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CLINICAL RESEARCH
Valvular heart disease

Predictors of embolism and death in left-sided infective endocarditis: the European Society of Cardiology EURObservational Research Programme European Infective Endocarditis registry

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Abstract

Background and Aims Even though vegetation size in infective endocarditis (IE) has been associated with embolic events (EEs) and mortality risk, it is unclear whether vegetation size associated with these potential outcomes is different in left-sided IE (LSIE). This study aimed to seek assessing the vegetation cut-off size as predictor of EE or 30-day mortality for LSIE and to determine risk predictors of these outcomes.

Methods The European Society of Cardiology EURObservational Research Programme European Infective Endocarditis is a prospective, multicentre registry including patients with definite or possible IE throughout 2016–18. Cox multivariable logistic regression analysis was performed to assess variables associated with EE or 30-day mortality.

Results There were 2171 patients with LSIE (women 31.5%). Among these affected patients, 459 (21.1%) had a new EE or died in 30 days. The cut-off value of vegetation size for predicting EEs or 30-day mortality was >10 mm [hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.13–1.69, $P = .0015$]. Other adjusted predictors of risk of EE or death were as follows: EE on admission (HR 1.89, 95% CI 1.54–2.33, $P < .0001$), history of heart failure (HR 1.53, 95% CI 1.21–1.93, $P = .0004$), creatinine >2 mg/dL (HR 1.59, 95% CI 1.25–2.03, $P = .0002$), *Staphylococcus aureus* (HR 1.36, 95% CI 1.08–1.70, $P = .008$), congestive heart failure (HR 1.40, 95% CI 1.12–1.75, $P = .003$), presence of haemorrhagic stroke (HR 4.57, 95% CI 3.08–6.79,

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$P < .0001$), alcohol abuse (HR 1.45, 95% CI 1.04–2.03, $P = .03$), presence of cardiogenic shock (HR 2.07, 95% CI 1.29–3.34, $P = .003$), and not performing left surgery (HR 1.30 95% CI 1.05–1.61, $P = .016$) (C-statistic = .68).

Conclusions Prognosis after LSIE is determined by multiple factors, including vegetation size.

Structured Graphical Abstract

Key Question

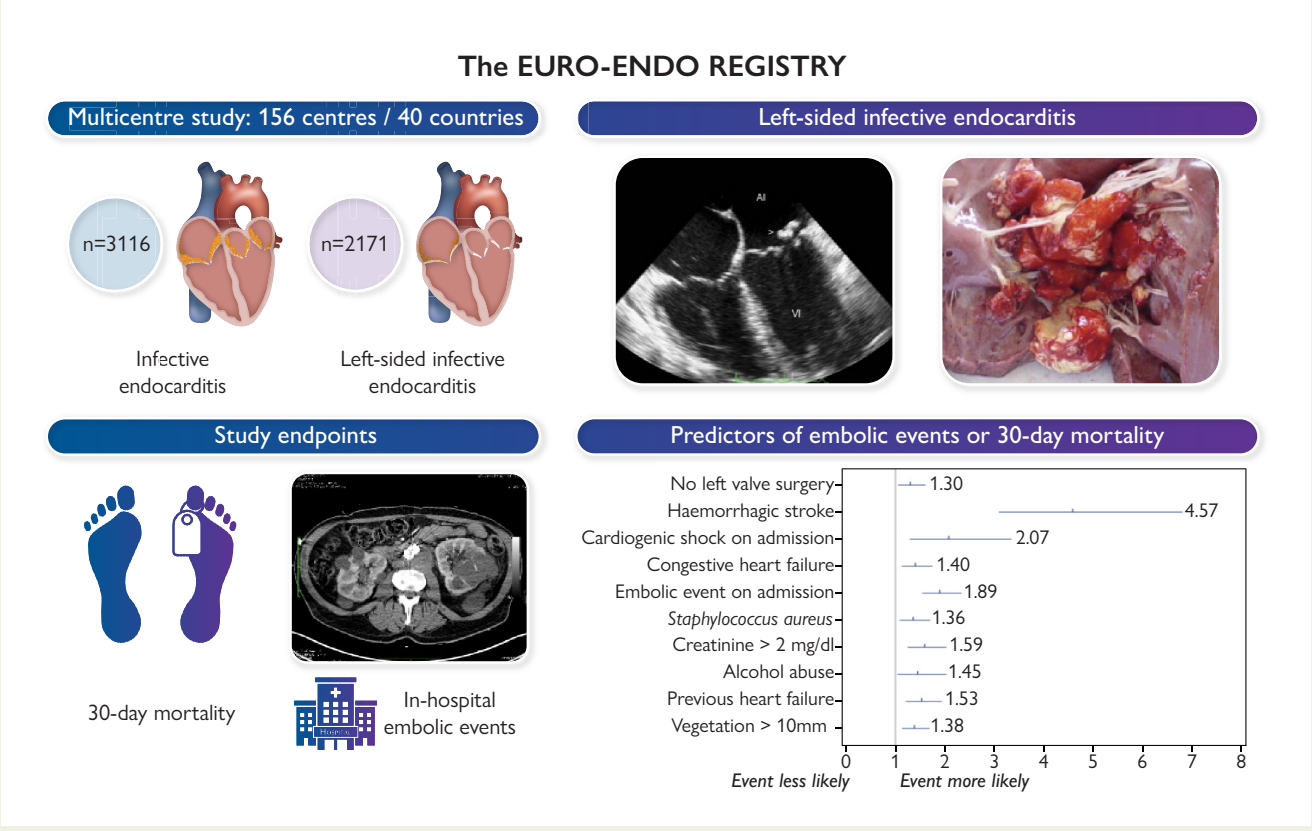
To assess the vegetation cut-off size and other risk predictors associated with in-hospital embolic events or 30-day mortality for left-sided infective endocarditis (LSIE).

