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CLINICAL STUDY

Clinical predictors of complications in patients with left–sided infective endocarditis: A retrospective study of 206 episodes

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ABSTRACT

PURPOSE: Early identification of specific patient subgroups at high risk of developing life–threatening infective endocarditis (IE) complications is of paramount importance. Better stratification may allow more intensive treatment of these patients and positively influences clinical outcomes.

METHODS: We carried out a retrospective survey of consecutive left–sided IE adult patients, admitted over a 15–year period to two main tertiary care centres in the Czech Republic.

RESULTS: Among a group of 196 patients (155 males; median age 64 years), a total of 206 left–sided IE episodes were identified. Perivalvular extension of infection was most frequently seen in prosthetic aortic valve endocarditis (OR 6.706, p<0.0001). Valve prolapse/perforation during IE episodes was significantly associated with mitral valve IE (OR 2.136, p=0.026) and vegetation length (OR 1.055, p=0.009). Septic shock was significantly related to two main risk factors: S. aureus infection (OR 8.459, p=<0.0001) and smoking (OR 8.403, p=0.001). Mitral valve IE with a vegetation length ≥13 mm was the strongest risk factor for this complication (OR 3.24, p=0.001), followed by S. aureus infection (OR 3.59, p=0.002). Finally, septic shock (OR 6.000, p=0.001) represented the most important risk factor of in–hospital mortality.

CONCLUSIONS**:** This study provides the most detailed profile of complication predictors related to left–sided IE in Central Europe. Early individual stratification of IE related occurrence of complications might help to decrease extremely high morbidity and mortality of this disease *(Tab. 5, Ref. 37)*. Text in PDF *www.elis.sk.*

KEY WORDS: infective endocarditis, *Staphylococcus aureus*, complications of infective endocarditis, mortality.

Introduction

Despite the most recent advances in both medical and surgical therapy, infective endocarditis (IE) continues to be associated with serious complications and remains a life-threatening infection. Complications of IE may involve cardiac structures in which the infection either spreads within the heart or in an extracardiac manner (either embolic- or immunocomplex-related) (1). The rate of complications varies according to the population studied. The literature reports one complication of IE in 57 %, two in 26 % and three or more in about 14 % of cases (2). The rate of IE-related complications also depends on factors such as infecting pathogens, the duration of disease before initiation of therapy and/or treatment modality (3). To initiate an early appropriate therapy, it is of crucial importance for identifying patients who are at the highest risk of such adverse events, preferably in the initial phase of their illness. Moreover, it is also important to determine the prognostic factors that may affect survival outcomes (4, 5). Therefore, we conducted the most comprehensive analysis in Central Europe that evaluates the predictive factors of the main IE-related complications.

Methods

We conducted a retrospective survey of consecutive left-sided IE adult patients, admitted over a 15-year period to the Department of Internal Medicine at University Hospital Hradec Kralove, Charles University, Czech Republic (between November 1998 and November 2006) and to the Department of Cardiology at the Institute for Clinical and Experimental Medicine, Prague, Czech Republic (between October 2009 and June 2016). All included cases met the modified and definite Duke criteria (1).

The following IE-related complications were identified: (1) perivalvular extension of infection (including cardiac abscess); (2) valve prolapse/perforation; (3) AV block; (4) heart failure; (5) septic shock; (6) systemic embolism; (7) in-hospital mortality.

Personal data, physical examination findings and the results of electrocardiogram, echocardiographic, radiographic and microbiological examinations were evaluated along with clinical courses,

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patient outcomes, complications and indications for surgery. In relation to the above-mentioned complications, we also analysed a wide variety of clinical variables, divided into the following three main categories: (1) patients' medical history and predisposing conditions; (2) microbiology of infective endocarditis; (3) characteristics of IE episodes.

Statistical analysis

Data are presented as mean ± standard deviation, median (interquartile range, IQR) and frequency (percent). To test the relationship between two discrete variables, we used the χ^2-test. Where expected frequencies were less than 5, we used Fisher's exact test. To search for independent predictors of IE complications, we used logistic regression, the results of which are presented as OR (odds ratio), and 95% confidence intervals for OR. Calculations were performed using SPSS 21 software (Chicago, IL, USA). A p value < 0.05 was considered significant.

