common [7–10], but little is known about factors causing it. To our knowledge, only two retrospective studies by and N'Guyen et al. [10] and Nishiguchi et al. [8] analysed such factors. The first study considered as outcome time to diagnosis from the onset of symptoms, while the second study considered time to diagnosis since either extra- or intra-hospital medical contacts have first occurred. It is particularly useful to evaluate time to diagnosis from the first medical contacts, as it is a modifiable variable that can potentially be improved with ameliorative measures, as opposed to counting time from symptoms. Moreover, considering only in-hospital medical contacts better reflects the nature of a severe illness requiring advanced in-hospital therapies. Finally, knowing factors that are responsible for in-hospital diagnostic delay is the first step to improve and fasten the diagnostic process of IE patients and, thus, to potentially improve the prognosis of a high-mortality disease.

This retrospective study aims to identify factors related to in-hospital diagnostic delay, analyse its association with in-hospital mortality and describe IE-related complications. We hypothesized that variables such as age, risk factors such as previous intervention on cardiac valves, clinical presentation, and laboratory findings might be associated with diagnostic delay in IE patients. Furthermore, we hypothesized that diagnostic delay is associated with increased risk of in-hospital mortality.

2. Methods

2.1. Study design

This is a monocentric retrospective observational study including patients who received a diagnosis of IE from January 2009 to November 2022 in a tertiary-care hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by institutional Review Board approval (ID 6056_04.06.2025_M, approved by Comitato Etico Territoriale Lombardia 3). Need for informed consent was waived based on the retrospective nature of the study, and the pseudonymization of collected data. The current study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement.

2.2. Patient population

All clinical episodes with a discharge coded diagnosis of IE based on the on the International Classification of Disease – Ninth revision (codes: 421.0, 421.1, 421.9) were searched and screened. Adults (≥18 years) with “definite” or “possible” IE diagnosis according to the Duke's criteria [11,12] were included. Exclusion criteria were age < 18 years, unconfirmed “definite” or “possible” IE diagnosis based on the Duke's criteria [11], patients with a previous diagnosis of IE undergoing unspecific admission, patients with uncompleted or inaccessible documents, patients with confirmed diagnosis prior to the admission.

2.3. Data collection and outcomes

Data were collected retrospectively by patients' medical records and included in a dedicated electronic case report form, according to the predefined protocol and variable definitions (Supplementary Table 1). Data regarding demography, comorbidities, characteristics at presentation, diagnosis, and in-hospital mortality were obtained retrospectively by patients' charts. Primary outcome was time to diagnosis defined as time from presentation at the hospital to IE diagnosis. Secondary outcomes were in-hospital mortality, in-hospital complications and length of stay (Supplementary methods and Supplementary Table 1).

2.4. Statistical analysis

The population was divided in two subgroups: IEs diagnosed within 5 days from hospital admission (<5d) were compared to those diagnosed from day 5 onwards (≥5d). Considering blood culture results as a cornerstone of IE diagnosis, the 5 days cut-off was chosen based on the standard duration of incubation of blood cultures to reduce the risk of diagnostic bias due to the intrinsic length of the microbiological analysis. Categorical variables were expressed as absolute frequency (percentage based on available data, excluding missing values), and continuous variables as median [interquartile range (25th, 75th), IQR]. Chi-square test (or Fisher's exact test when appropriate) was used to compare categorical variables and Mann–Whitney–Wilcoxon test to compare continuous variables, using a 95% confidence level. Boxplots and histograms were used to graphically represent time to IE diagnosis.

A Cox proportional hazards model was first applied to assess factors associated with time to diagnosis (as a continuous outcome), using backward stepwise variable selection with a p-value threshold of 0.1. Predictors retained in this model were subsequently used in a multivariable logistic regression to estimate the odds of delayed diagnosis (≥5 days).

Given that individuals could experience multiple hospitalizations, a generalized linear mixed model with a logit link and random intercept for each subject was fitted to estimate the odds of delayed diagnosis (≥5 days). Results were presented as odds ratios (OR) with 95% confidence intervals (CI). Kaplan-Meier curves and a log-rank test were used to represent the cumulative probability of IE diagnosis by age, presence of prosthetic valve or valvuloplasty, fever at presentation, and blood cultures in absence of antibiotic therapy.

