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Cerebral emboli as the predictor of mortality in patients with 'definite' infective endocarditis

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Abstract

Infective endocarditis (IE) is among the most fatal infectious diseases. Since the introduction of various intracardiac devices and interventions, the clinical aspects of IE have rapidly evolved. In this paper, we aim to define the contemporary characteristics of patients diagnosed with definite IE and to identify the predictors associated with mortality. Through retrospective analysis of patients with TEE proven vegetation, those fulfilling the modified Duke criteria for definite IE were identified. Patient characteristics in relation to clinical outcomes and mortality were analyzed. Out of 50 patients (mean age 57±15.9 years, 34% female), 72% was native-valve endocarditis of which only 32% had a predisposing valve disease such as rheumatic valve. The rate of prosthetic-valve IE was 10% and that of device-related IE was 18%. The most common causative organisms were S. aureus (16%), Coagulase-negative Staphylococci (16%), Enterococci (14%) and Viridans streptococci (12%). In-hospital mortality was 24% and was associated with concomitant diabetes, coronary artery disease, higher baseline creatinine, anemia, occurrence of cranial complications and absence of surgery during the index hospitalization. Regression analyses revealed that cerebral emboli were the only predictor of early mortality, possibly through delayed surgical treatment. In conclusion, our small cohort of definite IE patients showed that contemporary characteristics of IE has evolved with higher rates of device-related IE. Within established prognostic factors, cerebral emboli and timing of surgery are intervening factors, which suggests that the timing of surgical treatment, particularly in patients with neurologic complications, needs to be evaluated when shaping future perspectives on IE.

Keywords: Definite infective endocarditis, cerebral emboli, surgery

Introduction

Infective endocarditis (IE) is defined as the infection of the endocardial layer of the heart. It is among the most fatal infectious diseases with in-hospital mortality rates as high as 25-30% [1,2]. Predisposing heart conditions such as rheumatic valve disease or prosthetic valves are implicated in the pathophysiology of IE but the occurrence of the disease in presumably normal hearts make it hard to define exact etiology in healthy individuals [3]. Recent national consensus report for IE has established the outlines and standards of evaluation and the treatment and prevention of IE. This report also emphasized the need for more studies in this field [1].

The number of patients suffering from IE has been increasing due to the increase in number of patients with prosthetic material within the heart and those undergoing invasive procedures increases [3]. The rising numbers indicates that more data is needed on the current rates and responsible pathogens of IE worldwide. Several prognostic factors such as prosthetic valve endocarditis, certain microorganisms, vegetation size or cerebral emboli are well established poor-prognostic factors. However, the impact of many other factors such as early surgery or culture negative endocarditis are still debated [4]. Delay of surgery in patients with an insidious course complicated by embolic events represents a specific sub-population with higher mortality. Recent research indicates better long-term mortality in patients who undergo early surgery; yet no consensus exists on the short-term outcomes [5,6]. As a result, limited data on IE, complicated by cranial emboli, compromises early risk stratification and timely referral for surgery.

In this study, we aim to define the characteristics of patients diagnosed with definite IE and to identify the predictors associated with mortality.

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Materials and Methods

After obtaining local Ethics approval (2020.38.02.12), we retrospectively analyzed the data of patients with definite IE between 2015 and 2020 at our institution. For the diagnosis of IE, a suspected vegetation on both transthoracic (TTE) and transesophageal echocardiography (TEE) was a prerequisite. We defined "definite IE" either as the presence of a positive blood culture consistent with the major criterion of 2015 European Society of Cardiology IE guidelines or using the three minor criteria accompanying the presence of vegetation [7]. These minor criteria were modified Duke criteria and consisted of predisposition, fever, vascular phenomena, immunological phenomena and positive blood culture as suggested by the guidelines [8]. The demographic data and the comorbidities were derived from the medical records of the patients. Every patient had both TTE and TEE done. Out of 120 possible cases with a suspected vegetation in TTE and TEE, 50 patients fulfilled the aforementioned criteria.

