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CLINICAL RESEARCH
Valvular heart disease

The association between vegetation size and surgical treatment on 6-month mortality in left-sided infective endocarditis

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Aims In left-sided infective endocarditis (IE), a large vegetation >10 mm is associated with higher mortality, yet it is unknown whether surgery during the acute phase opposed to medical therapy is associated with improved survival. We assessed the association between surgery and 6-month mortality as related to vegetation size.

Methods and results Patients with definite, left-sided IE (2008–2012) from The International Collaboration on Endocarditis prospective, multinational registry were included. We compared clinical characteristics and 6-month mortality (by Cox regression with inverse propensity of treatment weighting) between patients with vegetation size ≤10 mm vs. >10 mm in maximum length by surgical treatment strategy. A total of 1006 patients with left sided IE were included; 422 with a vegetation size ≤10 mm (median age 66.0 years, 33% women) and 584 (median age 58.4 years, 34% women) patients with a large vegetation >10 mm. Operative risk by STS-IE score was similar between groups. Embolic events occurred in 28.4% vs. 44.3% ($P < 0.001$), respectively. Patients with a vegetation >10 mm was associated with higher 6-month mortality (25.1% vs. 19.4% for small vegetation, $P = 0.035$). However, after propensity adjustment, the association with higher mortality persisted only in patients with a large vegetation >10 mm vs. ≤10 mm: hazard ratio (HR) 1.55 (1.27–1.90); but only in patients with large vegetation managed medically [HR 1.86 (1.48–2.34)] rather than surgically [HR 1.01 (0.69–1.49)].

Conclusion Left-sided IE with vegetation size >10 mm was associated with an increased mortality at 6 months in this observational study but was dependent on treatment strategy. For patients with large vegetation undergoing surgical treatment, survival was similar to patients with smaller vegetation size.

Keywords Infective endocarditis • Vegetation size • Surgery • Antibiotics • Outcomes

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Introduction

A vegetation, the nidus of endocardial infection, is an important diagnostic and prognostic finding in patients with infective endocarditis (IE). Vegetations are apparent in most patients with IE,[1] and large vegetations are associated with a higher risk of embolization and early death.[2–4] In a small, randomized trial of very early surgery for patients with large, left-sided vegetations in IE, earlier surgery was found to significantly reduce the incidence of embolic events, but did not reduce overall mortality at 6 months.[5]

A recent meta-analysis of 21 IE studies found that patients with a vegetation size ≥10 mm had increased risks of embolic events and mortality.[6] Although both the American Heart Association/American College of Cardiology and the European Society of Cardiology recommend early surgery, before the completion of antibiotic therapy, for patients with large (>10 mm) vegetation, the level of evidence for these recommendations is not high and the relationship with subsequent mortality is not well defined.[7–9] In a study of 71 patients with left-sided IE, surgery in patients with vegetation length >10 mm was associated with higher long-term mortality.[10]

Thus, the relationship between vegetation size, surgical treatment, and outcome in IE is not well defined. We hypothesized that surgery during the acute phase of left-sided IE in patients with large vegetations >10 mm is associated with lower 6-month overall mortality. The objectives of this study were to evaluate (i) the clinical characteristics of patients with IE based on size of vegetation and surgical treatment and (ii) the association between surgery and 6-month mortality as related to vegetation size.

Methods

The study population for this analysis was the International Collaboration on Endocarditis-Plus (ICE-PLUS) cohort, a prospective, multinational registry of consecutive cases of definite IE by modified Duke criteria. The ICE-PLUS registry includes 2124 IE patients from 34 centres in 18 countries hospitalized between 1 September 2008 and 31 December 2012, with 6-month vital status follow-up data (all ICE sites listed in Acknowledgements section).[11]

Patients with definite, left-sided IE according to modified Duke criteria[12] were included in the study. Cases of device-related IE were excluded from the analysis. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was used. The study cohort is shown in *Figure 1*. The study was approved by the institutional review board or ethics committee at all participating sites, according to local standards.