Aalen-Johansen estimates were used to investigate in-hospital mortality and discharge (competitive outcomes) since diagnosis according to time to diagnosis. A Cox proportional hazards model investigated factors associated with in-hospital mortality, including categorical time to diagnosis (≥5 days), demographical characteristics, clinical variables at presentation and IE complications. To account for multiple hospitalizations from the same patient, a random effect was included using a log-normal frailty distribution. Results were reported as hazard ratios (HR) with 95% CI. Based on the key role of fever as showed by the Cox models, a post-hoc secondary analysis was conducted to compare patients with presence (fever) or absence (apyretic) of fever at presentation. A logistic regression model was performed to analyse if presence of fever was related to the presence of cancer and/or Human Immunodeficiency Virus (HIV) infection, used as proxy variables for immunocompromised status.

Two sensitivity analyses were conducted. To exclude differences in recalling the diagnosis of IE based on the patient's medical history of previous episodes of IE, a sensitivity analysis considering only patients with first episode of IE was conducted. The second sensitivity analysis included only IE diagnosis made since January 2016 to account for possible changes related to the introduction of the 2015 European Society of Cardiology guidelines on IE [11]. Type I error was set at 0.05. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

In total, 464 IE diagnoses were screened, and 349 episodes were included in the analysis (Supplementary Fig. 1), corresponding to 331 patients. Time to diagnosis was <5d for 196 episodes (56.2%) and ≥ 5d for 153 (43.8%, Table 1). Median age was 72 [60, 79], and female accounted for 31.2% (n = 109) of the study sample. Patients with ≥5d diagnosis were older (<5d: 69 years [55, 78]; ≥5d: 74 years [65, 80]; p = 0.001), had a higher Charlson Comorbidity Index [13] (<5d: 2 [0,3]; ≥5d: 2[1, 4]; p = 0.015) and a higher prevalence of pulmonary disease

Table 1
Baseline characteristics of the patients included in the study.

	Overall population ($n = 349$)	Time to diagnosis < 5 days ($n = 196$)	Time to diagnosis ≥ 5 days ($n = 153$)	p-value	Missing values [%]
Sex (female)	109 (31.2)	53 (27.0)	56 (36.6)	0.073	0.0
Age (years)	72 [60, 79]	69 [55, 78]	74 [65, 80]	**0.001**	0.0
Comorbidities and risk factors					
Arterial hypertension	203 (58.2)	115 (58.7)	88 (57.5)	0.914	0.0
Chronic kidney disease	77 (22.1)	39 (19.9)	38 (24.8)	0.330	0.0
Diabetes mellitus	87 (24.9)	49 (25.0)	38 (24.8)	1.000	0.0
Pulmonary disease	61 (17.5)	22 (11.2)	39 (25.5)	**0.001**	0.0
HIV	12 (3.4)	9 (4.6)	3 (2.0)	0.297	0.0
Drug use	21 (6.0)	16 (8.2)	5 (3.3)	0.093	0.0
Cancer	45 (12.9)	25 (12.8)	20 (13.1)	1.000	0.0
Invasive procedures (3 months before)	42 (12.0)	27 (13.8)	15 (9.8)	0.334	0.0
Prior endocarditis	37 (10.6)	22 (11.2)	15 (9.8)	0.801	0.0
Valvular prosthesis or annuloplasty	112 (32.7)	66 (34.7)	46 (30.3)	0.447	2.0
Implantable cardiac device	76 (21.8)	39 (19.9)	37 (24.2)	0.406	0.0
Cardiac alterations	104 (30.4)	55 (28.6)	49 (32.7)	0.494	2.0
Charlson comorbidity index	2 [0, 3]	2 [0, 3]	2 [1, 4]	**0.015**	0.3
Characteristics at presentation					
Presence of fever	227 (65.4)	142 (72.8)	85 (55.9)	**0.002**	0.6
Neurological signs and symptoms	59 (17.0)	34 (17.4)	25 (16.4)	0.921	0.6
Device infection	5 (1.4)	3 (1.5)	2 (1.3)	1.000	0.6
Syncope	14 (4.0)	9 (4.6)	5 (3.3)	0.728	0.6
Dyspnoea	49 (14.2)	25 (13.0)	24 (15.8)	0.553	1.1
Leukocytes [10^3/mm^3]	10.0 [7.2, 14.4]	10.0 [7.5, 14.4]	9.9 [6.6, 14.3]	0.568	0.6
Platelets [10^3/mm^3]	187 [127, 247]	189 [126, 253]	184 [134, 235]	0.529	0.6
Reactive C-protein [mg/dl]	7.8 [3.6, 14.0]	8.4 [4.2, 15.0]	7.1 [2.9, 12.1]	**0.042**	2.3

Data are reported as n (% as valid percentage excluding missing values) or median [interquartile range].
HIV, Human immunodeficiency virus.