The data on the place of vegetation and the predisposing heart conditions were derived from patients' echocardiography reports. Central database of the hospital was used to acquire data on IE-related risk factors such as the presence of diabetes mellitus (DM), hypertension (HT) previous stroke, presence of coronary artery disease (CAD), heart failure with reduced ejection fraction (HFrEF), chronic kidney disease (CKD), dialysis, presence of cancer or immunosuppressive condition, thyroid disease or chronic obstructive lung disease (COLD). History of angiographically proven CAD or a coronary angiography performed during the index hospitalization were used to determine CAD. Rheumatic valve disease, bicuspid aortic valve, mitral valve prolapse or hypertrophic cardiomyopathy were classified into 'predisposing native valve conditions'. Patients with prosthetic valves and those with intracardiac pacemaker or defibrillators were recorded. Laboratory data on initial presentation such as white blood cell (WBC), neutrophil, lymphocyte, platelet counts, hemoglobin levels, C-reactive protein (CRP), creatinine and bilirubin concentrations; erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF) were recorded. As part of the standard routine evaluation of IE, all patients had at least 3 sets of blood cultures drawn at the initial presentation and additional cultures were obtained whenever deemed appropriate during the hospital stay. Bactec cultures were used in which 3 for aerobe and 3 anaerobe cultures were cultivated; Brucella tests and possible fungal cultures were obtained for each patient.

Decision on antibiotic therapy was based on the blood cultures and complied with the guidelines on agent and duration. Antibiotic therapy was recorded for each patient [7]. Any symptomatic embolic event during the hospital stay and in-hospital death were also recorded. As part of the routine care of IE patients at our institution, the decision and timing of surgery is made by a multidisciplinary team of medical experts that consists of cardiologists, cardiovascular surgeons, infectious disease specialists and other relevant sub-specialities relevant for the needs of each patient. The medical records were retrospectively evaluated to obtain data on agreed-upon decisions of the medical experts and whether patients agreed with the given medical advice. Surgery was carried out in cases of failure to extract the intracardiac device percutaneously or as suggested by the experts in case of a device-related IE. In stable patients with native or prosthetic valve endocarditis and without factors that call for an immediate surgery (e.g., heart failure, uncontrolled infection or large left-sided vegetation), surgery was carried out as the planned treatment option following appropriate antibiotic therapy of a pre-determined duration. If the factors did call for immediate surgery, surgery was done earlier in the treatment course and the antibiotic therapy was completed after the surgery [7].

Statistical Analysis

Statistical analyses were performed using IBM® SPSS® Statistics for Windows, Version 20 software (IBM Corp., Armonk, NY). The continuous variables were represented as mean ±standard deviation (SD) or median (minimum-maximum). Categorical variables were represented as number (percentages). After testing the variables for normal distribution; the comparison of patients with and without mortality was done with independent samples t-test for normally distributed variables and by Mann Whitney U test for variables without a normal distribution. The categorical variables were compared by Chi square when the expected cell count was >25; by Continuity correction when the expected cell count was 5-20, and Fischer exact test when <5. The Kaplan-Meier and Cox Model methods were used for survival analysis and mortality predictors. The Log-Rank Test was used to evaluate differences between the curves. All possible explanatory variables were first tested in a univariate model in which DM, CAD, hemoglobin, baseline creatinine and cerebral embolic event were determined as possible predictors. As the number of study population was small, only the predictors with a p-value <0,05, were included into the multivariate model to determine the adjusted hazard ratios. The predictors with a p-value <0,05 in univariate analyses were presence of CAD and cerebral emboli with a p-value of <0.05 was considered statistically significant.

