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ORIGINAL RESEARCH

# Comprehensive Assessment of the Risk of Symptomatic Embolism in Patients With Infective Endocarditis

Sebastian D. Santos-Patarroyo, MD; Juan A. Quintero-Martinez, MD; Brian D. Lahr, MS; Supavit Chesdachai, MD; Daniel C. DeSimone, MD; Hector R. Villarraga, MD; Hector I. Michelena, MD; Larry M. Baddour, MD

**BACKGROUND:** Echocardiographic evaluation of vegetations is crucial in infective endocarditis (IE). Although several studies have noted a link between larger vegetations and an increased risk of embolization, a more comprehensive evaluation of vegetation characteristics in a contemporary cohort has not been conducted. Our study aimed to define the short-term risk of symptomatic embolization in patients with IE.

**METHODS AND RESULTS:** The Mayo Clinic IE registry was screened to identify patients from 2015 to 2021 who had undergone transesophageal echocardiography. Multivariable subdistribution hazards regression analysis was used to identify factors associated with the cumulative incidence of symptomatic embolism over 30 days accounting for the competing risk of death. Overall, 779 patients with IE were included, of whom 517 (66.4%) were men, median age was 65.0 (interquartile range, 52.9–74.8) years, and 89.3% were White. In total, 234 patients had a symptomatic embolic event, a 30-day cumulative incidence of 30.2%. In multivariable analysis, a highly mobile vegetation was the strongest predictor of embolism ($P$<0.001). Vegetation length with interaction of IE type was also associated with embolic risk ($P$<0.001), with a stronger effect in native valve IE ($P$ interaction=0.001). Other associated factors included multiple vegetations, younger age, and *Staphylococcus aureus*. A nomogram that incorporated these factors was constructed to facilitate the prediction of embolic risk.

**CONCLUSIONS:** Highly mobile, larger vegetations are associated with embolic events. Embolic risk could be assessed by evaluating length as a continuous variable, alongside other echocardiographic findings, using a newly developed scoring tool; external validation is warranted.

**Key Words:** echocardiogram ■ embolism ■ infective endocarditis ■ risk ■ vegetation

Embolism presents a significant and potentially life-threatening complication of infective endocarditis (IE), with occurrence rates ranging from 20% to 50% across diverse populations.[1–3] It encompasses a spectrum of clinical manifestations, such as stroke, peripheral embolization, pulmonary embolism, and visceral infarctions associated with high rates of complications. Despite advances in diagnostic and therapeutic approaches, right- and left-sided embolic events remain a significant cause of morbidity and mortality in patients with IE. Prompt evaluation of embolic risk is essential, as preventive strategies have affected mortality rates.[4]

Echocardiography has been crucial in defining cases of IE since it was initially showcased in the 1994 iteration of the Duke criteria.[5] This included detection of

Correspondence to: Sebastian D. Santos-Patarroyo, MD and Larry M. Baddour, MD, Division of Public Health, Infectious Diseases and Occupational Medicine, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905. Email: santospatarroyo.sebastian@mayo.edu and baddour.larry@mayo.edu

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## CLINICAL PERSPECTIVE

### What Is New?

- Our investigation assessed vegetation-related parameters, patient clinical features, and microbiologic results as predictors of early symptomatic embolic events in patients with infective endocarditis.
- Our work is novel as we sought to include multiple transesophageal echocardiographic variables in determining risk of symptomatic embolic events, rather than being limited to only vegetation length; moreover, a scoring tool was developed based on our findings that may be helpful in individual patient care by assisting in defining embolic risk; validation studies of the nomogram as a scoring tool, however, are needed before advocating its use.

### What Are the Clinical Implications?

- Advances in transesophageal echocardiography allow us to better define patients with infective endocarditis who are at increased risk of symptomatic embolic events.
- Based on the findings of our investigation, a nomogram was drafted as a scoring tool that may be useful in embolic risk prediction; validation of the current work, however, is needed to confirm these findings.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **IE** | infective endocarditis |
| **TEE** | transesophageal echocardiogram |

valvular vegetations as well as other cardiac structural complications. Valvular vegetations, the hallmark of IE, and their size have been linked to risk of embolic events. Of note, the presence of a vegetation size >10 mm or ≥10 mm has been designated as an indication for valve surgery by both the American Heart Association and the European Society of Cardiology, respectively.[6,7]

Indeed, a sentinel investigation published in 2012 used vegetation size coupled with severe valvular insufficiency to perform "early" surgery within 48 hours of randomization and compared outcomes to that of a "standard of care" cohort. Although mortality did not differ for the 2 groups, the subset of patients who underwent early surgery had a significantly reduced risk of emboli over 6 months of follow-up.[8]

The association between the echocardiographic vegetation profile and symptomatic embolic risk has emerged as a focal point in IE research, reflecting the clinical imperative to identify high-risk patients who may benefit from aggressive management strategies aimed at reducing embolic complications. Previous studies have yielded conflicting results regarding the association between vegetation characteristics and symptomatic embolic risk. Although some investigations have identified large, mobile vegetations as independent predictors of embolic events,[9,10] others have failed to establish a definitive correlation.[11]

Assessing the risk of embolism in IE as per today's guidelines has been based on predetermined cutoffs for vegetation length. However, recent reports have indicated that using length alone to answer whether surgery is needed to prevent embolic events may be insufficient.[12] Moreover, the landscape has changed as there have been advances in transesophageal echocardiography (TEE) that enable us to provide a more extensive evaluation of vegetations. Consequently, we sought to determine if multiple TEE features of IE and patient variables with microbiologic results could predict risk of symptomatic embolic events.

## METHODS

The data used in this study are not publicly available due to ethical restrictions and patient confidentiality requirements outlined by the institutional review board. Consequently, the data cannot be shared.

### Study Population

In this retrospective study, the Mayo Clinic IE case registry was screened to identify patients with an IE diagnosis assessed by the modified Duke criteria[13] admitted to a facility within the Mayo Clinic Enterprise (Minnesota, Florida, Arizona, Mayo Clinic Health System), between January 2015 and October 2021. Overall, 1229 patients with IE were initially identified. Only patients with at least 1 TEE and a detailed description of vegetation features on the report were included in the analysis. In patients with recurrent episodes of IE, only the first episode was included. Those who did not have research authorization or were <18 years old were excluded. Ultimately, 779 patients were included in our investigation (Figure S1). The study protocol was approved by the institutional review boards of Mayo Clinic and was deemed exempt from the requirement to obtain informed consent in accordance with 45 CFR 46.116 and Health Insurance Portability and Accountability Act authorization.