Definitions

Local structural complications involved prolapse or perforation of the valve leaflet and intracardiac abscesses. For the purposes of the study, only the following cases were considered: newly formed prolapses, prolapses of atypical localisation, prolapses with thinning in the prolapse area and apparent failure of chordae integrity.

The maximum dimension of vegetation was considered. In the presence of multiple vegetations, the largest was selected.

Conduction impairment was diagnosed in cases where a new 1st–3rd AV block associated with an IE episode was reported.

Congestive heart failure was diagnosed based on clinical assessments conducted by the team of attending physicians. Only new episodes showing conclusive IE-associated progression of heart failure were included.

Clinically significant embolism of vegetation was considered for the purposes of the study. Janeway lesions and splinter haemorrhages were not included. All patients underwent abdominal ultrasound throughout the course of the IE episode. A CT/MRI scan was indicated in cases where there was a clinical suspicion of an embolic episode.

Septic shock was defined as the presence of acute circulatory failure during sepsis, characterised by persistent arterial hypotension despite adequate volume resuscitation.

Culture-negative endocarditis was defined as endocarditis without aetiology following inoculation of at least three independent blood samples in a standard blood culture system with negative cultures after seven days of incubation and subculturing. Systematic serological testing was not part of the study.

Early prosthetic IE was defined as IE that occurred within 12 months after cardiac surgery.

Nosocomial IE was defined as endocarditis occurring after 72 hours of hospitalisation and/or occurring within 8 weeks after discharge from the hospital in which the invasive procedure was performed.

Hospital mortality was assessed as the patient dying during hospitalisation as a result of IE complications.

Results

A total of 206 left-sided IE episodes (105 from Hradec Kralove and 101 from Prague) were identified among 196 patients (155 males; median age 64 years; range: 20 to 87 years). The most common predisposing condition of IE was the presence of a prosthetic cardiac valve (70 episodes, 34 %), followed by rheumatic heart disease (28 episodes, 14 %) and a bicuspid aortic valve (27 episodes, 13 %). Intravenous drug use was observed in only four episodes (2 %) (Tab. 1).

Fifty-nine IE episodes caused by *S. aureus* were identified (29 %). The remaining 147 IE cases were caused by streptococci (38 episodes, 18 %), coagulase-negative staphylococci (34 episodes, 17 %) and enterococci (29 episodes, 14 %). Other agents were involved in 19 cases (9 %): Gram-negative bacteria (n = 11), polymicrobial IE (n = 4), *Candida albicans* (n = 2) and anaerobic

Tab. 1. Medical history of patients and predisposing conditions of IE.

	n=206 (mean±SD, %)
Age, years	60±15.2
Male gender, n (%)	155 (75%)
History of IE, n (%)	24 (12%)
Body mass index (kg/m2)	32±3
Diabetes mellitus, n (%)	57 (28%)
COPD, n (%)	16 (8%)
Cirrhosis, n (%)	5 (2%)
Immunosuppressive therapy, n (%)	15 (7%)
Implantable cardiac device, n (%)	24 (12%)
Prosthetic valve, n (%)	70 (34%)
Rheumatic heart disease, n (%)	28 (14%)
Bicuspid aortic valve, n (%)	27 (13%)
Dental procedure, n (%)	5 (2%)
Urologic procedure, n (%)	2 (1%)
Intravenous drug abuse, n (%)	4 (2%)
Active smoking, n (%)	47 (24%)

IE – infective endocarditis, COPD – chronic obstructive pulmonary disease.

Tab. 2. Characteristics of IE episodes.

	n=206 (median, min–max, %)
Duration of symptoms (days)	14 (1–180)
Aortic valve	119 (58%)
Mitral valve	65 (32%)
Multiple valve IE	22 (11%)
Native valve IE	136 (66%)
Vegetation length (mm)	9 (0–38)
Early prosthetic endocarditis	31 (15%)
Valve replacement	105 (51%)
Days to surgery	14 (1–150)
Community-acquired IE	163 (79%)
Nosocomial or healthcare-associated IE	43 (21%)
Creatinine (μmol/l)	99 (46–675)
Haemodialysis during IE episodes	18 (9%)
Leukocyte count ($x10^9$/l)	11.8 (2–34)
CRP (mg/l)	110.5 (3–451)
New onset of atrial fibrillation during IE episodes	59 (29%)

IE – infective endocarditis; CRP– C–reactive protein.

