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Impact of the initial clinical presentation on the outcome of patients with infective endocarditis

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Abstract

Background: *Infective endocarditis (IE) is a life-threatening disease. Despite advancements in diagnostic methods, the initial clinical presentation of IE remains a valuable asset. Therefore, the impact of clinical presentation on outcomes and its association with microorganisms and IE localization were assessed herein.*

Methods: *This retrospective study included 183 patients (age 68.9 ± 14.2 years old, 68.9% men) with definite IE at two tertiary care hospitals in Belgium. Demographic data, medical history, clinical presentation, blood cultures, imaging data and outcomes were recorded.*

Results: *In-hospital mortality rate was 22.4%. Sixty (32.8%) patients developed embolism, 42 (23%) shock, and 103 (56.3%) underwent surgery during hospitalization. Shock at admission predicted embolism during hospitalization (odds ratio [OR] 2.631, 95% confidence interval [CI] 1.119–6.184, p = 0.027). A new cardiac murmur at admission predicted cardiac surgery (OR 1.949, 95% CI 1.007––3.774, p = 0.048). Methicillin resistant Staphylococcus aureus predicted in-hospital mortality and shock (p = 0.005, OR 6.945, 95% CI 1.774–27.192 and p = 0.015, OR 4.691, 95% CI 1.348–16.322, respectively). Mitral valve and aortic valve IE predicted in-hospital death (p = 0.039, OR 2.258, 95% CI 1.043–4.888) and embolism (p = 0.017, OR 2.328, 95% CI 1.163–4.659), respectively.*

Conclusions: *In this retrospective study, shock at admission independently predicted embolism during hospitalization in IE patients. Moreover, a new cardiac murmur at admission predicted the need for cardiac surgery. This emphasizes the importance of a comprehensive initial clinical evaluation in combination with imaging and microbiological data, in order to identify high-risk IE patients early.*
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Key words: infective endocarditis, clinical presentation, cardiac surgery, in-hospital mortality

Introduction

Despite improvements in medical and surgical therapy, infective endocarditis (IE) remains a deadly disease, with a vast array of potential complications [1, 2]. While imaging, particularly echocardiography, is the main diagnostic tool in patients with suspected IE [2], the initial clinical presentation remains a valuable asset. However, clinical presentation of IE can be highly variable and

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non-specific, influenced by predisposing conditions, causative microorganisms and IE localization [3, 4]. This could cause a diagnostic delay with increased complications and mortality [5]. Therefore, the present study sought to assess the impact of initial clinical presentation on outcome of IE patients during hospitalization and its association with microorganisms and IE localization.

Methods

Patients with definite IE diagnosed by the modified Duke criteria [2] were retrospectively included in a comprehensive database from 2015 to 2018. This study was conducted at two tertiary care hospitals in Belgium: UZ Brussel and AZ Maria Middelares Gent.

Demographic data, medical history, clinical presentation at admission, blood cultures, imaging data and outcomes were recorded. Transthoracic and transoesophageal echocardiography had been performed in all patients.

Admission data was defined as data from the first 24 hours of hospitalization.

Outcomes during hospitalization (more than 24 h after admission) included: in-hospital mortality, embolic events (cerebro-vascular and non-cerebro-vascular, diagnosed with imaging modalities), shock (cardiogenic or septic) and cardiac surgery.

Cardiac surgery was performed following current guideline recommendations [2].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as percentages. Comparison of continuous variables was done with the Student t-test or Mann–Whithney U test. Comparison of binomial variables was done with a χ^2 or the Fisher exact test. In order to evaluate potential predictors of outcomes, a multivariate logistic regression modeling was used. Variables with a p-value < 0.10 in the univariate analysis along with variables of known clinical importance were included in the multivariate analysis. Statistical significance was considered for a p-value < 0.05. Statistical analyses were conducted using IBM SPSS Statistics (Version 26.0.0, SPSS, Chicago, IL, USA).