### Clinical Data

Clinical patient characteristics were abstracted from electronic medical records. Demographic information,

comorbidities, risk factors, Charlson Comorbidity Index,[14] microbiological findings, echocardiographic findings, and embolic events were collected. Additionally, specific data on the characterization of vegetations were abstracted from the TEE report during the IE episode of hospitalization. If multiple TEEs were performed, only the one where a vegetation was detected was considered. For patients who underwent valve surgery, the last TEE before surgery was evaluated. Additionally, length of hospitalization was calculated from the date of admission to the date of discharge for each patient.

## Microbiologic Findings

Results of blood cultures obtained from at least 2 separate sites were used to define an IE pathogen. Microorganisms were divided into 2 major categories: (1) *Staphylococcus aureus* that has been previously associated with a high risk of embolism; and (2) other than *S. aureus* to evaluate risk of symptomatic embolic event.

## Reported Echocardiographic Findings

As part of the study of suspected cases of IE, TEE was conducted during hospitalization and data were collected based on echocardiographic description of findings by expert cardiologists in echocardiography. Level III board-certified echocardiologists performed a comprehensive and extensive description of the images following current institutional protocols during hospitalization and guidelines for the use of echocardiography in the evaluation of cardiac source of embolism.[15] Extracted data included vegetation characteristics: maximal length and width (cm) measured from 2-dimensional TEE, location, high mobility, and multiplicity. Highly mobile vegetation was defined as vegetations described as echogenic masses that extend beyond the valve coaptation plane, moving with the cardiac cycle. For cases with multiple vegetations, the largest vegetation was used to capture these characteristics for these analyses. If vegetations were in 2 or more different valves, both measurements were collected, but only data from the largest one were included in the analysis. Two additional variables derived from these data were approximated maximal area ($cm^2$) (maximal length multiplied by maximal width) and vegetation shape, which was categorized as "globular" or "elongated" according to a <30% or ≥30% difference in the length and width of the vegetation based on prior study.[16] Additionally, valve dysfunction and its severity were graded based on echocardiographic findings and quantified on a 0 to 4 scale (none, mild, moderate, moderate to severe, and severe). For analysis of risk factors, only the presence of severe regurgitation or stenosis of the infected valve was used to evaluate its relationship with embolism. The detailed definitions of echocardiographic variables included in the study are presented in Table 1.

**Table 1. Definitions of Echocardiographic Characteristics Evaluated by TEE**

| Measure | Definition |
|---|---|
| Length of vegetation | Maximal length measured in multiple planes |
| Area of vegetation | Maximal length multiplied by the maximal width |
| Mobility | "Highly mobile" vegetations described as echogenic masses that extend beyond the valve coaptation plane, moving with the cardiac cycle |
| Location | Left-sided vegetations encompassing the mitral valve, aortic valve, left atrium or left ventricle, or within the aorta<br>Right-sided vegetations that involve the tricuspid valve, pulmonary valve, right atrium or right ventricle, or within the pulmonary artery<br>Device-related vegetation refers to microbial growths that can form on devices like pacemakers, defibrillators, and intravascular catheters and valve vegetations in patients with devices implanted |
| Multiple | Defined as presence of 2 or more vegetations |
| Globular vegetation | "Globular" is indicated by a minimal difference (<30%) between the length and width of the vegetation; otherwise, the shape is considered "elongated" |
| Significant valvular regurgitation/ stenosis of infected valve | Severe valve regurgitation or stenosis occurring in the valve impacted by infective endocarditis |

## Symptomatic Embolic Events

The primary outcome measure was the occurrence of a symptomatic embolism within a 30-day observation period, which is described later. Symptomatic emboli included events with symptoms suggestive of embolism (subsequently proven to be embolic events by imaging): sudden neurologic or visual dysfunction, chest discomfort, dyspnea, abdominal pain that were evaluated by imaging studies (computed tomography, magnetic resonance imaging, lung ventilation-perfusion scintigraphy or arteriography) confirmed by the multispecialty team caring for these patients. Importantly, cases of cutaneous manifestations or metastatic abscesses were not classified as embolic events.

For 638 patients (81.9%), the initial transthoracic echocardiogram/TEE was used to diagnose IE based on evidence of vegetation. Among those who underwent TEE as the initial imaging assessment, vegetation measurements were taken from that exam. The remaining 141 patients (18.1%) had an initial TEE if they had previously transthoracic echocardiogram only to adequately measure vegetation, with a median time of 1 day (interquartile range [IQR], 1–3) to obtain accurate vegetation measurements. Of these, only 18 required a second TEE due to high suspicion of IE when

vegetation was not found initially. We reviewed the patients' medical records to record the occurrence and timing of both competing outcomes—first symptomatic embolic event and death from any cause—within a 30-day follow-up period, with time of the echocardiographic assessment that defined vegetation designated as time zero. A total of 758 patients (97.3%) had at least 30 days of follow-up or suffered an embolic event or death before this time; the remaining 21 patients were lost to follow-up and were right-censored in the analysis. Follow-up is 97.0% complete based on the number of patient-days of observed 30-day follow-up divided by the number of patient-days of expected 30-day follow-up.

## Statistical Analysis

Patient and clinical characteristics were summarized using descriptive statistics, with median and IQR for continuous variables and percentage of patients for categorical variables. Study outcomes were assessed using time-to-event analyses to account for a small number of patients lost to follow-up over the 30-day period (by right-censoring such observations). Actuarial risk of 30-day all-cause mortality was calculated using the Kaplan–Meier estimator. For the primary outcome of interest, because of competing risks and potential masking of embolic events by earlier mortality from other causes, we assessed the "actual risk" of symptomatic embolism using competing risk analysis treating death as the competing event. In this analysis by use of the nonparametric cumulative incidence function estimator, patients who died during follow-up before the observation of a symptomatic embolic event are not censored but rather remain in the risk set to avoid overestimating the actual embolic risk. Both the competing end point (death within 30 days not preceded by embolism) and the secondary outcome for hospital length of stay (time until successful discharge, for which in-hospital death from any cause is a competing risk) were also described by cumulative incidence function incidence or quartile estimates.

For the primary analysis, Fine and Gray competing risk regression analyses based on the proportional subdistribution hazard approach were used to develop a model for predicting the cumulative incidence of symptomatic embolism over 30 days. Covariates were chosen a priori and included previously reported clinical risk factors as well as echocardiographic variables with emphasis on vegetation-related features. Each potential predictor was first checked graphically not only for its unadjusted relationship with the outcome but also for a proportional effect over time (ie, proportional subdistribution hazards assumption). Furthermore, because our cohort represents a mixture of native valve and nonnative valve (prosthetic valve, device-related with associated valve vegetation) IE cases, we considered the possibility that these subgroups may need separate study if they have different risk factors for embolism. To this end, we evaluated the evidence for differential associations by examining 2-way interactions between type of IE (native valve versus nonnative valve IE) and each variable in the model. Finally, we constructed our primary model using all 11 potential predictors, along with any significant interactions identified in the previous step ("full model").