(<5d: $n = 22$ [11.2%]; ≥5d: $n = 39$ [25.5%]; p = 0.001) compared to patients with <5d diagnosis. Fever at presentation was more common in IEs with <5d diagnosis (<5d: $n = 142$ [72.8%]; ≥5d: $n = 85$ [55.9%]; $p = 0.002$) and in the latter group C-Reactive Protein (CRP) had a higher value at presentation (<5d: 8.4 mg/dl [4.2, 15.0]; ≥5d: 7.1 mg/dl [2.9, 12.1]; $p = 0.042$).

3.2. Diagnostic process and time to diagnosis

Median time to diagnosis was 3 days (IQR [1; 8], Supplementary Fig. 2). IEs with ≥5d diagnosis had longer time from presentation to transthoracic (TTE) and transoesophageal echocardiography. Also, they had a delayed beginning of antibiotic therapy compared to <5d IEs diagnosis (Table 2). A definite diagnosis was more common in the ≥5d group, as well as a positivity of the major imaging criteria, while a possible diagnosis was more frequent in the <5d group. No differences were seen in the microbiological asset (Table 2).

After adjustment for covariates (Table 3), absence of fever showed an OR of 2.09 (95%CI [1.23; 3.56]; $p = 0.011$) and age ≥ 65 years an OR of 2.29 (95%CI [1.29; 4.06]; $p = 0.008$) for ≥5d diagnosis. The Cumulative incidence curves (Supplementary Fig. 3) showed that patients aged ≥65 years ($p = 0.045$), those with absence of fever at presentation ($p < 0.001$) and those without blood cultures before antibiotics ($p = 0.009$) experienced a longer time from hospital admission to diagnosis.

The sensitivity analysis including only first IE diagnosis ($n = 312$; Supplementary Tables from 2 to 5) confirmed that absence of fever at admission, age ≥ 65 and absence of blood cultures prior to antibiotics were associated to a time to diagnosis ≥5 days, while the sensitivity analysis including IEs diagnosed from 2016 to 2022 ($n = 218$, Supplementary Tables from 6 to 9) confirmed that age ≥ 65 years and absence of blood cultures sampling were associated with diagnosis ≥5 days.

3.3. In-hospital outcomes and mortality

Among patients discharged alive, IEs with ≥5d time to diagnosis had a longer hospital stay (<5d: 31 days [20, 41]; ≥5d: 33 days [24, 49]; $p = 0.031$). No differences between the two groups were seen for in-hospital mortality (<5d: $n = 27$ [13.8%]; ≥5d: $n = 25$ [16.3%]; $p = 0.606$; Fig. 1 and Supplementary Fig. 4). Diagnosis occurring ≥5 days after admission showed an HR of 0.96 (95%CI [0.49; 1.87]; $p = 0.905$) for in-hospital mortality. Each additional point in the CCI [13] was associated with a 15% (HR 1.15; 95%CI [1.01; 1.31]; $p = 0.039$) increase of in-hospital mortality risk (Table 3). Absence of fever at presentation was associated with a 2-fold increase in risk (HR 2.03; 95%CI [1.06; 3.90]; $p = 0.033$) of in-hospital mortality, while vascular phenomena were associated to a more than 2-fold increased risk (HR 2.15; 95%CI [1.11; 4.16]; $p = 0.023$; Table 3).

3.4. Post-hoc analysis: presence and absence of fever at presentation

Patients presenting with no fever ($n = 120$, 34.4%) had less frequently a history of prior endocarditis (apyretic: $n = 6$ [5.0%]; fever: $n = 31$ [13.7%]; $p = 0.021$) and lower CRP at presentation (apyretic: 5.9 mg/dl [2.3, 10.1]; fever: 8.9 mg/dl [4.2, 16.2]; $p = 0.001$; Supplementary Table 10). Time from presentation to TTE ($p = 0.002$), blood cultures ($p < 0.001$) and antibiotic therapy (p < 0.001) were longer in the apyretic subgroup (Supplementary Table 11).