Definitions

Definitions of the standard variables used in the ICE-PLUS database have been reported previously.[11] The presence and size of left-sided vegetation was determined by the site echocardiographers and recorded in the ICE-PLUS case report form. Large vegetation was defined as presence of any vegetation with maximum length >10 mm by transoesophageal echocardiography. All IE complications were events before the date of surgery. Early surgery was defined as replacement or repair of the affected valve during the initial hospitalization for IE before completion of antibiotic therapy. Indications for surgery included the following: heart failure, embolic event, persistent bacteraemia, paravalvular complication, severe valvular regurgitation, vegetation size, and microorganism. Data were collected on the case report form for timing of each IE complication and indication for surgery; surgery consultation and recommendation; timing of surgery; and the reasons for lack of surgery. The risk scoring system based on the Surgical Thoracic Society (STS) Adult Cardiac Surgery Database (STS-IE score) was used to calculate predicted risk of operative mortality for the study cohort.[13]

Descriptive statistics

Baseline characteristics and clinical events of the quartiles of surgical timing are presented as medians with 25% and 75% percentile for continuous variables and frequencies with proportions for categorical variables. We stratified the cohort according to treatment strategy (surgical vs. medically treated) and comparisons between groups were made with Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

Propensity score model

The goal of our study was to examine the relationship between vegetation size (large vs. small) and surgery and how this was related to 6-month mortality rates. Hence, we build a propensity model with surgery as outcome in order to balance surgery from known factors associated with surgery. A multivariable logistic regression model was fit to calculate a propensity score (probability) for early surgical treatment. The response variable was receipt of cardiac surgery for IE during the index hospitalization. The model included variables that were selected *a priori* by an experienced cardiologist (A.W.) and from practice guidelines and previous studies as those that would be evaluated in the decision to treat IE with surgery. These variables were age >70, history of dialysis, history of injection drug use, duration of symptoms >1 month, New York Heart Association (NYHA) Class III or IV, paravalvular complications, new moderate/severe aortic or mitral regurgitation, aortic or mitral vegetations, *Staphylococus aureus* IE, coagulase negative staphylococcus IE, viridans group IE, vegetation length >10 mm, and STS score (as a second order polynomial). The predicted probabilities of surgery were calculated and used as inverse probability weights in predicting outcome. Weights were trimmed at 20 to avoid overly influential observations.

Survival analysis

A Cox proportional hazards model to predict survival at 6 months after discharge was fit in the ICE-PLUS dataset, including variables associated with survival at $P < 0.15$ in univariable analysis. Surgery was included as a time-dependent variable. The model was weighted by the inverse probability (propensity) of early surgery in order to balance our sample for surgery and then assess the relationship between vegetation size and mortality at 6 months. To test the robustness of our results, we reran our analyses with propensity weighting for vegetation size instead of surgery and also without any propensity adjustment. Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA) and plots were generated with Splus 8.1 (TIBCO Software Inc., Palo Alto, CA, USA).

Results

Among 2124 patients in the ICE-PLUS registry, 1006 had definite left-sided IE with measurement of vegetation size recorded, surgical treatment, and timing confirmed. Large vegetations (>10 mm) were present in 586/1006 (58.2%) patients. The range of vegetation sizes is shown in *Figure 2*.