For our second model, we attempted to construct a parsimonious model that could provide a simpler and more useful tool for estimating embolic risk in the clinical setting ("reduced model"). With this in mind, we used a backwards stepdown procedure to delete the least predictive variables from the full model 1 at a time with the condition that, for each deletion, the remaining subset of predictors yielded a model performance at least 95% of the likelihood ratio $\chi^2$ achieved for the full regression. The relative contribution of variables to the full or reduced model was quantified with adjusted $\chi^2$ statistics, whereby subtracting the degrees of freedom from the Wald partial $\chi^2$ values their relative importance could be compared on the same scale. Subdistribution hazard ratios (sHR) and associated 95% CIs were used to estimate the relative effects of the model input variables on the subdistribution hazard of symptomatic embolism. We compared the full and reduced models using measures of prognostic information (global likelihood ratio $\chi^2$ statistic and Akaike information criterion) and predictive accuracy (discrimination and calibration). Predictive discrimination was quantified by the concordance index (C-index) and Somers' $D_{xy}$ statistics, and the overall accuracy of a model was demonstrated with a smooth nonparametric calibration curve comparing predicted and observed event-free rates. To estimate the likely predictive accuracy in a new sample, we used internal bootstrap validation with 500 resamples. By resampling (with replacement) the original data, the bootstrap can estimate the amount of overoptimism in any measure of predictive accuracy, which is then subtracted from the initial apparent measure to obtain a bias-corrected estimate. However, all prognostic models, including the presented ones to follow, should be externally validated in an independent prospective patient population before widespread use. Nevertheless, we present a nomogram based on the final reduced model to illustrate its ease of use for predicting embolic risk in individual patients.

For all models, continuous covariates were modeled with 3-knot restricted cubic splines to relax linearity assumptions. We performed secondary analyses to compare the prognostic value of alternative measures of vegetation size by replacing the continuous predictor

variable for vegetation length (both its main effect and interaction terms) in the full model by a dichotomous variable for length (≥10 mm versus <10 mm) and, separately, a continuous variable for vegetation area. We also explored potential predictors for the competing outcome of death but limited the risk modeling to univariable analyses given the constraints imposed by the lower number of events. Analyses were performed using the statistical programming language R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

# RESULTS

## Clinical Features

Overall, 779 patients diagnosed with definite or possible IE and confirmed vegetation were included in the analysis. Of these patients, 66.4% were men, median age was 65.0 (IQR, 52.9–74.8) years, and 89.3% were White. Left-sided IE accounted for 76.8% of cases, and 20.9% were diagnosed with right-sided IE; 2.3% of patients had bilateral IE. Native valve IE was the most common type, occurring in 66.4% of cases, followed by prosthetic valve IE (29.0%) and 4.6% device-related IE with lead vegetations but no associated valve vegetation. There were no instances of combined native and prosthetic valve IE. Among patients with positive blood cultures, *S. aureus* was the most prevalent pathogen identified, accounting for 38.2% of cases, followed by streptococcal species (28.2%) and enterococcal species (12.4%). Negative blood culture was found in (10.5%) of IE cases. Patient demographics, clinical characteristics, and microbiologic results are summarized in Table 2.

## Valvular Function

When evaluating valve function, approximately one-third (34.9%) of patients had severe regurgitation of any valve. Valvular disease of at least moderate severity included mitral regurgitation in 34.1% of patients and aortic regurgitation in 24.5% of patients. Additionally, in 26.7% of these IE cases, the infected valve exhibited severe regurgitation or stenosis (Table 3).

## Vegetation Features

The median (IQR) reported maximal vegetation length and width were 10 (8–16) mm and 6 (4–10) mm, respectively, corresponding to a median maximal approximated area of 64 (29–140) $mm^2$. Overall, the aortic valve was the most frequently affected, representing 41.3% of cases of IE, with the mitral valve following at 36.7%. However, among patients with native valve IE, the mitral valve was the most affected, comprising 43.7% (187/517) of cases. In patients with prosthetic

**Table 2. Baseline Demographic and Clinical Characteristics**

| Characteristic | Overall (N=779) |
|---|---|
| Age, y | 65.0 (52.9–74.8) |
| Male sex | 66.4% (517) |
| Race or ethnicity | |
| White | 89.3% (696) |
| Black | 3.3% (26) |
| American Indian/Alaska Native | 1.0% (8) |
| Other* | 6.3% (49) |
| Injection drug use | 5.9% (46) |
| Mitral valve prolapse | 6.7% (52) |
| Bicuspid aortic valve | 11.3% (88) |
| Hypertrophic cardiomyopathy | 1.8% (14) |
| Prosthetic valve | 31.2% (243) |
| Cardiac implantable electronic device | 24.0% (187) |
| Heart failure | 41.8% (326) |
| Chronic kidney disease | 34.9% (272) |
| Myocardial infarction | 24.3% (189) |
| Hypertension | 44.9% (350) |
| Chronic obstructive pulmonary disease | 15.7% (122) |
| HIV | 2.6% (20) |
| Diabetes | 42.9% (334) |
| Atrial fibrillation | 28.6% (223) |
| Moderate/severe liver disease | 5.3% (41) |
| Metastatic solid tumor | 0.8% (6) |
| Other tumors | 17.1% (133) |
| Charlson Comorbidity Index | 2 (0–5) |
| Definite IE | 91.3% (711) |
| Native valve IE | 66.4% (517) |
| Prosthetic valve IE | 29.0% (226) |
| Device-related IE | 14.6% (114) |
| Surgery for IE | 37.2% (290) |
| Microbiology of IE (N=697) | |
| Streptococci | 28.4% (198) |
| *Staphylococcus aureus* | 37.9% (264) |
| Enterococci | 12.5% (87) |
| Other staphylococci | 9.5% (66) |
| Other† | 11.8% (82) |
| Side of IE | |
| Left | 76.8% (598) |
| Right | 20.9% (163) |
| Bilateral | 2.3% (18) |

Values represent the median (lower to upper quartile) for continuous variables and percentages (frequencies) for discrete variables. Except where indicated otherwise, these data reflect a denominator of 779 patients with available information. IE indicates infective endocarditis.