Key Finding

In LSIE, the cut-off value of vegetation size for predicting in-hospital embolic events or 30-day mortality was >10 mm. Remarkably, the most powerful factor associated with in-hospital embolic event or 30-day mortality was the presence of haemorrhagic stroke.

Take Home Message

Prognosis after LSIE is determined by multiple factors, including vegetation size.



Method and main findings of the present study. LSIE, left-sided infective endocarditis.

Keywords Infective endocarditis • Vegetation size • Left-sided infective endocarditis • Embolic events • Mortality

Introduction

Despite recent improvements in diagnostic and therapeutic strategies, infective endocarditis (IE) is still associated with a high incidence of embolic events (EEs), ranging from 13% to 49%.[1–5] Embolic events are frequent and life-threatening complications, such as strokes, which tend to occur in 20%–40% of IE cases.[6,7] The risk of stroke is highest at diagnosis and decreases rapidly after the initiation of antibiotic therapy (incidence drops from 4.82/1000 patients in the first week of therapy to 1.71/1000 patients in the second week).[8] The evaluation of the embolic risk at admission is crucial in the management of IE to avoid such potentially catastrophic events. Several factors have been associated with EE in any location, such as the length and localization of vegetation (>10–13 mm), the causative microorganism (*Staphylococcus*

aureus), and the presence of previous emboli by outstanding observational studies and meta-analyses.[9–13] Although these factors have been highlighted in the European Society of Cardiology (ESC) IE guidelines, and there is evidence that early surgery and large vegetation significantly reduce the risk of death, there are little data about whether these risk factors are similar in left-sided IE (LSIE).[9–15]

On the other side, despite recent improvements in diagnostic and therapeutic strategies, IE is still associated with high in-hospital mortality due to a wide fan of complications. These wide ranges of complications underscore the heterogeneity of the disease and the critical need for baseline risk stratification according to different locations of IE to focus on aggressive management in high-risk subsets of patients.

We hypothesized that specific clinical characteristics of an IE episode, including surgical intervention, would be associated with 30-day mortality in IE. Therefore, the aims of this study are to distinguish the cut-off size of vegetation associated with EE or 30-day mortality risk and to determine other risk predictors of these outcomes.

Methods

Study design and data collection

The ESC EURObservational Research Programme European Infective Endocarditis (ESC-EORP EURO-ENDO) registry is a prospective multicentre observational study of patients presenting to hospitals in Europe and ESC-affiliated/non-affiliated countries with definite or possible IE. The detailed methodology of EURO-ENDO has already been reported.[16] Briefly, from 1 January 2016 to 31 March 2018, centres were asked to include consecutive patients aged over 18 years who presented with IE for 1 year. A total of 156 centres from 40 countries participated.