The clinical, microbiological, and IE characteristics for patients with small vs. large vegetations are shown in *Table 1*. Compared with

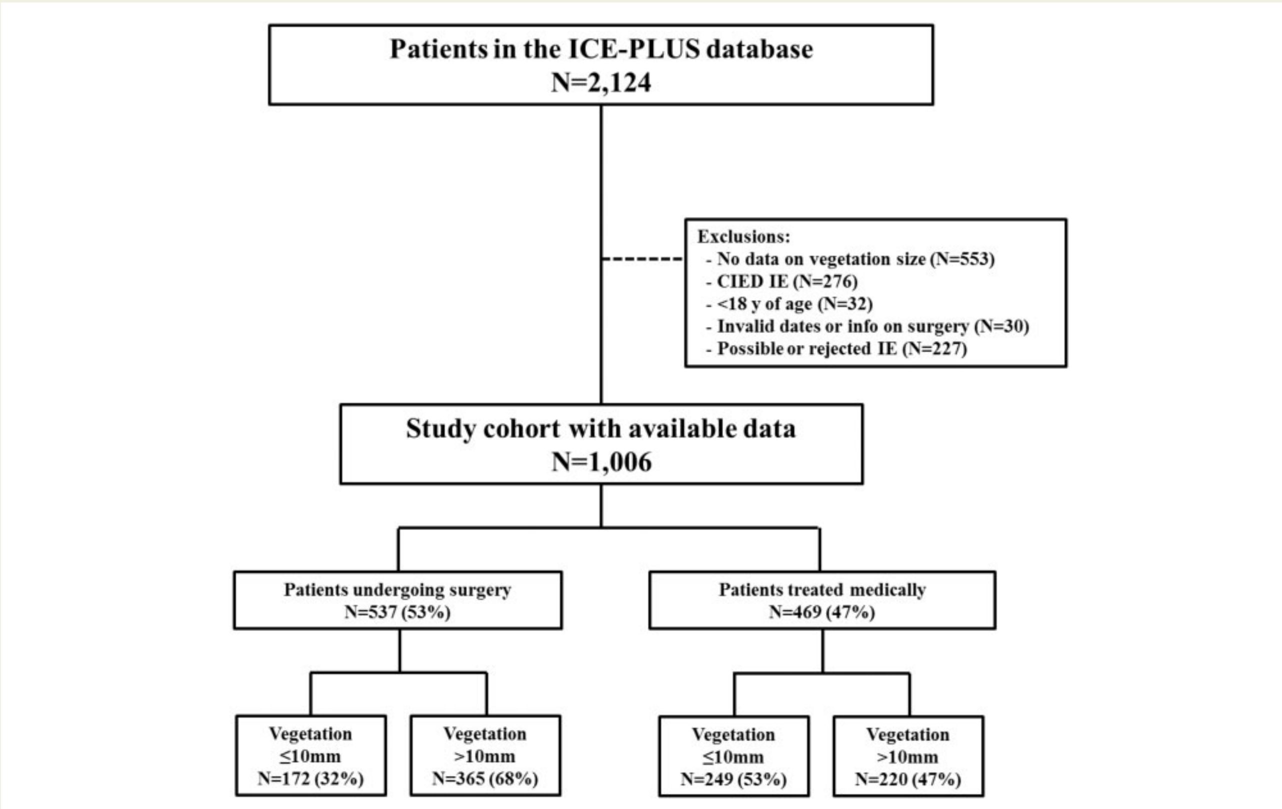

Figure 1 Patient selection.

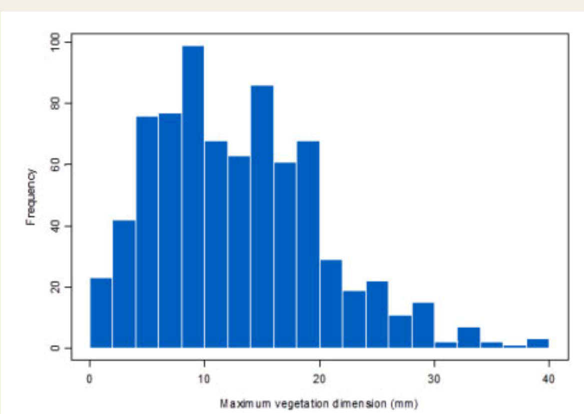

Figure 2 Histogram of vegetation size range.

patients with vegetation size ≤10 mm, patients with large vegetations were younger; had lower prevalence of comorbid conditions (prior heart failure, atrial fibrillation or flutter, coronary artery disease, previous cardiac surgery, immunosuppression or cancer), but a higher prevalence of mitral valve location. Microbiological causation was more frequently *S. aureus* and less frequently enterococci among patients with large vegetation. For IE-related characteristics and complications, prosthetic valve IE was less common among patients with large vegetations; but IE-related complications including stroke, embolic event, and persistent bacteraemia were more frequent.