*Other includes N = 12 ("Other", not Hispanic or Latino); N = 8 (Unknown); N = 7 (Hispanic or Latino); N = 6 (Choose not to disclose); N = 2 (No information).

†*Cardiobacterium hominis* (n=6), *Granulicatella adiacens* (n=6), *Mycobacterium chimaera* (n=5), *Pseudomonas aeruginosa* (n=4), *Klebsiella pneumoniae* (n=4), *Aerococcus urinae* (n=4), and others identified in <4 patients.

**Table 3. Echocardiographic Data on Vegetation Measures and Valve Disease**

| Characteristic | Overall (N=779) |
|---|---|
| Moderate/severe aortic stenosis (N=775) | 4.1% (32) |
| Moderate/severe aortic regurgitation (N=775) | 24.5% (190) |
| Moderate/severe mitral stenosis (N=774) | 1.8% (14) |
| Moderate/severe mitral regurgitation (N=773) | 34.0% (263) |
| Moderate/severe pulmonary regurgitation (N=738) | 3.4% (25) |
| Moderate/severe tricuspid regurgitation (N=767) | 30.0% (230) |
| Severe regurgitation/stenosis of the infected valve | 26.7% (208) |
| Highly mobile vegetation | 18.6% (145) |
| Maximum length of vegetation, mm | 10 (8–16) |
| Maximum width of vegetation, mm | 6 (4–10) |
| Maximum approximated area of vegetation, $mm^2$ | 64 (29–140) |
| Globular vegetation | 33.1% (258) |
| Location of vegetation | |
| Aortic | 41.3% (322) |
| Mitral | 36.7% (286) |
| Tricuspid | 13.2% (103) |
| Pulmonary | 1.5% (12) |
| Right atrium/right ventricle | 7.1% (55) |
| Other | 0.1% (1) |
| Multiple vegetations | 22.5% (175) |
| Number of vegetations | |
| 1 | 77.7% (605) |
| 2 | 15.8% (123) |
| 3 | 6.3% (49) |
| 4 or more | 0.3% (2) |

Values represent the median (lower to upper quartile) for continuous variables and percentages (frequencies) for discrete variables. Except where indicated otherwise, these data reflect a denominator of 779 patients with available information.

valve IE, vegetation of the aortic valve was most prevalent, accounting for 59.7% (135/226) of cases within this subgroup. Approximately one-third (33.1%) of vegetations were classified as globular, indicating a minimal difference (<30%) between their length and width. Based on TEE findings, 18.6% of the assessed patients had highly mobile vegetations, and 22.5% of patients had multiple vegetations (Table 3). When vegetation characteristics were analyzed by the sidedness of IE, the maximal vegetation length in patients with right-sided or bilateral IE was greater than that in left-sided patients with IE (median [IQR], 14 (9–18) mm versus 10 (7–15) mm, respectively; $P<0.001$) (Table S1).

## Embolic Risk and Associated Predictors

The primary outcome was a symptomatic embolic event, which occurred in 234 patients during short-term follow-up, for a 30-day cumulative incidence of 30.2% (95% CI, 26.9–33.4). The most frequently affected organs with emboli were the brain (56.8%) and the lungs (20.1%). The overall 30-day mortality rate was 13.5% (103 deaths), with the majority of these deaths (64.1%, 66/103) not preceded by embolism. Judging by the steepness of cumulative incidence curves in Figure 1, endocarditis entails a short early period of very high embolic risk (first 10–14 days) with relatively low risk thereafter, whereas the curve for death indicated a competing risk lower in magnitude but more sustained over 30-day follow-up. The median length of total hospital stay was 14 (IQR, 9–21) days (Table 4).

The impact of 11 prespecified variables (6 echocardiographic variables [including 5 vegetation measures], 4 clinical factors, and 1 pathogen variable) on the cumulative incidence of symptomatic embolism was examined with both univariable and multivariable analyses that accounted for the competing risk of death (Table 5). All variables except atrial fibrillation and location of vegetation were at least marginally univariately associated with embolic risk ($P<0.10$). The unadjusted relationship between each factor and cumulative risk over 30 days is further depicted by cumulative incidence plots in Figure S2. For multivariable analysis, we considered the possibility that risk factors may differ according to type of IE (native valve versus nonnative valve) and initially fitted a model including all 2-way interactions with IE type. Although the global

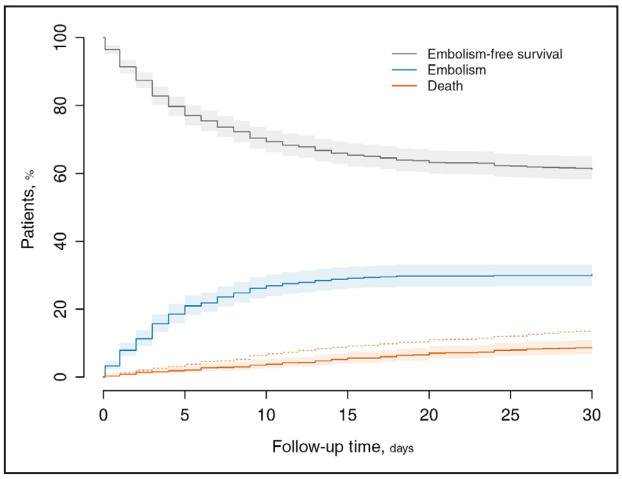


**Figure 1. Cumulative incidence plot for symptomatic embolism and death.**
The embolism curve (blue) is a cumulative incidence curve of symptomatic embolism accounting for the competing risk of death. The death curve (red) is a cumulative incidence curve of mortality in which death was not preceded by symptomatic embolism. For reference, the dotted line immediately above this curve represents the rate of all-cause mortality (irrespective of embolic events). At any given time during follow-up, the sum of the cumulative incidence function estimates for these 2 competing outcomes is the inverse of the Kaplan–Meier embolism-free survival estimate (gray).