Inclusion criteria were a diagnosis of definite IE (or possible IE considered and treated as IE) based on the 2015 ESC IE diagnostic criteria.[14] After informed consent, data were collected at admission and during hospitalization. They included demographics; patient history; Charlson comorbidity index; age and several comorbidities; clinical, biological, microbiological, and echocardiographic findings; use of other imaging techniques computed tomography (CT) scan, [18] F-Fluor-Desoxi-Glucosa(F-FDG) positron emission tomography (PET)/CT, and leucocyte scintigraphy], medical therapy, complications (EE and infectious and haemodynamic complications), theoretical indications for surgery, and in-hospital mortality.[17]

Clinical data

The following clinical and biological parameters were prospectively collected at diagnosis and during hospitalization: age, sex, fever (temperature ≥ 38°C), previous heart disease, intravenous drug abuse, HIV infection, diabetes, history of cancer, comorbidity, moderate or severe congestive heart failure diagnosed as previously described, and serum creatinine > 2 mg/dL.

Definitions

Definitions of the standard variables used in the ESC-EORP EURO-ENDO registry were previously reported.[17] The presence and size of vegetation were determined by the site's echocardiographers and recorded in the ESC-EORP EURO-ENDO case report form for the timing of surgery. All IE complications were events before the date of surgery, except for death, which was recorded at any time during the registry collection and through 1 year of follow-up.

Endpoint

The primary endpoint was the 30-day occurrence of EE or mortality. Diagnosis of EE was based on clinical or CT scan data or both. A specific diagnosis of cerebral embolism was eventually confirmed during the clinical course by an experienced neurologist, who was unaware of the microbiological and echocardiographic findings. Cutaneous manifestations and EE occurring after surgery were not included.

Statistical analysis

All patients enrolled with possible or definite IE were included in the analysis. Continuous variables were reported as mean ± standard deviation (SD) or as the median (25th–75th percentile). Between-group comparisons were made using the Mann–Whitney test. Categorical variables were reported as counts and percentages. Between-group comparisons were made using the chi-square test or Fisher's exact test if any expected cell count was <5.

We applied regression modelling to study the relation between size of vegetation as determinant of EE and 30-day mortality [Cox proportional hazard (PH) regression]. Size of vegetation was dichotomized. The threshold was calculated with a time-dependent receiver operating characteristic (ROC), and the value with the highest Harrell's concordance (*C*) statistic was considered. We report the crude, unadjusted relations [hazard ratio (HR)] between dichotomized size of vegetation and outcome.

Taking the above-described multivariable regression models as starting point, we subsequently reduced the model sizes by applying backward elimination, until all variables had a *P*-value of <.05. We report on the HRs of the variables that compose this final model.

The PH assumption was checked using the global Schoenfeld residual test, whereas model performance was evaluated using the *C*-statistic and the goodness-of-fit test.

Analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided *P*-value of <.05 was considered statistically significant. All estimates are presented together with the corresponding 95% confidence intervals (CIs).

Results

Baseline patient demographics and characteristics

During the study period, 3116 cases of IE were included. The patient cohort demographics and characteristics were previously described.[17] In summary, among the 3116 patients, 1764 (56.6%) had native valve IE, 939 (30.1%) prosthetic valve IE, and 308 (9.9%) cardiac device-related IE, with similar proportions observed within and outside Europe.[17] The mean age was 59.25 ± 18.03 years (46.3% ≥ 65 years and 12.0% ≥ 80 years) and 969 (31.1%) were female. Among 3116 cases of IE, only 2660 cases were considered for this analysis (patients with unknown locations of IE or without data on vegetation were excluded), of which 2171 (81.6%) were LSIE, 263 (9.9%) on right-sided IE (RSIE), and 226 (8.5%) device-related IE. Transthoracic echocardiography (TTE) was performed in 1552 (71.5%) and transoesophageal echocardiography (TOE) in 1745 (80.4%), with TOE being more frequently used in suspected prosthetic

Table 1 Use of transthoracic and transoesophageal echocardiography in left-sided infective endocarditis (*n* = 2171)