Surgical treatment

During the index hospitalization for IE, 537/1006 (53.4%) patients underwent surgery at median time of 7 (interquartile range 2–16) days from admission to the participating site. The propensity model for surgical treatment is shown in Supplementary material online, *Table S1*. Large vegetations were present in 365/537 (68%) patients treated with surgery vs. 220/469 (47%) in the medically-treated group ($P < 0.001$), and larger vegetation was independently associated with surgery. The characteristics of the IE patients relative to surgical treatment and vegetation size are shown in *Table 2*. Patients with large vegetations undergoing surgery had lower frequency of prosthetic valve; more *S. aureus* infection; higher incidence of embolic events and new mitral valve regurgitation.

In comparing patients with large vegetations treated with surgery vs. those treated with medical therapy alone, patients treated with surgery were younger (median age 55.9 vs. 63.9 years, respectively; $P < 0.001$); had lower prevalence of prior cardiac surgery (16.4% vs. 25.9%, $P = 0.006$) and prosthetic valve IE (13.7% vs. 25.5%, $P < 0.001$); lower incidence of *S. aureus* causation (22.5% vs. 31.8%, $P = 0.012$); had higher rate of paravalvular complications (37.9% vs. 23.9%, $P < 0.001$), embolic events (48.1% vs. 38.2%, $P = 0.021$); new mitral regurgitation (51.0% vs. 39.4%, $P < 0.001$) and aortic regurgitation (38.2% vs. 20.9%, $P < 0.001$). Among patients with a large vegetation

Table 1 Baseline characteristics of IE patients based on vegetation length

	Vegetation ≤10 mm (*N* = 422)	Vegetation >10 mm (*N* = 584)	*P*-value
Demographics			
Age, median (IQR)	66.0 (49.9–76.2)	58.4 (44.2–71.2)	<0.001
Women	140 (33.3)	197 (33.7)	0.895
Medical history			
Previous IE	39 (9.3)	39 (6.7)	0.131
CVA	32 (7.6)	36 (6.1)	0.369
Previous heart failure	82 (19.8)	76 (13.2)	0.006
Atrial fibrillation/flutter	90 (22.4)	81 (14.8)	0.003
Coronary artery disease	79 (19.3)	80 (13.9)	0.024
Cardiac surgery	141 (33.5)	122 (20.9)	<0.001
Coronary artery bypass	37 (8.8)	29 (5)	0.016
Chronic obstructive lung disease	64 (15.4)	96 (16.6)	0.613
Diabetes mellitus	89 (21.1)	115 (20)	0.660
Moderate/severe renal disease	53 (12.8)	59 (10.2)	0.215
Haemodialysis	24 (5.7)	29 (4.9)	0.604
HIV	6 (1.5)	8 (1.4)	0.947
Injection drug use	14 (3.4)	53 (9.1)	<0.001
Immunosuppressive therapy	29 (6.9)	24 (4.1)	0.048
Moderate/severe liver disease	15 (3.6)	21 (3.7)	0.959
Cancer	67 (16.2)	65 (11.2)	0.023
STS score Q1	118 (28)	173 (29.5)	0.921
STS score Q2	117 (27.7)	163 (27.8)	
STS score Q3	99 (23.5)	128 (21.8)	
STS score Q4	88 (20.9)	122 (20.8)	
IE related characteristics			
IE onset to admission <30 days	268 (64.1)	353 (61.1)	0.328
Healthcare-acquired infection	98 (24.7)	111 (20.7)	0.144
Transferred from another facility	171 (40.8)	351 (60.1)	<0.001
Prosthetic valve IE	122 (28.9)	106 (18.1)	<0.001
Echocardiographic findings			
Vegetation location			
Mitral	187 (44.3)	332 (56.7)	<0.001
Aortic	244 (57.8)	241 (41.1)	<0.001
Left ventricular ejection fraction (%), median (IQR)	60 (50–65)	60 (53–65)	0.096
Microbiology			
Staphylococus aureus	84 (19.9)	152 (25.9)	0.026
Coagulase-negative Staphylococi	37 (8.8)	45 (7.7)	0.533
Viridans group Streptococci	70 (16.6)	92 (15.7)	0.705
Enterococci	74 (17.5)	64 (10.9)	0.003
Fungi	6 (1.4)	12 (2)	0.459
Gram negatives	20 (4.7)	25 (4.3)	0.720
Complications			
Heart failure	286 (67.7)	225 (58.2)	0.002
Stroke	82 (19.8)	155 (27)	0.008
Embolic event	119 (28.4)	258 (44.3)	<0.001
Paravalvular complications	114 (27.1)	191 (32.8)	0.056
Valve perforation	52 (12.4)	109 (18.7)	0.008
Persistent bacteraemia	42 (11)	81 (15.5)	0.048