Ethical approval

The study was approved by the local Ethics Committee of both hospitals and was carried out in accordance with the ethical principles for medical research involving human subjects established by the Helsinki Declaration, protecting the privacy of all participants, as well as the confidentiality of their personal information.

Table 1. Baseline and demographic characteristics.

	Total (n = 183)
Age [year]	69.0 ±14.2
Male	68.9%
Medical history	
Previous endocarditis	11 (6.0%)
Heart failure	25 (13.7%)
Coronary artery disease	43 (23.5%)
Atrial fibrillation	41 (23.3%)
Cardiac device	25 (13.7%)
Arterial hypertension	86 (47.0%)
Diabetes mellitus	16 (8.7%)
Previous stroke	24 (13.1%)
Chronic kidney disease	40 (21.9%)
Cancer	23 (12.6%)
Valve disease	93 (50.8%)
History of cardiac surgery/ /invasive interventions	86 (47.0%)
History of non-cardiac invasive intervention in the last 6 months	28 (15.3%)
Medication	
Anticoagulants	50 (27.3%)
Acetylsalicylic acid	62 (33.9%)

Results

Baseline population characteristics

One hundred eighty-three patients with definite IE (age 69 ± 14.2 years old, 68.9% males) were included. 51% of patients had previous valvular heart disease. Baseline characteristics are shown in Table 1.

At admission, clinical presentation consisted primarily of fever, general non-wellbeing and dyspnea. 61 (33.3%) patients presented with a new cardiac murmur at admission. 28 (15.3%) patients presented with shock and 33 (18%) patients had embolic events at admission. Initial clinical presentation can be found in Table 2.

Microbiological data are presented in Table 3. An average of 3.5 ± 2.3 antibiotic therapies was used per patient.

Echocardiography at admission showed native aortic valve IE in 56 (30.6%) and aortic valve prosthesis IE in 37 (20.2%) patients, among the 51 (27.8) patients with aortic valve prosthesis.

Table 2. Clinical presentation at admission.

	Total (n = 183)
Fever	114 (62.3%)
General non-wellbeing	56 (30.6%)
Dyspnea	38 (20.8%)
Cough	14 (7.7%)
Acute pulmonary edema	4 (2.2%)
Chest pain	6 (3.3%)
Embolic events	33 (18.0%)
Dizziness	6 (3.3%)
Syncope	8 (4.4%)
Other	57 (31.1%)
Shock:	28 (15.3%)
Cardiogenic shock	10 (5.4%)
Septic shock	18 (9.8%)
Congestive heart failure	15 (8.2%)
New cardiac murmur	61 (33.3%)
Osler noduli	4 (2.2%)
Janeway lesions	7 (3.8%)
Roth spots	2 (1.1%)
Splinter hemorrhages	5 (2.7%)
Conjunctival hemorrhages	2 (1.1%)

Table 3. Microbiological data.

	Total (n = 183)
Staphylococcus aureus	45 (24.6%)
Methi – S Staphylococcus aureus	34 (18.6%)
Methi – R Staphylococcus aureus	11 (6%)
Coagulase negative Staphylococcus	27 (14.8%)
Methi – S Staphylococcus CN	13 (7.1%)
Methi – R Staphylococcus CN	14 (7.7%)
Streptococcus viridans	50 (27.3%)
Enterococcus	21 (11.5%)
Streptococcus gallolyticus	21 (11.5%)
Other	17 (9.3%)
Coxiela burnetii IgG anti phase I > 1:800	1 (0.5%)
Blood culture negative	5 (2.7%)

Methi – S — methicillin sensitive; Methi – R — methicillin resistant; CN — coagulaso-negative

Native mitral valve IE was found in 70 (38.2%) patients and prosthetic mitral valve IE in 10 (5.4%) patients, among them 14 (7.6%) patients had a mitral valve prosthesis. 23 (12.5%) patients had multivalvular endocarditis.