Echocardiography *n*°1	
TTE	1552/2171 (71.5%)
TOE	1745/2171 (80.4%)
TTE only	426/2171 (19.6%)
TOE only	619/2171 (28.5%)
TTE and TOE	1126/2171 (51.9%)

TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 2 Characteristics of left-sided infective endocarditis patients based on the presence of embolism or death within 30 days

	Total ($n = 2171$)	Embolism or death ($n = 459$)	No embolism nor death ($n = 1712$)	*P*-value
Demography				
Male	1487/2171 (68.5%)	315/459 (68.6%)	1172/1712 (68.5%)	.945
Female	684/2171 (31.5%)	144/459 (31.4%)	540/1712 (31.5%)	
Age (years), mean ± SD	60.79 ± 16.99	61.65 ± 17.48	60.56 ± 16.85	.067
History of cardiovascular disease				
Previous endocarditis	178/2171 (8.2%)	33/459 (7.2%)	145/1712 (8.5%)	.375
Previous heart failure	437/2010 (21.7%)	126/419 (30.1%)	311/1591 (19.5%)	<.001
Previous atrial fibrillation	520/2045 (25.4%)	116/425 (27.3%)	404/1620 (24.9%)	.321
Previous cardiac surgery	916/2077 (44.1%)	212/440 (48.2%)	704/1637 (43.0%)	.052
Valvular intervention	803/2171 (37.0%)	177/459 (38.6%)	626/1712 (36.6%)	.431
Implanted PM/ICD/cardiac resynchronization therapy	186/2171 (8.6%)	38/459 (8.3%)	148/1712 (8.6%)	.804
Risk factors				
Previous stroke/TIA	255/2026 (12.6%)	61/420 (14.5%)	194/1606 (12.1%)	.179
Intravenous drug dependency	77/2146 (3.6%)	16/455 (3.5%)	61/1691 (3.6%)	.926
Diabetes mellitus	493/2168 (22.7%)	129/459 (28.1%)	364/1709 (21.3%)	.002
Alcohol abuse	144/2103 (6.8%)	44/442 (10.0%)	100/1661 (6.0%)	.004
Chronic renal failure	384/2169 (17.7%)	115/459 (25.1%)	269/1710 (15.7%)	<.001
Dialysis	106/2169 (4.9%)	35/459 (7.6%)	71/1710 (4.2%)	.002
Serum creatinine > 2 mg/dL	296/2147 (13.8%)	101/455 (22.2%)	195/1692 (11.5%)	<.001
Oral anticoagulation	584/2051 (28.5%)	131/429 (30.5%)	453/1622 (27.9%)	.287
Vitamin K antagonists	462/2171 (21.3%)	95/459 (20.7%)	367/1712 (21.4%)	.731
Direct oral anticoagulant	122/2026 (6.0%)	36/424 (8.5%)	86/1602 (5.4%)	.016
Any antiplatelet	580/2060 (28.2%)	114/430 (26.5%)	466/1630 (28.6%)	.394
Type of endocarditis				
Definite IE	1832/2171 (84.4%)	405/459 (88.2%)	1427/1712 (83.4%)	.010
Possible IE	339/2171 (15.6%)	54/459 (11.8%)	285/1712 (16.6%)	
Location of left side IE				
Native	1369/2171 (63.1%)	286/459 (62.3%)	1083/1712 (63.3%)	.708
Native aortic valve	766/1339 (57.2%)	145/272 (53.3%)	621/1067 (58.2%)	.146
Native mitral valve	877/1138 (77.1%)	207/263 (78.7%)	670/875 (76.6%)	.470
Prosthesis or valvular repair	802/2171 (36.9%)	173/459 (37.7%)	629/1712 (36.7%)	.708
CDRIE	35/2171 (1.6%)	9/459 (2.0%)	26/1712 (1.5%)	.504
Echocardiographic findings				
Vegetation size (mm), mean ± SD	9.87 ± 8.62	10.96 ± 8.96	9.58 ± 8.51	.065
Vegetation length > 10 mm	917/2171 (42.2%)	229/459 (49.9%)	688/1712 (40.2%)	<.001
Abscess	314/2106 (14.9%)	68/444 (15.3%)	246/1662 (14.8%)	.787
Severe regurgitation	918/2171 (42.3%)	199/459 (43.4%)	719/1712 (42.0%)	.601
Severe stenosis	144/2171 (6.6%)	36/459 (7.8%)	108/1712 (6.3%)	.241
Left ventricular ejection fraction (%), median (IQR)	59 (50–65)	58 (50–65)	59 (50–65)	.338