S. aureus positive blood cultures were more common in the fever subgroup (apyretic: $n = 19$ [15.8%]; fever: $n = 74$ [32.6%]; p = 0.001), while apyretic IEs had more negative blood cultures (apyretic: $n = 22$ [18.3%]; fever: $n = 21$ [9.3%]; $p = 0.023$). Apyretic patients had a more frequent diagnosis of aortic endocarditis (apyretic: $n = 66$ [57.9%]; fever: $n = 91$ [43.5%]; $p = 0.019$). Vascular phenomena (apyretic: $n = 46$ [38.3%]; fever: $n = 54$ [23.8%]; $p = 0.007$) and in-hospital mortality (apyretic: $n = 28$ [23.3%]; fever: $n = 24$ [10.6%]; $p = 0.003$) were also more frequent in the apyretic subgroup. Immunocompromised status (presence of cancer and/or HIV infection) demonstrated an OR of 0.787 (95% CI [0.41–1.52]; $p = 0.451$, Supplementary Table 12) for presence of fever.

In the multivariable analysis of apyretic patients (Supplementary Table 13), absence of blood cultures sampling before antibiotic therapy was associated with a more than 6-fold increased odds of diagnosis ≥5 days (OR 6.74; 95%CI [1.45; 31.26]; $p = 0.015$). Among apyretic patients, each additional point in the CCI was associated with a 24% increased risk of in-hospital mortality (HR 1.24; 95%CI [1.06; 1.46]; $p = 0.007$, Supplementary Table 14).

Table 2
Diagnosis and outcomes.

	Overall population (n = 349)	Time to diagnosis < 5 days (n = 196)	Time to diagnosis ≥ 5 days (n = 153)	p-value	Missing values [%]
Localization of IE					
Aortic valve	158 (48.6)	89 (51.1)	69 (45.7)	0.384	6.9
Mitral valve	125 (38.5)	67 (38.5)	58 (38.4)	1.000	6.9
Tricuspid valve	23 (7.1)	14 (8.0)	9 (6.0)	0.607	6.9
CIEDRIE	52 (14.9)	26 (13.3)	26 (17.0)	0.424	0.3
Native valve	203 (59.7)	112 (59.9)	91 (59.5)	1.000	2.6
Prosthetic valve	102 (30.0)	61 (32.6)	41 (26.8)	0.295	2.6
Time [days]					
From symptoms to presentation	5 [1,23]	5 [1, 23]	7 [2, 25]	0.562	7.2
From presentation to diagnosis	3 [1, 8]	1 [0, 3]	9 [7, 13]	–	0.0
From presentation to TTE	4 [0, 9]	1 [0, 4]	7 [4, 13]	**<0.001**	26.1
From presentation to TEE	5 [3,10]	3 [1, 6]	9 [6, 14]	**<0.001**	19.5
From presentation to blood cultures	0 [0,1]	0 [0, 1]	0 [0, 5]	**<0.001**	9.2
Blood cultures prior to antibiotics	298 (85.9)	174 (89.2)	124 (81.6)	0.061	0.6
Result of blood cultures					
Staphylococcus aureus	93 (26.6)	54 (27.6)	39 (25.5)	0.757	0.0
Coagulase-negative staphylococci	34 (9.7)	17 (8.7)	17 (11.1)	0.562	0.0
Enterococcus	58 (16.6)	30 (15.3)	28 (18.3)	0.548	0.0
Streptococcus viridans	45 (12.9)	31 (15.8)	14 (9.2)	0.092	0.0
Streptococcus gallolyticus	35 (10.0)	24 (12.2)	11 (7.2)	0.167	0.0
Other *streptococci*	13 (3.7)	4 (2.0)	9 (5.9)	0.111	0.0
Fungi	1 (0.3)	0 (0.0)	1 (0.7)	0.901	0.0
Other	31 (8.9)	17 (8.7)	14 (9.2)	1.000	0.0
Polymicrobic	8 (2.3)	4 (2.0)	4 (2.6)	1.000	0.0
Negative	43 (12.3)	21 (10.7)	22 (14.4)	0.385	0.0
Duke's criteria					
Major - blood cultures	281 (80.5)	163 (83.2)	118 (77.1)	0.202	0.0
Major - imaging	262 (75.1)	127 (64.8)	135 (88.2)	**<0.001**	0.0
Minor - embolic vascular phenomena	100 (28.7)	62 (31.6)	38 (24.8)	0.203	0.0
Minor - immunological phenomena	6 (1.7)	4 (2.0)	2 (1.3)	0.914	0.0
Minor - microbiological evidence	24 (6.9)	14 (7.2)	10 (6.5)	0.982	0.3
Minor - predisposing conditions	235 (67.3)	141 (71.9)	94 (61.4)	0.050	0.0
Minor - fever >38 °C	262 (75.3)	158 (81.0)	104 (68.0)	**0.007**	0.3
Definite endocarditis	244 (70.1)	124 (63.6)	120 (78.4)	**0.004**	0.3
Possible endocarditis	103 (29.6)	71 (36.4)	32 (20.9)	**0.002**	0.3
Length of stay (alive only*) [days]	31 [21, 43]	31 [20, 41]	33 [24, 49]	**0.031**	0.0
Time from presentation to antibiotics [days]	0 [0,2]	0 [0, 1]	1 [0, 4]	**0.017**	7.7
Surgery	102 (77.9)	64 (83.1)	38 (70.4)	0.130	62.5
In-hospital mortality	52 (14.9)	27 (13.8)	25 (16.3)	0.606	0.0