Predictors of outcome

Univariate analysis is shown in Supplemental material (**Suppl. Table 1**). Multivariate analysis can be found in Table 4.

In-hospital mortality. In-hospital mortality rate was 22.4% (41 patients). Clinical presentation at admission was not predictive for in-hospital mortality. However, by multivariate analysis, both Methicillin resistant *Staphylococcus aureus* (MRSA) and mitral valve IE were independent predictors for in-hospital mortality (p = 0.005, odds ratio [OR] 6.945, 95% confidence interval [CI] 1.774–27.192 and p = 0.039, OR 2.258, 95% CI 1.043–4.888, respectively).

Embolic events. Sixty (32.8%) patients developed embolic events during hospitalization. Shock at admission independently predicted embolism (OR 2.631, 95% CI 1.119–6.184, p = 0.027). When adjusted by IE localization, aortic valve IE was also an independent predictor of embolic events (OR 2.328, 95% CI 1.163–4.659, p = 0.017).

Shock. Forty-two (23%) patients developed cardiogenic shock (16 patients) or septic shock (26 patients) during hospitalization. Initial clinical presentation was not predictive for shock. When

Table 4. Multivariate independent predictors of outcomes.

Outcomes	Predictor	Odds ratio	95% CI	P
In-hospital mortality	Age	1.035	1.004–1.067	0.028
	MRSA	6.945	1.774–27.192	0.005
	Mitral valve IE	2.258	1.043–4.888	0.039
Embolic events	Shock at admission	2.631	1.119–6.184	0.027
	Aortic valve IE	2.328	1.163–4.659	0.017
Shock	MRSA	4.691	1.348–16.322	0.015
Surgery	New cardiac murmur	1.949	1.007–3.774	0.048

MRSA — Methicillin resistant *Staphylococcus aureus*; IE — infective endocarditis; CI — confidence interval

adjusted for microorganisms, MRSA IE independently predicted shock during hospitalization (OR 4.691, 95% CI 1.348–16.322, p = 0.015).

Cardiac surgery. Surgery was performed in 103 (56.3%) patients. The presence of a new cardiac murmur at admission independently predicted the need for cardiac surgery (OR 1.949, 95% CI 1.007–3.774, p = 0.048).

Discussion

This retrospective study showed that: 1) A new cardiac murmur at admission independently predicted cardiac surgery; 2) Shock at admission was an independent predictor of embolic events during hospitalization; 3) MRSA infection was an independent predictor of in-hospital mortality and shock during hospitalization; 4) Mitral valve IE was an independent predictor of in-hospital mortality; 5) Aortic valve IE independently predicted embolic events during hospitalization.

In-hospital mortality

In-hospital mortality (22.4%) was comparable to previous studies, but remains unacceptably high despite optimal medical and surgical management [1, 6–8]. In this study, the initial clinical presentation was not predictive for in-hospital mortality, while previous studies found congestive heart failure and embolic events at admission to be predictive of in-hospital death [7–11]. Other recent studies found in-hospital development of heart failure and septic shock to be predictive of in-hospital mortality [12]. However, in this current analysis only the initial presentation at admission was considered.

When adjusting for causative microorganisms, MRSA was predictive of in-hospital mortality. Previously, *S. aureus* has been identified as a predictor of in-hospital mortality, but no distinction between MRSA and Methicillin-susceptible *Staphylococcus aureus* (MSSA) was made [5, 7, 8, 11]. Nonetheless, another previous, prospective study showed a statistically non-significant increased mortality in MRSA vs. MSSA IE [13].

Moreover, mitral valve IE was associated with increased in-hospital mortality, as previously described by Murdoch et al. [5]. Patient characteristics may be responsible for the worse outcome in mitral valve IE [14]. However, in this study, no association was found between mitral valve IE and characteristics such as causative microorganisms, age or other complications. Furthermore, other studies did not find a significant difference in mortality between aortic and mitral valve IE [15].