Results

Out of 120 patients who had suspected vegetation on TTE and/or TEE; 50 patients with a vegetation who were diagnosed to have 'definite IE' were included in the analyses. The demographic and baseline characteristics of the overall study population and study groups with regard to mortality are presented in Table 1. The mean age of the IE patients was 57±15.9 years, of whom 34% (17 patients) was female. The majority of the patients (72%) had native valve endocarditis with similar aortic and mitral valve locations. The rate of prosthetic valve endocarditis was 10% and that of device related IE was 18%. When the patients with and without mortality were compared; no difference was found in terms of the type of IE or the location of the disease (all p values>0.05).

DM and HT were the most common risk factors among the study population with frequencies of 52% and 78%, respectively; followed by CAD, CKD and HFrEF. When patients with and without mortality were compared, DM and CAD were found to be more common in the patients who died. (83.3% vs 42.1%, p=0.031 for DM and 23.7 % vs 41.7%, p=0.036 for CAD). There was no significant difference between the study groups in terms of HT, previous stroke, CKD, rate of dialysis, presence of catheter, autoimmunity, immune suppression, HFrEF or COLD.

Of patients with an identifiable predisposing native valve

Table 1. Demographic and clinical characteristics of the overall study population and study groups with regard to mortality

	Study population	Without mortality (n:38)	With mortality (n:12)	p value
Age, years	57±15.9	57±17	60±12.3	0.265
Female gender, n(%)	17(34)	14(36.8)	3(25%)	0.510
Type of IE				
Native valve, n(%)	36(72)	28(73.7)	8(66.7)	0.536
Mitral	15	14(50)	3(37)	
Aortic	11	9(32)	4(50)	
Mitral+aortic	2	2(7)	0(0)	
Tricuspid	3	3(10)	1(12.5)	1
Prosthetic valve, n(%)	5(10)	4(10.5)	1(8.3)	1
Mitral	2(4)	3(7.9)	1(8.3)	0.920
Aortic	3(6)	2(5.3)	1(8.3)	
Device-related, n(%)	9(18)	6(15,8)	3(25)	0.660
Pace	1(2)	1(2.6)		
ICD	1(2)	0(0)	1(8.3)	0.301
CRT	7(14)	5(13.2)	2(16.7)	
Risk Factors, n(%)				
Diabetes mellitus	26(52)	16(42.1)	10(83.3)	0.031
Hypertension	39(78)	30(78.9)	9(75)	1
Previous stroke	5(10)	5(13.2)	0	0.319
CAD	16(32)	9(23.7)	5(41.7)	0.036
CKD	17(34)	11(28.9)	6(50)	0.294
Dialysis	4(8)	2(5.3)	2(16.7)	0.240
Catheter	5(10)	3(7.9)	2(16.7)	0.582
Autoimmunity	3(6)	3(7.9)	0(0)	1
Cancer	5(10)	5(13.2)	0(0)	0.319
Immune suppression	7(14)	6(15.8)	1(8.3)	1
Heart failure	14(28)	9(23.7)	5(41.7)	0.285
Thyroid disease	7(14)	7(18.4)	0(0)	0.174
COLD	4(8)	2(5.3)	2(16.7)	0.240
Predisposing native valve condition, n(%)				
Rheumatic valve	8(16)	5(13.2)	3(25)	0.600
Mitral valve disease	3(6)	2(5.3)	1(8.3)	
Obstructive HCM	1(2)	1(2.6)	0(0)	0.801
Bicuspid aortic valve	1(2)	1(2.6)	0(0)	

IE:Infective endocarditis, ICD:Intracardiac cardioverter defibrillator, CRT:Cardiac resynchronization therapy, CAD:coronary artery disease, CKD:Chronic kidney disease, COLD:Chronic obstructive lung disease, HCM:Hypertrophic cardiomyopathy

condition, 8 patients had rheumatic valve disease, 3 had mitral valve prolapse, 1 obstructive hypertrophic cardiomyopathy and 1 bicuspid aortic valve. The results of the blood cultures revealed that 28% of cases had negative blood cultures during the course of the disease. Among the identified causes, 8 patients had coagulase negative staphylococci, 8 patients staphylococcus aureus, 6 patients viridans sterprococci, 7 patients enterococci, 3 patients enterobacteriacea spp, 2 patients Brucella spp and 1 patient Gemella as the infection-causing organism. The study groups were similar in terms of predisposing native valve condition, blood culture results and antibiotic treatment received (Table 2).