Data are reported as n (% as valid percentage excluding missing values) or median [interquartile range].
CIEDRIE, Cardiac Implantable Electronic Device Related Infective Endocarditis; IE, Infective Endocarditis; TTE, Transthoracic echocardiography; TEE, Transesophageal echocardiography.
* Length of stay was calculated only among patients discharged alive (n = 297).

4. Discussion

The present study demonstrated that median time from first in-hospital contact to IE diagnosis was 3 days and 44% of the patients received a diagnosis from the fifth day onward after hospital admission. Absence of fever at admission and age ≥ 65 years were associated with an increased risk of diagnosis from the fifth day onward. While diagnosis from the fifth day onward was not associated with increased risk of in-hospital death, apyretic patients at admission had a 2.03-fold increased risk of in-hospital mortality. Vascular phenomena, which were more frequent in apyretic patients, were associated with a twofold increased risk of mortality.

Delay in IE diagnosis occurs frequently [7–10]. This study demonstrated that median time from hospital admission to IE diagnosis was 3 days. While none of the previous studies on this topic investigated this specific time interval, Nishiguchi et al. [8] observed a median time of 10 days from first medical contact (considering also general practitioners and clinics) to IE diagnosis. These different median times account for the variability among study designs and healthcare systems [14] in terms of access to primary care and referrals to tertiary hospitals (the current study was developed in a tertiary referral hospital on patients having direct access to the emergency department). These results are, thus, of particular interest to improve the in-hospital IE diagnostic process. Being a patient-dependent variable, time from the beginning of IE symptoms to diagnosis was not considered in the analysis and dedicated studies should be developed to optimize patients' ability to recognize IE symptoms, in order to shorten this time interval.

Although median time was 3 days, 44% of IE diagnoses occurred from fifth day after admission. According to current guidelines [4], prompt recognition of suspected IE implies blood sampling for cultures before initiation of antibiotics. The standard period of incubation of blood cultures is 5 days, however, the high percentage of diagnoses after the fifth day could not be attributed only to this time span, highlighting the need to identify modifiable factors that can be targeted to reduce time to diagnoses. A high suspicion threshold of IE should be developed for patients with atypical presentation, particularly those without fever. These patients represented the 34.4% of the population analysed in this study and had higher odds of ≥5d diagnosis. Similarly, a longer time to IE diagnosis in apyretic patients was also described by Nishiguchi et al. [8] and N'Guyen et al. [10] (despite differences in the study designs). Fever is the most expected clinical feature of IE, as shown by the European Infective Endocarditis (EURO-ENDO) Registry [2], in which more than 70% of IE patients presented with fever. For this reason, absence of fever at presentation leads to a less clear clinical picture, preventing a prompt diagnosis. A retrospective study considering IEs from 1970 to 2006 [15] compared apyretic to febrile endocarditis, and

Table 3
Logistic regression model for time to diagnosis ≥5 days (upper) and Cox proportional hazards model for in-hospital mortality (lower).