**Table 4. Cumulative Incidence of Symptomatic Embolism and Other Outcomes**

| Primary outcome | Number of events | Cumulative event rate (95% CI)* |
|---|---|---|
| Primary event | | |
| Symptomatic embolism | | |
| In-hospital† | 220 | 28.2% (25.2–31.5) |
| 30-day‡ | 234 | 30.2% (26.9–33.4) |
| Location of embolism, % (n) | 234 | |
| Brain | | 56.8% (133) |
| Lung | | 20.1% (47) |
| Other | | 23.1% (54) |
| Competing event | | |
| Death not preceded by embolism | | |
| In-hospital† | 42 | 5.4% (4.0–7.2) |
| 30-day‡ | 66 | 8.6% (6.6–10.6) |
| Secondary outcomes | | |
| Overall all-cause mortality | | |
| In-hospital† | 70 | 9.0% (7.2–11.2) |
| 30-day§ | 103 | 13.5% (11.1–15.9) |
| Hospital LOS (days)‡, median (interquartile range) | | |
| LOS from admission | … | 14 (9–21) |
| LOS from diagnosis | … | 11 (6–19) |

LOS indicates length of stay.
*Except where noted otherwise.
†Crude (ie, simple percentage) event rate (95% Wilson score test-based CI).
‡Cumulative incidence function event rate (95% CI based on Aelen asymptotic variance estimates) or quartile estimates accounting for competing risk of death.
§Inversed Kaplan–Meier 30-day survival estimate (95% CI based on Greenwood's formula for variance).

test of interaction showed mild evidence of differential risk factors (likelihood ratio $\chi^2$=22.2, 14 degrees of freedom, $P$=0.074), only the individual interaction between type of IE and vegetation length (likelihood ratio $\chi^2$=12.1, 2 degrees of freedom, $P$=0.002) was significant. Therefore, we refitted the final model (termed "full model") with all 11 predictor variables and the 1 significant 2-way interaction.

In this full model, mobility of the vegetation was the strongest predictor of developing a symptomatic embolism (Wald $\chi^2$=83.5; $P$<0.001), corresponding to a subdistribution hazard that was 3.7-fold higher for those with highly mobile vegetation than those without (sHR high versus <high, 3.7 [95% CI, 2.8–4.9]) (Figure 2). Vegetation length with interaction for type of IE was the next strongest predictor (combined effect: $\chi^2$=27.4, $P$<0.001; interaction effect: $\chi^2$=13.2, $P$=0.001), demonstrating that greater length was associated with an elevated subdistribution hazard of embolism in both IE subgroups but with different magnitudes (sHR, 75th versus 25th centile: 2.1 [95% CI, 1.5–2.8] for native valve IE; sHR, 75th versus 25th centile, 1.3 [95% CI, 1.0 versus 1.8] for nonnative valve IE). Figure 3 depicts the estimated relationship between length and cumulative incidence of embolism over 30 days according to the type of IE, showing a sharp rise in cumulative risk within the range from length 3 mm to ~15 mm (and no incremental risk >15 mm) for patients with native valve IE and a more gently rising hazard over the entire range of lengths in patients with nonnative valve IE. Other vegetation factors significantly associated with an elevated subdistribution hazard of embolism included having multiple vegetations (sHR, 1.8 [95% CI, 1.4–2.4]) and location, specifically, having a vegetation on the aortic valve (sHR, 2.0 [95% CI, 1.3–2.9]) or the mitral valve (sHR, 1.9 [95% CI, 1.3–2.8]) as compared with the right side of the heart. Other significant but less important factors identified from the model were younger age and *S. aureus* IE (Table 5).

Because a parsimonious model would be more practical for clinical application, we aimed to simplify the full model while preserving overall prognostic information. Using backwards stepdown procedure to delete the least predictive variables from the full model until the prespecified model performance was reached, the final simplified model (termed "reduced model") retained the following predictors: IE type, organism, vegetation number, mobility, location, and length (with length×type interaction). Combined, these 6 characteristics provide approximately 95% of the total prognostic information contained in the original 11 variables. A nomogram based on the final reduced model is presented in Figure 4 to assist the clinician in estimating the risk of symptomatic embolism for an individual patient. To use the nomogram, the number of points associated with each listed measure are summed and the resulting "Total Points" are then translated to "30d Cumulative Risk" scale to derive the patient's estimated risk of embolism.

Both the full and reduced models demonstrated good predictive accuracy (eg, C-index=0.754 and 0.744, respectively), with comparable internal bootstrap validation results (bootstrap C-index=0.736 and 0.731, respectively) (Table S2). The bias-corrected curves in Figure S3 depict the optimism-adjusted calibration of the full and reduced models over the entire range of predictions, both showing overall accuracy that approaches the ideal situation (diagonal line) where each predicted probability is equal to the actual observed fraction free from embolic events. In secondary analysis where the measure for vegetation length was replaced in the full model by dichotomized length (≥10 mm versus <10 mm) or vegetation area (as a continuous variable), these alternative size variables showed similarly strong overall effects on embolic risk, although their differential effects by type of IE were only marginally significant (Table S3). Finally, although the number of competing death events was insufficient to permit a detailed

**Table 5. Competing Risk Models for the Subdistribution Hazard of Symptomatic Embolism**

| Predictor | Predictor level | Univariable | | Multivariable | | | |
|---|---|---|---|---|---|---|---|
| | | | | Full model | | Reduced model | |
| | | sHR (95% CI) | *P* value | sHR (95% CI) | *P* value | sHR (95% CI) | *P* value |
| Age, y | | | <0.001 | | 0.020 | | |
| | 35 | 1.8 (1.4–2.5) | | 1.6 (1.2–2.3) | | — | |
| | 65 | 1.0 (reference) | | 1.0 (reference) | | — | |
| | 80 | 0.9 (0.7–1.1) | | 1.0 (0.8–1.3) | | — | |
| Diabetes | | 0.7 (0.5–0.9) | 0.003 | 0.9 (0.7–1.2) | 0.433 | — | |
| Atrial fibrillation | | 0.9 (0.6–1.2) | 0.325 | 1.0 (0.7–1.3) | 0.770 | — | |
| IE organism | | | 0.060 | | 0.005 | | <0.001 |
| | Non-*Staphylococcus aureus* | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | |
| | *Staphylococcus aureus* | 1.3 (1.0–1.8) | | 1.5 (1.1–2.0) | | 1.6 (1.2–2.1) | |
| | Culture negative | 0.9 (0.6–1.4) | | 0.8 (0.5–1.2) | | 0.8 (0.5–1.3) | |
| Regurgitation/ stenosis | Severe vs nonsevere | 1.4 (1.0–1.8) | 0.024 | 1.0 (0.7–1.3) | 0.856 | — | |
| Vegetation shape | Globular vs elongated | 0.8 (0.6–1.0) | 0.084 | 1.1 (0.8–1.5) | 0.631 | — | |
| Vegetation mobility | High vs nonhigh | 4.5 (3.5–5.8) | <0.001 | 3.7 (2.8–4.9) | <0.001 | 3.7 (2.8–4.9) | <0.001 |
| Vegetation location | | | 0.393 | | 0.002 | | 0.021 |
| | Aortic valve | 1.2 (0.8–1.7) | | 2.0 (1.3–2.9) | | 1.6 (1.1–2.4) | |
| | Mitral valve | 1.3 (0.9–1.8) | | 1.9 (1.3–2.8) | | 1.6 (1.1–2.3) | |
| | Right sided | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | |
| Vegetation number | Multiple vs single | 2.3 (1.8–3.0) | <0.001 | 1.8 (1.4–2.4) | <0.001 | 1.9 (1.4–2.5) | <0.001 |
| Vegetation length (mm) | 16 vs 8 | | <0.001[a] | | <0.001[b] | | <0.001[c] |
| | Nonnative valve | 1.3 (1.0–1.7) | | 1.3 (1.0–1.8) | | 1.3 (1.0–1.7) | |
| | Native valve | 2.5 (1.9–3.3) | | 2.1 (1.5–2.8) | | 2.1 (1.6–2.9) | |