Tab. 3. Complications of IE.

	n=206
Perivalvular extension of infection	78 (38%)
Valve prolapse/perforation	56 (27%)
AV block	24 (12%)
Heart failure	94 (46%)
Systemic embolism	75 (36%)
Septic shock	35 (17%)
In–hospital mortality	45 (22%)

AV – atrio-ventricular.

Tab. 4. Predictors of IE-related complications.

		OR	p
Perivalvular extension of infection	Prosthetic aortic valve endocarditis	6.706	< 0.0001
AV block	Haemodialysis during IE episodes	4.778	0.006
	Aortic valve IE	3.653	0.045
Valve prolapse/ /perforation	Mitral valve IE	2.136	0.026
	Vegetation length	1.055	0.009
Heart failure	Valve prolapse/perforation	2.959	0.002
	Higher age during IE episodes	1.031	0.005
	Septic shock	4.045	0.001
	AV block	3.172	0.017
Septic shock	S. aureus IE	8.459	< 0.0001
	Smoking	8.403	0.001
	CRP level	3.870	0.005
In–hospital mortality	Heart failure	3.829	0.003
	Septic shock	6.000	0.001
	Stroke	4.425	0.002
	Higher age during IE episodes	1.039	0.031
	Haemodialysis	5.007	0.003
	Valve replacement	0.205	0.001

AV – atrio-ventricular; IE – infective endocarditis; *S. aureus* – *Staphylococcus aureus*; CRP – C-reactive protein; OR – odds ratio

bacteria (n = 2). In 27 episodes (13 %), the causal agent was not identified (culture-negative IE).

The mean time elapsed between symptom onset and diagnosis of IE was 14 days (range: 1 day to 6 months). Aortic valve infection was observed in 119 episodes (58 %) compared to mitral valve infection in 65 cases (32 %). Valve replacement was performed during the acute phase of treatment in 105 episodes (51 %). Acute renal failure requiring haemodialysis occurred in 18 cases (9 %), while new onset of atrial fibrillation during IE episodes occurred in 59 cases (29 %) (Tab. 2).

The most frequently observed cardiac complications were heart failure (46 %) and perivalvular extension of infection (38 %) (Tab. 3). Systemic embolism occurred in 75 episodes (36 %), brain emboli/stroke in 46 episodes (22 %), spleen emboli in 21 episodes (10 %), kidney emboli in 12 episodes (6 %), extremity emboli in 15 episodes (7 %), coronary artery emboli in 9 episodes (4 %) and spine emboli in 7 episodes (3 %) and a liver embolus in 1 episode (1 %), respectively.

Table 4 shows multivariate analysis of predictors of IE-related complications. Perivalvular extension of infection was most frequently seen in prosthetic aortic valve endocarditis (42/61, 69 %) (OR 6,706, p < 0.0001). Incidence of this complication in other valves ranged from 21 % in native aortic valve IE (17/80) to 33 % in prosthetic mitral valve IE (3/9).

Acute renal failure requiring haemodialysis (OR 4.778, p = 0.006) and aortic valve IE (OR 3.653, p = 0.045) were the only clinical predictors of new AV block development.

Valve prolapse/perforation during IE episodes was significantly associated with mitral valve IE (OR 2.136, p = 0.026) and vegetation length (OR 1.055, p = 0.009).

Septic shock (OR 4.045, p = 0.001), a new AV block during IE episodes (OR 3.172, p = 0.017) and valve prolapse/perforation (OR 2.959. p = 0.002) represented the most significant risk factors in terms of heart failure development.

Septic shock was significantly related to two main risk factors: *S. aureus* infection (OR 8.459, p ≤ 0.0001) and smoking (OR 8.403, p = 0.001).

Finally, with regard to in-hospital mortality, septic shock (OR 6.000, p = 0.001), indication for haemodialysis (OR 5.007, p = 0.003) and stroke (OR4.425, p = 0.002) represented the most important risk factors. In contrast, valve replacement during IE episodes was associated with better mortality outcomes (OR 0.205, p = 0.001).

Regarding systemic embolism, mitral valve IE with a vegetation length ≥ 13 mm proved to be the most potent risk factor of this complication (OR 3.24, p = 0.001), followed by *S. aureus* infection (OR 3.59, p = 0.002). On the contrary, higher age was associated with less frequent systemic embolism during IE episodes (OR 0.976, p = 0.02) (Tab. 5).