IEs = 338, ≥5d = 150	Odds ratio	95% confidence interval		p-value
		Lower limit	Upper limit	
Age ≥ 65 years (reference: <65 years)	2.291	1.292	4.064	**0.008**
Absence of valvular prothesis or annuloplasty (reference: Presence)	1.597	0.908	2.811	0.096
Absence of fever at presentation (reference: Presence)	2.089	1.228	3.555	**0.011**
Absence of blood cultures before antibiotics (reference: Presence)	1.677	0.808	3.482	0.149

IEs = 343, ≥5d = 51	Hazard ratio	95% confidence interval		p-value
		Lower limit	Upper limit	
Time to diagnosis ≥5 days (reference: <5 days)	0.960	0.493	1.869	0.905
Male sex (reference: Females)	1.868	0.951	3.672	0.070
Age ≥ 65 years (reference: <65 years)	2.004	0.877	4.578	0.099
Charlson comorbidity index	1.148	1.007	1.308	**0.039**
Absence of fever at presentation (reference: Presence)	2.031	1.058	3.900	**0.033**
Absence of blood cultures before antibiotics (reference: Presence)	1.983	0.891	4.415	0.094
Presence of vascular phenomena (reference: Absence)	2.153	1.113	4.164	**0.023**

≥5d, time to diagnosis ≥5 days; IE, infective endocarditis.

observed a longer symptom duration before the diagnosis in the first group. This confirms that diagnostic delay in apyretic patients at presentation is not an uncommon event. Moreover, in these patients, it is of paramount importance to obtain blood cultures samples before the start of antibiotics. While this variable was not associated with diagnostic timing in febrile patients, absence of blood cultures before starting antibiotics in apyretic patients was associated with a sixfold increase in the odds of ≥5d diagnosis. Among apyretic patients, 18.3% of them had negative blood cultures, twice as much as patients with initial fever. Similarly, in the ESC-EORP EURO-ENDO registry [16] blood culture-negative IE represented 16.8% of total IEs, with fever at presentation being less frequent in this subgroup. Moreover, it was found that blood culture-negative IE carried a higher 30-day mortality risk and a higher 1-year mortality in patients treated with medical therapy alone compared to those with a positive result [16]. These findings further emphasize the importance of blood culture sampling on antibiotic wash-out, especially in apyretic patients, to increase the test sensibility.

Surprisingly, time to diagnosis per se was found not to be related to a higher in-hospital mortality. Based on the overall clinical features of the investigated patients, we can hypothesize that IE diagnosed ≥5d could have been caused by a sub-clinical or chronic infection, determining an overall milder clinical presentation and a better prognosis. Similarly, N'Guyen [10] et al. observed that in-hospital mortality was higher in the early-diagnosed IE (within 1 month from the first symptom) compared to the late-diagnosed IE. Another study [17] proposing 6-month mortality risk score in IE found that a duration of symptoms >1 month prior to admission, was a protective factor against adverse outcomes.

While an increased risk of mortality based on time to diagnosis was not found in the general population of the study, the subgroup of apyretic patients showed significant findings regarding this topic. Absence of fever at presentation was associated with a 2.03-fold increased risk of in-hospital mortality, and vascular phenomena, which were more frequent in apyretic patients, were associated with a twofold increased risk of in-hospital mortality. Although fever could represent the marker of a stronger infection, absence of fever has been associated with higher mortality in patients with bacteriemia [18]: several hypotheses could be identified to explain this aspect. First, presence of fever at admission could direct the physician's attention towards the correct diagnostic process. On the opposite, apyretic patients have delayed sampling of blood cultures and echocardiographic exams. Second, a rapid diagnosis and, thus, therapy start could reduce the impact of IE complications, such as embolic events [5] that were associated with in-hospital mortality in the current study and were more frequent in apyretic patients. Thus, vascular embolic phenomena could represent an intermediary factor for in-hospital mortality in apyretic patients, leading to a worse prognosis [4]. Third, apyretic patients were more often characterized by aortic valve IE localization, which is known to frequently lead to acute left ventricular failure [19] and perivalvular complications [4]. Further analyses are warranted to investigate these hypotheses and their long-term effects. So far, a retrospective study considering IEs from 1970 to 2006 [15] found no difference in long-term mortality between apyretic