CVA, cerebrovascular accident; HIV, human immunodeficiency virus.

Table 2 Characteristics of IE patients based on treatment strategy and vegetation size

	Surgery group ($N = 537$)		Medically treated group ($N = 469$)	
	Vegetation ≤10 mm ($N = 172$)	Vegetation >10 mm ($N = 365$)	Vegetation ≤10 mm ($N = 249$)	Vegetation >10 mm ($N = 220$)
Demographics				
Age, median (IQR)	60.2 (43.3–71.8)	55.9 (43.0–66.8)	70.1 (55.2–77.7)	63.9 (47.6–75.9)
Women	46 (26.9)	116 (31.9)	94 (37.9)	81 (37)
Medical history				
Previous IE	15 (8.8)	20 (5.5)	24 (9.7)	19 (8.7)
CVA	10 (5.8)	17 (4.7)	22 (8.8)	19 (8.6)
Previous heart failure	26 (15.3)	38 (10.7)	56 (23)	38 (17.5)
Atrial fibrillation/flutter	28 (17.1)	43 (12.7)	62 (26.2)	38 (18.4)
Coronary artery disease	23 (13.5)	40 (11.1)	56 (23.6)	40 (18.8)
Cardiac surgery	45 (26.2)	61 (16.8)	96 (38.7)	61 (27.7)
Coronary artery bypass	10 (5.8)	12 (3.3)	27 (10.9)	17 (7.8)
Chronic obstructive pulmonary disease	20 (11.8)	52 (14.5)	44 (18)	44 (20.1)
Diabetes mellitus	29 (17)	58 (16.4)	60 (24.1)	57 (25.9)
Moderate/severe renal disease	14 (8.3)	26 (7.2)	39 (15.9)	33 (15.3)
Haemodialysis	5 (2.9)	14 (3.8)	19 (7.6)	15 (6.8)
HIV	1 (0.6)	6 (1.7)	5 (2.1)	2 (0.9)
Injection drug use	6 (3.6)	32 (8.8)	8 (3.3)	21 (9.7)
Immunosuppressive therapy	5 (2.9)	15 (4.1)	24 (9.7)	9 (4.1)
Moderate/severe liver disease	3 (1.8)	9 (2.5)	12 (4.9)	12 (5.6)
Cancer	19 (11.2)	35 (9.7)	48 (19.8)	29 (13.5)
STS score Q1	49 (28.5)	102 (27.9)	69 (27.7)	71 (32.3)
STS score Q2	46 (26.7)	112 (30.7)	70 (28.1)	51 (23.2)
STS score Q3	38 (22.1)	68 (18.6)	61 (24.5)	59 (26.8)
STS score Q4	39 (22.7)	83 (22.7)	49 (19.7)	39 (17.7)
IE related characteristics				
IE onset to admission <30 days	109 (63.4)	210 (58.7)	158 (64.5)	142 (64.8)
Healthcare-acquired infection	28 (17.4)	59 (18.2)	70 (29.9)	52 (24.8)
Prosthetic valve IE	43 (25)	50 (13.7)	79 (31.7)	56 (25.5)
Echocardiographic findings				
Left ventricular ejection fraction (%), median (IQR)	60 (50–64)	60 (54–65)	60 (50–65)	60 (50–65)
Vegetation location				
Mitral	65 (38.2)	203 (55.8)	122 (49.4)	129 (59.4)
Aortic	114 (66.7)	166 (45.7)	130 (52.4)	75 (34.7)
Microbiology				
Staphylococus aureus	28 (16.3)	82 (22.5)	55 (22.1)	70 (31.8)
Coagulase-negative Staphylococi	13 (7.6)	30 (8.2)	24 (9.6)	15 (6.8)
Viridans group Streptococci	32 (18.6)	57 (15.6)	38 (15.3)	34 (15.5)
Enterococci	24 (14)	42 (11.5)	50 (20.1)	22 (10)
Fungi	1 (0.6)	6 (1.6)	5 (2)	6 (2.7)
Gram Negatives	10 (5.8)	16 (4.4)	10 (4)	9 (4.1)
Surgical indications				
Heart failure	68 (39.5)	118 (32.3)	16 (6.4)	29 (13.2)
Paravalvular complication	43 (25)	54 (14.8)	9 (3.6)	21 (9.5)
Persistent bacteraemia	13 (7.6)	45 (12.3)	15 (6)	19 (8.6)
Embolic event	29 (16.9)	112 (30.7)	19 (7.6)	30 (13.6)
Complications				
Local				
Paravalvular complications	72 (42.4)	138 (37.9)	41 (16.5)	52 (23.9)
Valve perforation	34 (20.1)	79 (21.7)	18 (7.2)	29 (13.3)