Continued

Table 2 *Continued*

	Total ($n = 2171$)	Embolism or death ($n = 459$)	No embolism nor death ($n = 1712$)	*P*-value
New valvular and paravalvular complication	302/996 (30.3%)	61/179 (34.1%)	241/817 (29.5%)	.227
Paraprosthetic regurgitation	61/996 (6.1%)	7/179 (3.9%)	54/817 (6.6%)	.173
PET/CT performed	342/2171 (15.8%)	60/459 (13.1%)	282/1712 (16.5%)	.076
Microorganisms on admission				
Enterococci	302/2171 (13.9%)	65/459 (14.2%)	237/1712 (13.8%)	.861
Streptococcus viridans	239/2171 (11.0%)	36/459 (7.8%)	203/1712 (11.9%)	.015
Streptococcus bovis	133/2171 (6.1%)	18/459 (3.9%)	115/1712 (6.7%)	.027
Staphylococcus aureus	441/2171 (20.3%)	130/459 (28.3%)	311/1712 (18.2%)	<.001
Coagulase-negative staphylococci	205/2171 (9.4%)	46/459 (10.0%)	159/1712 (9.3%)	.633
Others (including gram negative bacillus)	469/2171 (21.6%)	89/459 (19.4%)	380/1712 (22.2%)	.195
Negative blood cultures	453/2171 (20.9%)	85/459 (18.5%)	368/1712 (21.5%)	.163
Embolic events				
Embolic events on admission	532/2171 (24.5%)	162/459 (35.3%)	370/1712 (21.6%)	<.001
Embolic events during the first 30 days	282/2171 (13.0%)	282/459 (61.4%)	0/1712	<.001
Pulmonary	29/282 (10.3%)	29/282 (10.3%)	-	
Cerebral	161/282 (57.1%)	161/282 (57.1%)	-	
Spleen	62/282 (22.0%)	62/282 (22.0%)	-	
Coronary	12/282 (4.3%)	12/282 (4.3%)	-	
Renal	23/282 (8.2%)	23/282 (8.2%)	-	
Hepatic	6/282 (2.1%)	6/282 (2.1%)	-	
Peripheral	32/282 (11.3%)	32/282 (11.3%)	-	
Other type	27/282 (9.6%)	27/282 (9.6%)	-	
Cardiac surgery performed	1165/1584 (73.5%)	199/358 (55.6%)	966/1226 (78.8%)	<.001

CDRIE, cardiac device-related infective endocarditis; CT, computed tomography; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; IQR, interquartile range; PET, positron emission tomography; PM, pacemaker; TIA, transient ischemic attack.

valve IE ($P < .0001$). The use of TTE and TOE in LSIE is summarized in *Table 1*. Surgery was performed on 1165 patients (53.7%).

Risk of in-hospital embolic events or death

Among the 2171 patients affected by LSIE, 459 (21.1%) had a new EE or died in 30 days. Causes of death are summarized in Supplementary data online, *Table S1*. Patient characteristics by EE and death are summarized in *Table 2*. Patients affected by a new EE and death showed more frequent diabetes, alcohol abuse, chronic renal failure, dialysis, or creatinine > 2 mg/dL, had previous heart failure, and received non-vitamin K antagonist oral anticoagulants more frequently compared with patients without those events. The microorganism more frequently associated with those events was *S. aureus*, and less frequently associated were *Streptococcus viridans* and *Streptococcus bovis*. The cut-off value for the best vegetation size associated with EE and death in LSIE was >10 mm (*C*-statistics: 0.54). Cardiac surgery was less performed in patients who suffered those events (55.6% vs. 78.8%, $P < .001$).