During their hospital stay, 14 patients suffered an embolic event. When the patients with and without mortality were compared, significantly higher number of patients with mortality had suffered cranial emboli. Cox regression analysis revealed that cerebral emboli were the single independent predictor of in-hospital mortality (HR:3.4 [95%CI 0.998 to 11.416] p=0.0445) (Table 3 and Figure 1).

Table 2. Laboratory characteristics and clinical outcomes of the overall study population and study groups with regard to mortality

	Study population	Without mortality(n:38)	With mortality (n:12)	p value
Laboratory Findings				
WBC,10³/uL	9.55(3.2-37.7)	9.4(3.2-37.7)	13.1(5.8-23.7)	0.265
NE,10³/uL	7.1(2.38-30.1)	7.1(2.4-30.1)	7.9(3.4-18.5)	0.229
LYM,10³/uL	1.5(0.4-4.1)	1.4(0.5-4.1)	1.8(0.4-4.1)	0.345
Hb,gr/dL	10.7(5.5-16.5)	11.4(5.5-16.5)	9.6(6.4-13.6)	0.04
PLT,10³/uL	228(33-483)	218(35-446)	261(33-483)	0.525
CRP,mg/L	76(1-559)	67.1(1-559)	134(4.1-387)	0.140
ESR	(53(3-163)	53(4-131)	85(20-163)	0.325
Cr, mg/dL	1.2(0.5-9.9)	0.88(0.47-6.4)	1.76(0.79-9.9)	0.002
Bilirubin, mg/dL	0.5(0.2-5.4)	0.52(0.16-5.4)	0.69(0.22-3.2)	0.676
RF	14±8.9	13(0-38.5)	17.5(15.9-19)	0.366
Blood culture, n(%)				
Culture negative	14(28)	10(26.3)	4(33.3)	0.718
Staphylococcus aureus	8(16)	5(13.2)	3(25)	
Viridans Streptococci	6(12)	6(15.8)	0(0)	
Enterobacteriacea	3(6)	3(7.9)	0(0)	
Enterococci	7(14)	6(15.8)	1(8.3)	0.396
Brucella spp	2(4)	1(2.6)	1(8.3)	
Gemella	1(2)	1(2.6)	0(0)	
KNS	8(16)	6(15.8)	2(16.7)	
Candida	1(2)	0(0)	1(8.3)	
Antibiotic treatment*				
Ampicillin+Sulbactam	8(16)	5(13.2)	3(25)	
Ceftriaxone	15(30)	13(34.2)	2(16.7)	
Vancomycin	3(6)	1(2.6)	2(16.8)	
Ceftriaxone+Gentamicin	1(2)	1(2.6)	0	0.172
Ceftriaxone+Vancomycin	5(10)	2(5.3)	3(25)	
Vancomycin+Gentamicin	8(16)	7(18.2)	1(8.3)	
Ampicillin+Gentamicin	9(18)	8(20.8)	1(8.3)	
Doxycycline	1(2)	1(2.6)	0	
Embolic event, n(%)				
Peripheral	2(4)	2(5.2)	0	
Spleen	4(8)	3(7.8)	1(8.3)	0.001
Cranial	9(18)	3(5.2)*	6(50)*	
Absence of surgery, n(%)	21(42)	10(26.3)	11(91.6)	<0.001

* indicates subgroups with significant difference
WBC: White blood cell, NE: neutrophile, LYM:Lymphocyte, Hb:Hemoglobin, PLT:Platelet, CRP:C reactive protein, ESR: Eritrocyte sedimentation rate, Cr: Creatinine, RF: Rheumatic factor, KNS:Koagulase negative staphylococci.
*Additional use of Rifampicin is not expressed in the table to avoid abundant data