Continued

Table 2 Continued

	Surgery group (*N* = 537)		Medically treated group (*N* = 469)	
	Vegetation ≤10 mm (*N* = 172)	Vegetation >10 mm (*N* = 365)	Vegetation ≤10 mm (*N* = 249)	Vegetation >10 mm (*N* = 220)
Intracardiac fistula	4 (2.4)	14 (3.9)	3 (1.2)	5 (2.3)
Prosthetic dehiscence	13 (10.7)	13 (5.1)	4 (2.3)	8 (5.4)
Systemic				
New of worsening heart failure	92 (54.8)	181 (49.9)	42 (16.9)	59 (27.8)
Stroke	31 (18.1)	89 (24.7)	51 (21)	65 (30.5)
Embolic event	50 (29.4)	175 (48.1)	69 (27.8)	83 (38.2)
Persistent bacteraemia	19 (12.3)	53 (16.2)	23 (10.1)	28 (14.5)

CVA, cerebrovascular accident; HIV, human immunodeficiency virus.

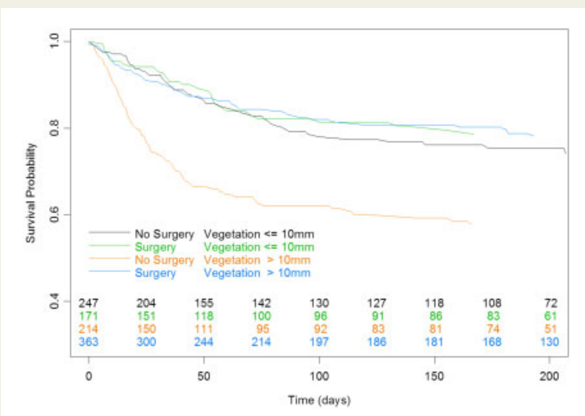

Figure 3 Risk of death by vegetation size and surgical treatment. There were 11 patients missing data for 6 months follow-up for mortality and these were excluded (one among those with the vegetation ≤10 mm who underwent surgery, two among those with the vegetation >10 mm who underwent surgery, two among those with the vegetation ≤10 mm who did not undergo surgery, and six among those with the vegetation >10 mm who did not undergo surgery).