Results obtained from univariable and multivariable proportional subdistribution hazard (Fine and Gray) regression models for time until symptomatic embolism, accounting for the competing risk of death. Point and interval estimates of predictor effects are presented as subdistribution hazard ratios with 95% CI. To calculate sHRs for age, we selected 35 and 80 years (corresponding to approximately 10th and 90th percentile values in our sample) for comparison against a reference value of 65 years (the 50th percentile value). Note that all models with vegetation length included a statistical interaction term for length×IE type, which is represented as separate length effects (sHR per interquartile range increase in length, from 8 mm to 16 mm) for nonnative valve IE and native valve IE subgroups. The statistical test for vegetation length reported here is based on its combined main effect and interaction effect, which tests for a significant effect of length in either IE subgroup. Corresponding tests for the length×IE type interaction effects are [a]*P*<0.001; [b]*P*=0.001; [c]*P*=0.001. IE indicates infective endocarditis; and sHR, subdistribution hazard ratio.

multivariable examination of risk factors of its own, univariable (unadjusted) competing risk analysis suggested that none of the top 6 risk factors of symptomatic embolism in our reduced model were predictive of death (all *P*>0.20). However, among the other 5 factors screened, 3 were univariately associated with increased 30-day mortality, including older age (*P*=0.022), severe valve regurgitation or stenosis of the infected valve (*P*=0.022), and history of atrial fibrillation (*P*=0.074).

## DISCUSSION

The endocarditis team managing the complexities of IE is initially faced with input from 3 major types: clinical input (demographics, symptoms, comorbidities, etc), microbiologic input (the pathogen itself), and echocardiographic report input. We aimed to identify the specific weight difference of each of these inputs as they pertain to their association with a major patient-important outcome: symptomatic embolism. Therefore, we wish to reconcile this real-world scenario in a contemporary cohort of patients with IE.

The current investigation provides an assessment of symptomatic embolic risk in patients with IE based on vegetation characteristics detected by TEE, and patient features and pathogen identification were also examined. The major findings include (1) reported echocardiographic vegetation features were robust predictors of symptomatic embolism, with mobility of vegetation the strongest overall determinant; (2) vegetation length also contributed significantly to the prediction of symptomatic embolic risk, particularly for IE with native valve involvement; (3) presence of multiple vegetations and vegetation location, specifically those on the aortic or mitral valves, were associated with increased symptomatic embolic risk; and (4) younger age and IE due

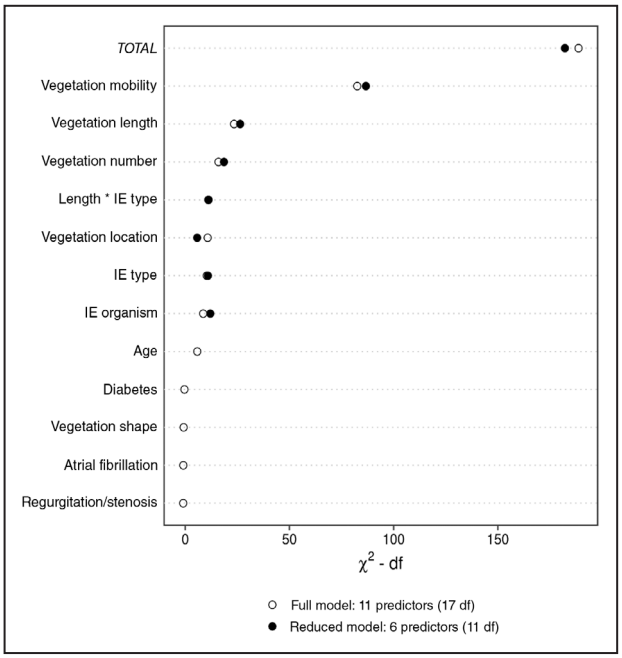


**Figure 2. Relative importance of predictor variables.**
The relative contribution of each predictor to the full and reduced models, as judged by the partial Wald $\chi^2$ statistic minus df, is displayed in descending order of importance. The higher the $\chi^2$ – df value, the more the predictor contributed to the prediction of time to symptomatic embolism. As *TOTAL* represents the joint contribution of all predictors from the multivariable regression, the reduced model appears to be competitive with the full model in overall prognostic information. Among the individual factors, vegetation mobility stands out as the dominant predictor in both models. df indicates degrees of freedom; and IE, infective endocarditis.

to *S. aureus* were important but less significant risk factors of increased symptomatic embolic risk.

When assessing the impact of type of IE (native valve versus prosthetic/device related) on the predictive value of vegetation length for symptomatic embolic risk, we observed a stronger effect of length in patients with native valve IE. Similar differential trends were observed when length measurement was replaced in the modeling by dichotomized length (at the commonly used cutoff of 10 mm) and approximate vegetation area. Our findings contradict the results described in Thuny et al's study, where they reported that neither length nor mobility were predictive factors for embolism in patients with IE not associated with native valve involvement,[9] a factor that could affect the results of this investigation was that in that study only 91 patients had prosthetic IE.