Tab. 5. Risk factors of systemic embolism.

	OR	p
S. aureus	3.24	0.001
Mitral valve IE and vegetation length		0.018
Aortic valve IE, vegetation ≥13 mm vs. Aortic valve IE, vegetation <13 mm	1.26	0.657
Mitral valve IE, vegetation <13 mm vs. Aortic valve IE, vegetation <13 mm	1.99	0.08
Mitral valve IE, vegetation ≥13 mm vs. Aortic valve IE, vegetation <13 mm	3.59	0.002
Higher age during IE episodes	0.976	0.02

S. aureus – *Staphylococcus aureus*; IE – infective endocarditis; OR – odds ratio

Discussion

The principal findings of this study can be summarized as follows: Firstly, our relatively large cohort consisted of solely left-sided IE episodes, excluding less harmful right-sided IE episodes and cardiac device-related infective endocarditis (6). Secondly, a large set of variables in a multivariate analysis was used to predict the clinical IE complications. Finally, compared to previous studies that either report associations between risk factors and mortality or a specific complication (embolism, heart failure, etc.) (7, 8, 9, 10), we provide a detailed predictive analysis of all major IE-related complications.

Perivalvular extension of infection

Formation of abscesses, pseudoaneurysm or valve perforation is one of the most fearful complications observed in patients with IE. The association between endocarditis-associated perivalvular complications and prosthetic valve endocarditis has been widely reported (11, 12). These observations were also confirmed in our study, where prosthetic aortic valve endocarditis proved to be an independent predictor of infection spread beyond the valve cusps (OR 6.706). Hence, broad regimen antibiotic treatment and meticulous assessment of possible signs of perivalvular extension, such as AV conduction impairment, should be the essential component of prosthetic valve IE management.

AV block

ECG conduction changes are associated with increased mortality and invasive infection (13). This complication is most frequently seen in aortic valve infections due to the close proximity of the non-coronary cusp to the AV node (14). Our study confirmed that involvement of the aortic valve is an independent predictor of a new AV block (OR 3.653). In IE patients, the ominous development of heart block and a poor response to antibiotic therapy implies significant extension of the infection. AV block frequently occurs in chronically dialysed patients, possibly due to an association with diffuse calcifications of the heart, including the cardiac skeleton, as well as frequent significant changes in ionic equilibrium (15). Most likely, the ion disorder that results from renal failure, along with the local spread of infection beyond the valve ring, was another predictor of AV block in our cohort (OR, 4.778).

Valve prolapse/perforation

Newly developed valvular prolapse or perforation is usually a consequence of aggressive infection. In one study, the presence of this complication was reported to be more frequent in association with mitral valve infection and in patients on haemodialysis, where valve damage almost doubled the mortality rate (16). Mitral valve endocarditis was also an independent predictor of new prolapse/perforation in our cohort (OR 2.136). We can only speculate whether this phenomenon occurred because of the greater fragility of the mitral valve, or whether it was due to the more frequent presence of prosthetic endocarditis in the aortic position (61 vs. 9). Another study demonstrated the relationship between vegetation length and the development of abscesses, which could be explained by greater bacterial burden and virulence or the easier spread of infection (17). This parallel can be similarly applied to our multivariate analysis results, according to which vegetation length was an independent predictor of local aggression (valve perforation/prolapse; OR 1.055).

Heart failure

In our patients with left-sided IE, heart failure was clinically observed in 46 % of all cases. We found new valvular prolapse/perforation to be a significant predictor of heart failure occurrence (HR 2.959). As per guidelines, such patients have to be referred for early surgical intervention. Total systemic inflammatory response syndrome may be an alternative cause of heart failure (18), as observed in our sample where septic shock increased the risk of its development four-fold. First-degree AV block has been previously shown to be a risk factor for the development of heart failure (19), especially its sudden onset, which can be applied to the course of IE (20). In our group, newly presented AV block significantly increased the risk of HF (OR 3.172).