Table 3. Hazard ratios for the predictors of in-hospital mortality

	Unadjusted Hazard ratios				Adjusted Hazard ratios			
	HR	95 % Confidence interval		P value	HR	95 % Confidence interval		P value
DM	4.2	0.921	19.794	0.064				
CAD	3.2	1.011	10.319	0.048	2.4	0.727	8.217	0.149
Hemoglobin	0.8	0.655	1.043	0.109				
Creatinine	1.1	0.972	1.424	0.096				
Cerebral emboli	4.2	1.320	13.605	0.015	3.4	0.998	11.416	0.045
Lack of surgery	141.2	0.734	27182.932	0.065				

DM:Diabetes mellitus, CAD:Coronary artery disease

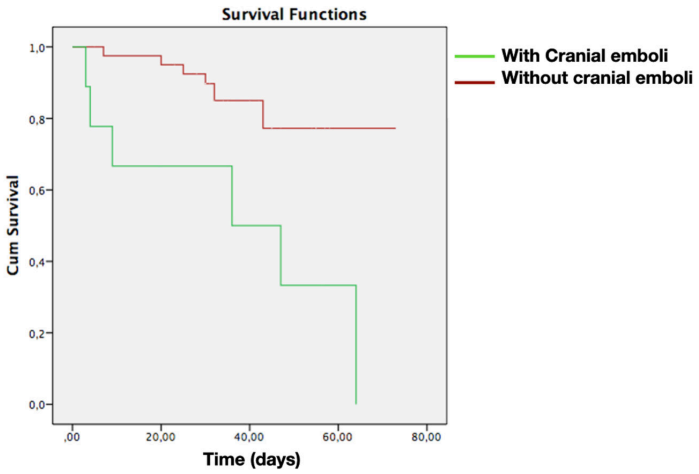

Figure 1. Kaplan-Meier curves displaying the estimated survival probability for patients with and without cranial emboli

Although the absence of surgery was closely associated with mortality, it was not found as a mortality predictor irrespective of cerebral emboli in regression analyses. The relationship between cranial emboli and the absence of surgery during index hospitalization was interesting due to a potential collinearity. To clarify the relationship between cranial emboli and mortality, a flow-diagram was created (Figure 2). Out of nine patients with cranial emboli, two patients demonstrated mild symptoms of stroke and were operated urgently with hemorrhagic transformation and mortality in one patient. Among the remaining seven patients with cerebrovascular accident, 5 patients could not be operated either due to rapid deterioration in neurological status or due to occurrence of hemorrhagic stroke. On the other hand, none of the patients died in the group of patients without cranial emboli undergoing surgery. The absence of surgery in patients without cranial emboli was caused either by patient refusal or by hemodynamic collapse due to septic shock in six surgery-awaiting patients. In conclusion, as suggested in Figure 2, the occurrence of cranial emboli hinders feasibility of surgery which in turn results in increased mortality.