By univariable Cox regression, factors associated with a new EE or 30-day mortality were as follows: vegetation size > 10 mm; some previous conditions such as diabetes mellitus, alcohol abuse, chronic renal failure, dialysis, previous heart failure, or direct oral anticoagulant (DOAC) therapy at admission; and factors associated with infection, such as intra-vascular catheter, source of infection (nosocomial vs. community-acquired), and *S. aureus*. Moreover, other factors associated with systemic complications such as congestive heart failure, cardiogenic shock, creatinine > 2 mg/dL, or presence of EE at admission were also associated with EE or 30-day mortality. The most powerful factor associated with these outcomes during admission was the presence of a haemorrhagic stroke at admission (HR 4.74, 95% CI 3.44–6.53, $P < .001$) (see Supplementary data online, *Table S2*).

By multivariable Cox regression analysis, vegetation > 10 mm (HR 1.38, 95% CI 1.13–1.69, $P = .0015$) was independently associated with EE or 30-day mortality in LSIE, and haemorrhagic stroke was the most powerful risk predictor (HR 4.57, 95% CI 3.08–6.79, $P < .0001$) of this primary endpoint (*Table 3*; *Figure 1*).

Discussion

Despite recent advances in diagnostic and therapeutic strategies, IE remains a devastating disease with a high incidence of EE and with high

mortality rate. The current study allowed identifying the specific cut-off vegetation size and predictor factors of high risk for EE and mortality in LSIE patients (*Structured Graphical Abstract*).

Risk of embolic events and death regarding vegetation size

A cut-off vegetation size > 10 mm in LSIE was associated with EE or 30-day mortality. A meta-analysis including 21 studies with 6646 patients concluded that a vegetation size > 10 mm is associated with EE, independent of the location of IE.[13] In this sense, although other investigations have previously identified the cut-off vegetation size associated with EE risk in LSIE, none have tried to determine a different cut-off size for EE and mortality in LSIE in the same cohort.[10,11,13,15,18–23] In agreement with these results, the ESC guidelines suggest the consideration of surgical options in aortic or mitral vegetation > 10 mm with one or more EE despite antibiotic therapy (Class I, level of evidence B) irrespective of IE location.[14] However, the evidence behind these recommendations comes from relatively small observational studies with varying degrees of bias. Therefore, our study provides to the existing literature, concordant findings regarding the cut-off vegetation size in LSIE in a large prospective cohort.

Remarkably, we found that previous treatment with DOAC on admission was associated with EE risk in LSIE. This finding is in accordance with the current ESC guidelines[14] and the American Heart Association statement,[18] which do not recommend anticoagulation, although we lack well-designed clinical randomized studies in IE to out rule the use of anticoagulant therapy in native endocarditis.

In addition, in this location, other important factors to be considered for EE or death risk were haemorrhagic stroke (that precludes surgical intervention at least for a time, favouring new EE in the case of persistent vegetation) and EE on admission. Some previous conditions such as previous heart failure or alcohol abuse and systemic complications (creatinine > 2 mg/dL, congestive heart failure, or cardiogenic shock) also were factors carrying the worst prognosis. In accordance with other authors, *S. aureus* was the microorganism associated with a poor prognosis.[1,2,9] Remarkably, not performing left valve surgery was another factor that suggests the importance of indicating surgery in complicated LSIE.

Previously, we reported a higher risk of death in women with IE on the left side, but we did not find differences in the EE risk in both sexes according to the current series.[24]

Table 3 Multivariable Cox regression for embolic event or death

Variable	HR	95% CI	*P*-value
Vegetation size >10mm	1.38	1.13–1.69	.0015
Previous history heart failure	1.53	1.21–1.93	.0004
Alcohol abuse	1.45	1.04–2.03	.0300
Creatinine > 2 mg/dL	1.59	1.25–2.03	.0002
Staphylococcus aureus	1.36	1.08–1.70	.0080
Embolic event on admission	1.89	1.54–2.33	<.0001
Congestive heart failure	1.40	1.12–1.75	.0026
Cardiogenic shock on admission	2.07	1.29–3.34	.0026
Haemorrhagic stroke	4.57	3.08–6.79	<.0001
No left valve surgery	1.30	1.05–1.61	.0156

CI, confidence interval; HR, hazard ratio.