Assessment of risk of embolism in patients with IE is crucial due to the high rate of complications as a consequence of it.[17] Although high rates of embolic events have been reported in patients with IE, there are no consistent findings on clinical risk factors associated with high rates of embolism. Some studies have reported comorbidities such as diabetes and atrial fibrillation as factors associated with higher risk of embolism.[18] More recently, a study that evaluated factors associated specifically with higher risk of embolization in left-sided IE found that a history of alcohol abuse, previous heart failure, hemorrhagic stroke, and vegetation size >10 mm among others were predictors of embolization.[19]

Although standard clinical predictors of symptomatic embolism have not been described, one echocardiographic predictor—vegetation size >10 mm—has been widely accepted as a factor associated with a high risk of embolization.[21–23] However, the assessment often relied solely on this cutoff without providing a comprehensive evaluation of size as a continuous variable. Our work underscores the significance of including measurements such as length as well as key qualitative findings when characterizing vegetations and assessing their prognostic value. The partial effects plot presented previously shows how the estimated cumulative incidence of embolism changes continuously with vegetation length (and differentially by type of IE) across the range of data. The statistical model that gave rise to these estimates assumed a smooth graded relationship of length with risk, which is more plausible than assuming a step change in prognosis at a given threshold. Moreover, some studies

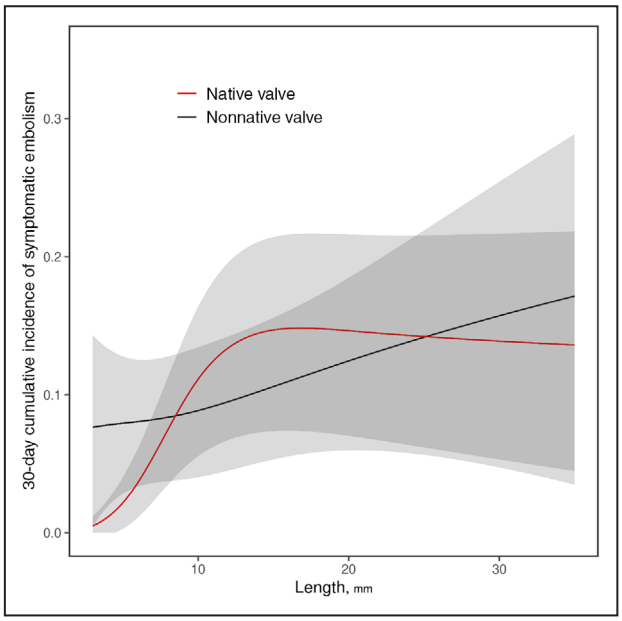


**Figure 3. Vegetation length and embolic risk for patients with native valve IE and nonnative valve IE.**
Visual representation illustrates the nonadditive impact of length on native valve IE (in red) and nonnative valve IE (in black). The likelihood of symptomatic embolism rises with increasing length for both groups, but the rise for patients with native valve IE is initially much steeper before leveling off after a length of ~15 mm, whereas for those with nonnative IE the embolic risk increases gradually with length over the entire range of data. IE indicates infective endocarditis.

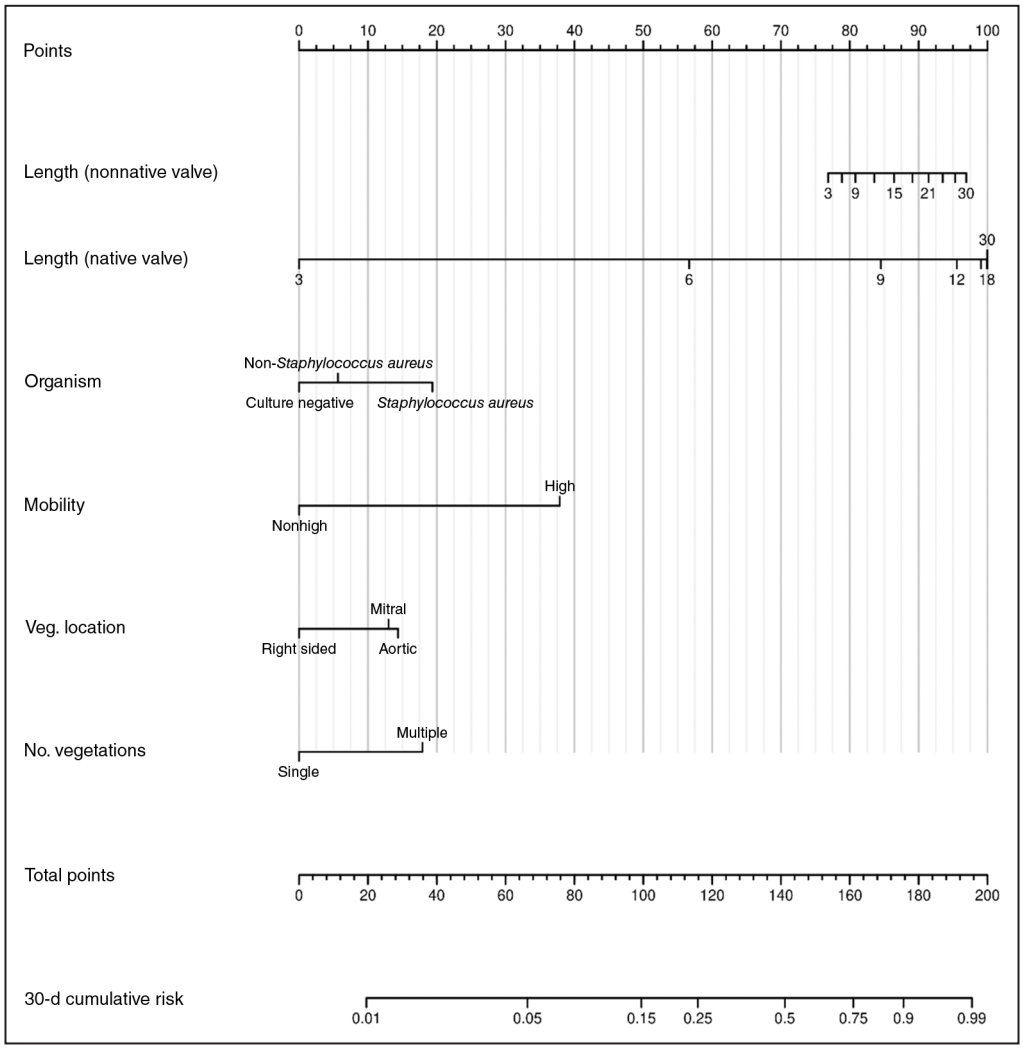


**Figure 4. Nomogram to predict 30-day cumulative risk of symptomatic embolic events.**
To use the nomogram on an individual patient, the number of points (0–100) for each variable is first assigned using the gridline on top. Next, sum these individual scores to calculate the total number of points. Lastly, draw a vertical line from this value on the Total Points gridline down to the 30-d Cumulative Risk gridline to obtain the model estimate of 30-day cumulative incidence of symptomatic embolism. For example, a patient with native valve IE due to *Staphylococcus aureus* who has a single vegetation that is highly mobile, 9 mm in length, and located on the aortic valve would receive 0+15+20+37.5+85 = 157.5 total points, corresponding to an estimated 30-day cumulative incidence of 0.70. IE indicates infective endocarditis.

have demonstrated that a 10-mm cutoff could be an indication for valve surgery[24,25] and is also associated with worse outcomes.[25] Nevertheless, the detailed characterization of vegetations presented in the study, based on TEE findings and implementation of the continuous measurement, rather than a cutoff, of vegetation length may provide a more accurate prediction of the risk of symptomatic embolism.