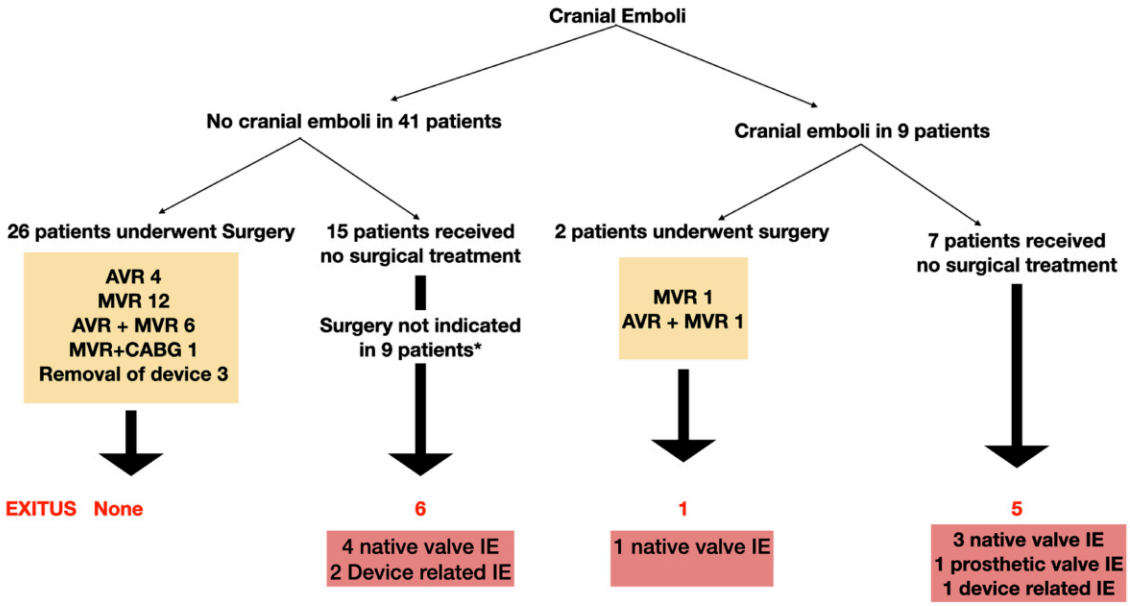

Figure 2. Flow diagram showing the clinical course in patients with regard to cranial emboli.(Nature of performed surgery is indicated in yellow boxes while the type of IE in patients with mortality is indicated in red boxes)

Discussion

This study has provided insights into the relationship between IE and mortality based on on the cardiac and non-cardiac predisposing factors, laboratory data, microbiologic analyses and clinical outcomes of patients with definite IE in a referral center within 5 years. Our analyses showed that most patients with IE had native valve endocarditis without previously a known predisposing heart condition. Our study revealed that the mortality rate was 24% and it did not differ with regard to the type of IE or culture-positivity. However, the presence of DM, CAD, increased baseline creatinine, or occurrence of cranial emboli and absence of surgery at index hospitalization were associated with higher mortality. The occurrence of cranial emboli was the single independent predictor of mortality possibly through delay in surgical treatment.

The mean age of the study population was 57±17 years which was relatively young when compared to European countries but compatible with the data from developing countries [1,4]. The mean age of the IE patients is younger in countries where predisposing conditions such as rheumatic valve disease are more prevalent [1]. This is consistent with our study results which showed that the most common predisposing condition was rheumatic valve disease with a rate of 16%. Intracardiac prosthetic material such as prosthetic valve or device leads increase the risk of IE several folds [9]. In our study, 10% of patients with IE had prosthetic valves and 18% had an intracardiac device such as a pacemaker or a defibrillator. When compared to the literature which reported average rates of prosthetic valve IE as 30%, the number of prosthetic valve-related IE was smaller in our study [10]. The number of device-related IE; however, was higher than the average national rate of 7% [11]. This discrepancy is probably due to the routine antibiotic prophylaxis of prosthetic valve patients prior to invasive or dental procedures involving prosthetic valves. There are, however, no current recommendations for patients with pacemakers or defibrillators before medical procedures which may pose higher risk of IE in this specific sub-group.

The rate of culture negative IE in our study was 28% which aligns with the average rate of 37% reported in studies conducted in Turkey. This rate is, however, slightly higher than those reported in European studies [1,4]. In our data, culture negative IE was not associated with increased in hospital mortality. Although no consensus exists, several studies have reported comparable outcomes in culture positive and negative IE, particularly in terms of short-term mortality [6].

The microbiology of the IE has evolved since the introduction of various medical techniques and invasive procedures [3,12]. The most common causative organism in the current study was staphylococci; with equal numbers of coagulase negative IE, particularly in terms of short-term mortality [6].