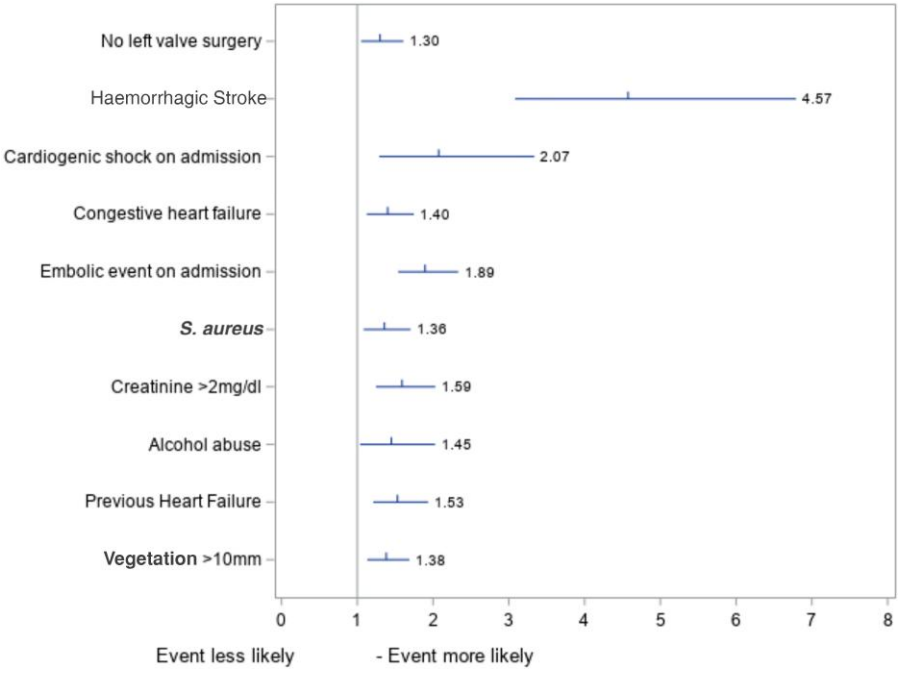


Figure 1 Forest plot: multivariable model for embolic event or 30-day mortality. *S. aureus*, *Staphylococcus aureus*.

Limitations

The EURO-ENDO registry has inherent limitations regarding the inclusion of all consecutive patients since the study was based on the volunteer participation of each centre. Another limitation of the EURO-ENDO registry is that information on the number of patients transferred from centres without cardiac surgery to centres with cardiac surgery was missing. Finally, there were some patients who did not undergo surgery and had a critical situation (such as cardiogenic shock or refractory heart failure) due to their pre-mortem situation. All of this might have influenced the outcome of the patients but could not be included in the multivariate analysis of predictors of death, since they were not collected in the case report form. PET/CT was performed in half of the patients, and therefore, it is not possible to rule out patients with silent embolism. Nonetheless, the limitations of the current registry were counterbalanced by important strengths. It is an observational study of patients that saw active participation in different centres that are tertiary referrals with the cardiac surgical programme. Furthermore, a high number of patients were enrolled, the quality of case report form completion was very high, and the research included a wide range of both university and non-academic hospitals in different countries around the world.

The *C*-statistic when only size of vegetation is in the model is poor (= 0.54) and leaves room for improvement. Nonetheless, the dichotomized size of vegetation stays significant in the model and the concordance of the final model is 0.68.

Conclusions

In summary, our results show that prognosis in LSIE is determined by multiple factors, including vegetation size. We believe that it should be established surgery treatment when the EE risk is high, before considering that the risk of death is unaffordable, and the patients are at high risk of severe complications during the post-operative period. Interestingly, we found independent predictors of mortality that are considered indicators for surgical intervention in ESC guidelines.[14] Likewise, since EE was related to mortality in IE, the presence of a large vegetation size was also a predictor of death, which, in turn, helps detect which factors allow identifying patients at high risk for EE or death.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

European Infective Endocarditis registry (EURO-ENDO) — Appendix

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Declarations

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None potential conflict of interest were reported by the authors.

Data Availability

All data are incorporated into the article and its online supplementary material.

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Ethical Approval

The study complies with the Declaration of Helsinki, locally appointed ethics committee has approved the research protocol and informed consent has been obtained from all subjects (or their legally authorized representative).

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