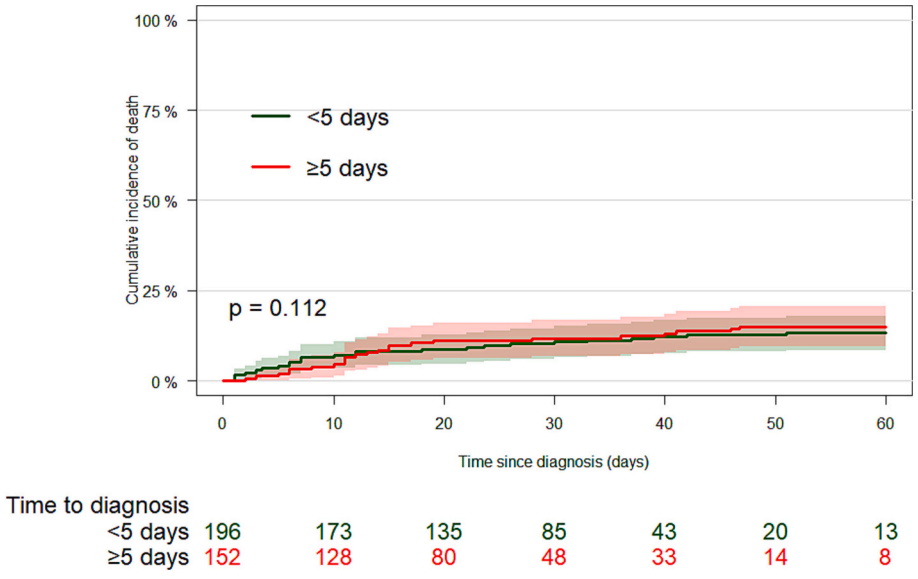

Fig. 1. Aalen-Johansen curves for cumulative incidence of death by time to infective endocarditis diagnosis (p-value = 0.112).

and febrile endocarditis but more is required to analyse and optimize these patients' outcomes.

Our study has limitations that prevent extensive generalization of its results, given its monocentric nature. First, patients' characteristics and causative germs are influenced by local epidemiology and different use of antibiotics. Moreover, since this study was conducted in a tertiary-care hospital for IE, results may not be applicable to an in-patient population of different centres. Finally, female sex was underrepresented in study population. Furthermore, the selection of patients might have missed those patients who died before establishing an IE diagnosis, and 45 patients with an IE diagnosis were excluded because of inaccessible documentation. Additional variables that were not retained in the final models may also be associated with delayed diagnosis. Details about immunocompromised status were not available, thus presence of HIV infection or cancer were used as proxy variables. Lastly, the relation between time to diagnosis and mortality had not been analysed considering a stratification of patients based on the severity of clinical presentation.

This study showed that IE diagnosis occurred after the fifth day from first in-hospital medical contact in 44% of cases and that absence of fever at presentation was associated with an increased chance of delayed diagnosis. Despite longer time to diagnosis does not seem to be associated with reduced in-hospital survival, apyretic patients, beside the higher odds for a delayed diagnosis, also had an increased rate of embolic vascular phenomena and a higher risk of in-hospital mortality. Efforts should be made to reduce IE diagnostic delay, especially in apyretic patients, and further studies are warranted to assess whether an earlier disease recognition, especially in these patients, might have an impact on long-term outcome.

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CRediT authorship contribution statement

Giulia Brioschi: Writing – original draft, Validation, Methodology, Data curation, Conceptualization, Visualization, Supervision. **Silvia Mariani:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization, Investigation. **Giuseppe Occhino:** Writing – review & editing, Methodology, Formal analysis. **Felice Achilli:** Writing – review & editing, Conceptualization, Supervision. **Nicolò Capsoni:** Writing – review & editing, Conceptualization. **Davide Carlo Corsi:** Writing – review & editing, Methodology, Conceptualization. **Alessandra Fagnani:** Writing – review & editing, Data curation. **Paola Rebora:** Writing – review & editing, Methodology, Formal analysis. **Maria Sosio:** Methodology, Data curation, Writing – review & editing. **Maddalena Lettino:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Conceptualization. **Giovanni Marchetto:** Writing – review & editing, Supervision, Methodology, Conceptualization, Project administration, Visualization. **Michele Bombelli:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Conceptualization.

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Declaration of competing interest

Nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2026.134449.

Data availability statement

Data will be shared on reasonable request to the corresponding author.

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