Septic shock

S. aureus is the most virulent causative agent of IE episodes and is considered to be the most common cause of septic shock (21). In our cohort of patients with *S. aureus* infection, the presence of septic shock was diagnosed in 42 % of cases (OR 8.459). A previous study observed that cigarette smoke greatly reduces the antibacterial function of leukocytes, including neutrophils, monocytes, T-lymphocytes and B-lymphocytes (22). This might explain why active smokers are at increased risk of septic shock (OR 8.403). Further studies analysing the relationship between smoking and the course of IE are certainly warranted. As the specificity of CRP as a marker is questionable, it is more suitable for evaluating the significance of inflammation rather than for distinguishing sepsis from SIRS (23). Despite its low specificity in sepsis assessment, in our study elevated levels of CRP highly correlated with the development of septic shock, representing a strong predictor of this serious complication (OR 3.870).

Systemic embolism

Predicting an individual's risk of embolism is very difficult. Vegetation length and mitral valve affection are widely accepted risk factors associated with systemic embolization (24). These two clinical variables were the main predictors of embolization in our study (OR 3.59). *S. aureus* infection is considered another major risk factor of this severe complication. Two simple calculator systems for predicting embolic risk upon admission of patients with IE have been designed; one French (25) and one Italian (26). Both include *S. aureus* infection as an excellent predictor of embolic risk. This is in accordance with our results, which suggest that *S. aureus* infection is, of all the most common causative agents of IE, associated with the highest risk of systemic embolisation (OR 3.24). Despite *S. aureus* being recently increasingly reported as a risk factor of embolisation, current IE guidelines (1) do not explicitly include S. aureus infection as an indication for early cardiac surgery to prevent systemic embolism.

The finding that the younger age of a patient is another risk factor of embolisation was rather surprising, although one research group has already described this phenomenon (27). One possible explanation may be that younger patients respond more vigorously to inflammatory stimuli (bacteraemia) than the elderly, which in turn leads to more frequent embolisation.

In-hospital mortality

Despite advances in antibiotic and surgical therapy of IE, septic shock remains one of the major factors associated with mortality (1). According to our data, septic shock was reported as the strongest risk factor of IE mortality. Therefore, antibiotic treatment escalation should be considered in patients with diabetes mellitus,

older age, renal insufficiency and S. aureus infection, as these factors may predispose to increased incidence of septic shock (20).

Renal failure requiring haemodialysis represents an additional, remarkable risk factor. In a one-year French national study, the incidence of IE was 1.7–2 cases/1000 dialysed patients, which is 50–60 times higher than the normal population (28). In our data set, haemodialysis increased mortality risk 5-fold.

Many studies conducted over the last two decades have shown that the development of heart failure has the greatest impact on patient survival out of all the IE complications (29, 30). In our study, heart failure was one of the major predictors of hospital death (OR 3.829), therefore urgent surgery should be always considered.

Systemic embolisation occurs in up to 50 % of IE episodes (31, 32), with the central nervous system the most commonly affected. In one study of patients that had experienced a neurological event, early mortality was 45 % compared to 24 % in patients who did not have this complication (33). In our patients, stroke was associated with a four-times higher risk of death. Although it remains unclear whether early cardiac surgery improves the prognoses of patients, optimal timing seems to be of great importance (34, 35). Compared with conventional treatment, an early surgery strategy may be associated with improved clinical outcomes by effectively decreasing systemic embolism in patients with IE (36). Recent meta-analysis suggested that early surgical intervention is associated with significantly lower risk of mortality in patients with IE (37). Our results clearly confirm that early surgery during IE episodes is a significant protective factor of in-hospital mortality (OR 0.205). This suggests that earlier surgical intervention in patients may decrease mortality risk.

Study limitations

The primary limitation was that the retrospective nature of case identification and data acquisition did not allow for the complete ascertainment of patient information. A secondary drawback was that the investigation did not include valve surgery patients who had been referred directly from other institutions to the cardiovascular surgery department of the authors' institution. Finally, both centres can be considered as tertiary centres with referrals of more complicated cases, and thus the profile of the cases was most likely affected by referral bias.

Conclusions

Early and accurate prediction of IE-related complications appears to be important in reducing morbidity and mortality associated with IE. This study provides the most detailed profile of complication predictors related to this disease in Central Europe. Septic shock, indication for haemodialysis, and stroke during IE episode represented the most important risk factors of in-hospital mortality. Individual risk stratification towards conservative or surgical treatment is crucial, as early surgical intervention might be associated with a significantly lower risk of mortality.

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