who did not undergo surgery, 52% had one or more reasons documented for not undergoing surgery. Of those with a documented reason, the five most frequent reasons were a poor prognosis (31%), good prognosis without surgery (21%), stroke (21%), surgeon declined to operate (19%), and other (16%).

Mortality and treatment relationship

In the overall study population, patients with large vs. small vegetation had a higher rate of both in-hospital [20.8% vs. 15.2%, respectively; odds ratio (OR) 1.45, 95% confidence interval (CI) 1.04–2.03] and 6-month mortality (25.1% vs. 19.4%, respectively; OR 1.37, 95% CI 1.01–1.87). However, in comparing patients with large vs. smaller vegetations treated with surgery, there were no differences in the in-hospital (14.8% vs. 14.5%, respectively; $P = 0.927$) or 6-month mortality rates (18.1% vs. 18.0%, respectively; $P = 0.976$).

Figure 3 shows the unadjusted mortality by treatment strategy and vegetation size. Interaction between vegetation size and treatment strategy was statistically significant ($P < 0.0001$), indicating that vegetation size (large vs. small) was associated with higher mortality only in those patients who did not undergo surgery. There was no difference between the in-hospital (*Table 2*) and 6-month mortality rates (*Figure 3*) between patients with large vs. smaller vegetation who underwent surgery, whereas vegetation >10 mm vs. ≤10 mm was associated with higher mortality in the medically treated group. In the propensity-adjusted Cox proportional hazard analysis (*Table 3*), larger vegetation size was significantly associated with higher 6-month mortality in the overall study population and in the subgroup of patients treated without surgical intervention. Among surgically-treated patients, vegetation size was not associated with 6-month mortality.

We tested the robustness of our results in a model without inverse probably weighting by propensity for surgery and the results were similar [*P* for interaction <0.001 and hazard ratio (HR) 1.94 (1.40–2.71) for vegetation >10 mm vs. ≤10 mm in the medically treated group and 1.00 (0.57–1.79) in the surgery subgroup, respectively]. Further, in a model using inverse probability weighting for vegetation size instead of surgery as the shown in the main analysis our results remained similar [*P* for interaction <0.001 and HR 1.89 (1.48–2.41) for vegetation >10 mm vs. ≤10 mm in the medically treated group and 1.25 (0.82–1.92) in the surgery subgroup, respectively].

Discussion

The main objective of this study was to evaluate the association between treatment strategy of left-sided IE and 6-month mortality as related to vegetation size. Our results show that IE patients with large vegetation >10 mm have a higher rate of embolic events and mortality, but that early surgery for large vegetation was associated with lower 6-month overall mortality than medical therapy alone after adjustment for surgical selection and operative risk.

Vegetation size is an important prognostic factor in IE as studies have shown its relationship to embolization risk and in-hospital mortality.[2–4] Vegetation size has been studied closely for short-term

Table 3 Propensity and multivariable adjusted hazard ratios for 6-month mortality

	Hazard ratio (95% CI)	*P*-value
Vegetation >10 mm vs. ≤10 mm	1.55 (1.27–1.90)	<0.0001
Medical therapy subgroup		
Vegetation >10 mm vs. ≤10 mm	1.86 (1.48–2.34)	<0.0001
Surgery subgroup		
Vegetation >10 mm vs. ≤10 mm	1.01 (0.69–1.49)	0.95