The 2015 American Heart Association Scientific statement that addressed the diagnosis and management of IE highlighted both vegetation size >10 mm and mobility as echocardiographic measurements associated with risk for embolic events and included recommendations for early valve surgery based on these features.[6] Most recently, the 2023 European Society of Cardiology guidelines for IE management reviewed multiple valvular and nonvalvular features that were associated with embolic risk, and they emphasized vegetation size ≥10 mm as the sole echocardiographic finding to consider surgery as a management strategy,[7] omitting other relevant echocardiographic findings that could be important in embolic risk assessment.

Although the current European Society of Cardiology guidelines include only vegetation length cutoff as a critical TEE finding in recommendations to evaluate the

risk of embolism, we found that the continuous value of length and the underlying type of IE (which modifies the effect of length), as well as the description of other vegetation characteristics, are essential to accurately assess the risk of symptomatic embolic events. Vegetation mobility particularly stood out as the dominant overall prognostic factor, whereas the number and location of vegetations also contribute additional independent prognostic information. Consideration of these multiple factors will yield a more accurate estimate of prognosis and help inform treatment decisions, such as surgical intervention to prevent embolism. To illustrate the use of our proposed nomogram for symptomatic embolic risk in Figure 4, we present a hypothetical case of IE where vegetation length was <10 mm but the risk of embolization remained high based on the presence of several other risk factors.

Although TEE is considered the premier imaging technique for assessing IE, the role of TEE in prediction of embolic events has been subject to conflicting findings.[26] Additionally, lack of standardization has impeded the proper assessment of embolic risk.[20,28,29] Although there have been advances in the quality of TEE images, lacking a specific uniformity in reporting characteristics of vegetations is a limitation.[29] Although guidelines for using echocardiography to evaluate cardiac sources of embolism have described how to correctly identify vegetations, there are still challenges in standardizing the description of their length and mobility. Notably, a classification for mobility was described in 1991.[21] However, its reproducibility has been limited due to a lack of consensus on how to report the movement of vegetations and the difficulty in describing it accurately. Of note, the implementation of harmonic imaging and 3-dimensional echocardiography has enhanced accuracy by reducing artifacts and improving both axial and lateral resolution. These advances have improved the description of vegetations. In our study, a highly mobile vegetation was more important than length when evaluating the risk of symptomatic embolism. This sets a precedent for establishing a consensus on how the mobility of a vegetation should be quantified. It also emphasizes that even smaller vegetations, less than 10 mm, which move beyond the valve coaptation plane during the cardiac cycle, have a high risk of embolization.

Moreover, contemporary investigations have highlighted significant variability among blinded echocardiographers in describing vegetation characteristics. A recent study assessing echocardiographic agreement of vegetation findings in diagnosis and management of IE demonstrated only moderate to low intraobserver agreement.[30] Similarly, a 2022 study revealed only moderate correlation in measurements among different observers.[31] Both studies involved level III faculty echocardiography readers. Considering these findings and recognizing that clinicians rely on descriptive echocardiographic reports to assess the risk of embolism in patient management, we collected TEE data from individual patient reports that represent the real-world experience using TEE for IE assessment.

Models aiming to predict the risk of embolism have been limited. Huber et al[18] introduced a scoring system in 2013 that relied on comorbidities, a vegetation length of 10 mm, and the presence or absence of *S. aureus* as a pathogen. However, their scoring system was primarily focused on an established cutoff for vegetation size and did not consider other important echocardiographic findings. In addition, no information was included regarding the type of echocardiography used in a cohort that extended back to 2000.[18] Although the scoring system introduced innovation, the relevance of echocardiography was limited. In contrast, our investigation demonstrated the strength of TEE in the prediction of embolic events in patients with IE. Moreover, this represents what a clinician faces with the evaluation of patients who may have IE.

To the best of our knowledge, this is the first time a proposed nomogram has been crafted that provides a probability of symptomatic embolic risk of IE. Although this scoring tool holds promise, validation in a different cohort is required.

## Limitations

We recognize the following limitations. First, although derived from an IE registry, our study was based on a retrospective chart review, as the observational nature of the research lacks the strengths of a randomized clinical trial. The consistent reporting of variables that could have affected outcome development was lacking in clinical records. Second, no routine template was used by echocardiographers to describe echocardiographic measurements; this resulted in exclusion of some patients. Third, our study did not include de novo measurement of vegetation measurements; however, our plan was to show the real-world assessment of embolic risk. Due to the nature of our institution (a tertiary referral center), there likely was selection bias and data may not be generalizable. However, the patients included in this investigation were from multiple Mayo Clinic Enterprise sites (Rochester, Minnesota, Florida, Arizona, Mayo Clinic Health System) at different geographic locations in the United States. Additionally, because the symptomatic embolic risk analysis was limited to the first 30 days after IE diagnosis, we may have underestimated the burden of embolic events that occurred beyond this time frame. However, it is important to note that previous studies have demonstrated that up to ~75% of embolic events typically occur within the 2 weeks following the diagnosis of IE and initiation of antimicrobial treatment. Lastly, there were 7 patients

with vegetations in either the right or left ventricle/atrium where mobility assessment was not done due to the anatomic location of the vegetation.

## CONCLUSIONS

Multiple characteristics, including several echocardiographic findings, clinical factors, and microbiologic results, are important in defining symptomatic embolic risk in the patient population with IE and confirmed vegetation. Our work has identified a prognostic scoring tool that may be helpful in defining embolic risk in individual patients with IE. Validation of the present work is needed to confirm the predictive accuracy of the scoring tool.

## ARTICLE INFORMATION

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### Affiliations

Division of Public Health, Infectious Diseases and Occupational Medicine, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN (S.D.S., J.A.Q., S.C., D.C.D., L.M.B.); Department of Internal Medicine, University of Miami, Jackson Memorial Hospital, Miami, FL (J.A.Q.); Division of Clinical Trials and Biostatistics (B.D.L.) and , Department of Cardiovascular Medicine (D.C.D., H.R.V., H.I.M., L.M.B.), Mayo Clinic College of Medicine and Science, Rochester, MN and , Cardiac Arrhythmia Service, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (S.D.S.).

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### Disclosures

None.

### Supplemental Material

Tables S1–S3
Figures S1–S3

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