The microbiology of the IE has evolved since the introduction of various medical techniques and invasive procedures [3,12]. The most common causative organism in the current study was staphylococci; with equal numbers of coagulase negative staphylococci and staphylococcus aureus. Staphylococcus aureus is well-known for its tendency to affect normal native valves, which was also more common in our study [13]. Staphylococci are also notorious for leading to highly mortal infections as also shown in our results where 5 out of 7 of culture positive deaths were related to staphylococci infections [13]. Streptococci and Enterococci constituted other common types of bacteria in IE patients with one death being due to enterococci and no cases due to streptococci.

Several factors such as prosthetic valve endocarditis [14], age, embolic events [15], chronic kidney and liver disease [16], absence of surgery [17] were identified as the main factors associated with mortality in IE patients. In our study, we could not demonstrate a difference in mortality among native, prosthetic and device-related IE patients. The mortality was higher in patients with DM, CAD, increased baseline creatinine and cranial embolic events. Comorbidities such as DM, CAD and renal disease are elements of Charlson index and together with cerebral complications, were shown to increase mortality in IE [4,18]. In our study, absence of surgery at the index hospitalization was also associated with higher mortality.

The decision on surgical timing is one of the major therapeutic challenges in IE. While early IE prior to control of infection increases the perioperative mortality, delay in surgery increases embolic and hemodynamic complications [19]. In patients with IE who already suffered cerebral embolic complications, the timing of surgery requires a careful assessment of risks and benefits. A striking finding in the current study was the relationship between cranial embolic events and surgery. Out of nine patients with cranial emboli, two patients were urgently operated with hemorrhagic transformation and mortality in one patient. Current guidelines also advise against immediate surgery in patients with intracranial hemorrhage, coma, severe comorbidities and stroke with severe damage [7]. In our study, immediate surgery was contraindicated in seven patients with severe debilitating cerebral emboli which resulted in rapid deterioration and eventually mortality in five patients. Kaplan Meier curves also demonstrate this rapid deterioration within the first few weeks in patients with cerebral emboli (Figure 2). Consequently, the relationship between cranial emboli, mortality and the absence of surgery during index hospitalization was striking due to a potential collinearity between cerebral emboli and the absence of surgery. This explains why the absence of surgery during index hospitalization was not found to be a predictor of mortality, irrespective of cerebral emboli.

The occurrence of cranial emboli in early courses of IE is a common finding complicating 10-40% of all IE cases [20]. Our numbers of cranial embolic events, however, underestimate the true incidence of cerebral embolism as routine cerebral magnetic resonance imaging was not employed to detect silent infarcts. The decision-making in this sub-population of IE patients will depend on the case-based assessment and further evidence. Routine and serial cranial imaging to detect recent silent cerebral ischemia can be used to guide treatment and extrapolate imminent stroke particularly in patients with left-sided IE. With this approach, patients can retain the chance of surgical treatment.

The major limitations of this study were its retrospective nature and the small number of patients which limited the ability of Cox analyses to reveal the effect of various predictors. Small study population resulted from the rigorous selection of patients with inclusion of only those with TEE-proven vegetation. All patients in the study had TEE proven vegetations. The sensitivity of TEE to demonstrate a vegetation in native and prosthetic valves are 96%

and 92% respectively [21]. The specificity of TEE is >90% for both valves. The 2015 ESC guidelines of IE do not require the presence of a vegetation for the definite IE. Nevertheless, a positive blood culture and three minor criteria were deemed not to be specific for IE, particularly in patients with multiple comorbidities and sepsis in a retrospective analysis. We therefore did not include patients without a vegetation which further limited the number of patients in the study population.

In this retrospective cohort of patients with definite IE, we revealed that contemporary profile of the IE patients is subject to a change in which rate of device- related IE was increased and that mortality of prosthetic valve IE was comparable to that of native valve IE. More concerning was the increased mortality in patients with cerebral emboli in whom surgery could not be performed during index hospitalization. Our data suggest that the timing of surgical treatment, particularly in patients with neurologic complications, needs to be evaluated when shaping future perspectives on IE.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
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Ethical approval
Ethics approval was obtained before the study. (2020.38.02.12)

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