Models were adjusted for age, dialysis, diabetes, IE hospital acquisition, prosthetic valve IE, bacteriological aetiology, paravalvular complications, vegetation placement (mitral or aortic), NYHA Class III or IV, stroke, evidence of persistent bacteraemia, and STS score.

embolization risk and in-hospital mortality, yet data on subsequent mortality are sparse.[6–9] In one of the largest studies of vegetation size and prognosis in IE, vegetation length >10 mm was independently associated with higher rate of new embolic events, and length >15 mm was associated with higher 1-year mortality.[3] The current study confirms that a large vegetation >10 mm was associated with higher in-hospital and 6-month mortality. Based on this consistent association between vegetation size >10 mm and worse outcome, treatment guidelines for IE recommend surgical intervention in this setting.[7–9]

The role of surgery to reduce mortality in IE patients with large vegetations has not been well evaluated and surgery in patients with vegetation length >10 mm has been associated with higher long-term mortality.[10] In contrast, the Early Surgery vs. Conventional Treatment in Infective Endocarditis (EASE) trial randomized 76 patients with left-sided IE and vegetation >10 mm to early surgery vs. conventional therapy. The EASE study demonstrated that very early surgery (within 48 h of IE diagnosis) in patients with large vegetations was associated with lower risk of embolic events, but no difference in 6-month mortality.[5] Importantly, the majority of patients in the conventional therapy arm of the study underwent surgery during the index hospitalization,[5] representing a cross-over to surgery that may have influenced the survival analysis.

We found that patients with large vegetations treated with surgery had lower rates of in-hospital and 6-month mortality in unadjusted analysis. There were significant differences in these patients selected for surgical intervention compared with patients with larger vegetations who received only medical therapy during the index hospitalization. Notably, patients with larger vegetations who underwent surgery were younger, but had more IE complications. After adjustment for both operative risk by STS score and treatment selection by propensity adjustment, IE patients with large vegetations treated with surgery had similar 6-month mortality as those with smaller vegetations.

Although the association between larger vegetation size and embolic events is strong, it remains unclear if the cause of death in patients with larger vegetations not treated with surgery is related to embolic events. The risk of embolic events decreases after initiation of appropriate antibiotic therapy,[14] but large vegetations have been associated with a higher risk of recurrent or new embolic event during antibiotic treatment.[15] We found that large vegetations >10 mm were associated with more IE-related complications in the present study, including embolic events, heart failure, paravalvular complications, valve perforation, and persistent bacteraemia. Therefore, the lower mortality rates observed in patients with large vegetations treated with surgery may be related to improvement in several of these prognostic complications, including treatment of heart failure and infection source control. The lack of data regarding cause of death in this study cohort is a limitation that precludes assessing the relationship between additional embolic events on antibiotic therapy and mortality.

This study has additional limitations. This was a retrospective analysis using data from a voluntary multinational clinical registry. All participating ICE sites are referral centres with multidisciplinary experience in the management of IE and the availability of cardiac surgery, which may affect the generalizability of the results. The use of surgery was not pre-specified by a study protocol but rather at the discretion of the treating care teams. However, we have previously found that surgery was performed for guideline-directed indications in this cohort,[11] and propensity analysis was used to adjust for treatment selection bias. A high percentage of all IE cases in this registry did not have size of vegetation collected or recorded. Vegetation size was determined by cardiologists at each site but not centrally adjudicated. Other morphologic characteristics of the vegetations such as mobility or volume were not collected. In addition, although risk estimates were adjusted as best possible, some known risk factors for death such as body mass index, albumin, mental health, and cachexia were not available. Finally, we examined all-cause mortality; cause-specific mortality was not available to us.

In conclusion, although larger vegetation size in IE is associated with more complications and higher mortality, surgery during the index hospitalization was associated with lower 6-month mortality after adjustment for treatment selection and operative risk. Additional randomized prospective studies are needed to evaluate the benefit and timing of surgery in IE patients with larger vegetations on both mortality and morbidity.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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ICE participating sites

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