In the ESC-EORP European endocarditis registry, in hospital mortality was associated with the Charlson index, creatinine > 2 mg/dL, congestive heart failure, cerebral complication, perivalvular abscess, vegetation length and unperformed cardiac surgery (when indicated) by multivariate analysis [1]. No such associations were found in this retrospective series.

Embolic events

32.8% of IE patients developed an embolic event during hospitalization, which is higher than in the ESC-EORP European endocarditis registry (20.5%) [1] and the ICE cohort (23%) [5]. An initial presentation with shock (septic or cardiogenic) at admission was an independent predictor of embolic events. In shock, systemic inflammation, circulatory changes and hypercoagulopathy may be underlying contributors to the development of embolic events [16–18]. Shock-induced atrial fibrillation could also predispose to embolization [19]. Previous data have shown that septic shock increases the risk of stroke [18, 20]. In the Embolic Risk French calculator proposed by Hubert et al. [21], shock has not been analyzed as a possible predictor of embolic risk. Future research might be helpful to determine whether shock at admission could be incorporated into an adapted embolic risk calculator.

Additionally, aortic valve IE independently predicted embolic events during hospitalization, as also found in the ESC-EORP European endocarditis registry [1]. In contrast, Hubert et al. [21] and Thuny et al. [22] found embolic risk to be independent of valve localization. Vilacosta et al. [23] found embolization to be associated with mitral valve IE when vegetation size exceeds 10 mm. However, in this series there was no significant difference in vegetation size between aortic and mitral valve IE (13.4 ± 6.7 mm vs. 13.5 ± 5.8 mm, p = 0.949). Another study showed that embolism was more frequently seen in mitral prosthetic than aortic prosthetic valve thrombosis [24]. In this series, aortic valve prosthesis IE (20.2%) was more common than mitral valve prosthesis IE (5.4%).

In the ESC-EORP European endocarditis registry, in-hospital embolic events were also associated with staphylococcal infection [1]. A microbiological association could not be confirmed in this study. Thus, it remains uncertain why aortic valve IE was predictive of embolism in this series.

Shock

23% of IE patients developed shock (septic or cardiogenic) as a complication during hospitalization, compared to 16% in the ESC-EORP European endocarditis registry [1]. Other studies have shown a lower incidence for isolated septic shock [8, 25]. In this study, initial clinical presentation was not predictive of shock. In contrast, MRSA bacteriemia was an independent predictor of shock during hospitalization. Similarly, Olmos et al. [25] showed *S. aureus* to be and independent predictor of septic shock, without distinguishing between MRSA and MSSA. Shock has previously been identified as a common complication of MRSA bacteremia [26]. Severe shock has been shown to be more frequent in *S. aureus* IE compared to other pathogens [27].

Cardiac surgery

Cardiac surgery was performed in 56% of IE patients, which is comparable to previously reported operative rates [1, 5, 11, 28]. In this study, a new cardiac murmur at admission was predictive of surgery. The presence of a new cardiac murmur in IE patients may reflect important turbulence due to valvular damage. This finding confirms that a thorough physical examination at admission remains invaluable despite the readily availability of imaging modalities such as echocardiography in current clinical practice. Detection of a new clinical murmur could help in the identification of patients eligible for early surgery, in dialogue with the endocarditis "Heart Team" [2]. Therefore, advanced investigations should be considered as a supplement, but not a replacement of a careful clinical examination.

Limitations of the study

This is a retrospective study with a limited number of patients. Therefore, larger prospective clinical studies are warranted to confirm the present findings.

Conclusions

In this retrospective study, shock at admission independently predicted embolism during hospitalization in IE patients. Moreover, a new cardiac murmur at admission predicted the need for cardiac surgery. These findings emphasize the importance of a comprehensive initial clinical evaluation, in spite of the availability of medical imaging and microbiological information, for an early identification of IE patients at high-risk of complications or a need for surgery.

Conflict of interest: None declared

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