Valvular Heart Disease

Echocardiographic Findings Predict In-Hospital and 1-Year Mortality in Left-Sided Native Valve Staphylococcus aureus Endocarditis

Analysis From the International Collaboration on Endocarditis-Prospective Echo Cohort Study

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Background—Staphylococcus aureus left-sided native valve infective endocarditis (LNVIE) has higher complication and mortality rates compared with endocarditis from other pathogens. Whether echocardiographic variables can predict prognosis in S aureus LNVIE is unknown.

Methods and Results—Consecutive patients with LNVIE, enrolled between January 2000 and September 2006, in the International Collaboration on Endocarditis were identified. Subjects without S aureus IE were matched to those with S aureus IE by the propensity of having S aureus. Survival differences were determined using log-rank significance tests. Independent echocardiographic predictors of mortality were identified using Cox-proportional hazards models that included inverse probability of treatment weighting and surgery as a time-dependent covariate. Of 727 subjects with LNVIE and 1-year follow-up, 202 had S aureus IE. One-year survival rates were significantly lower for patients with S aureus IE overall (57% S aureus IE versus 80% non-S aureus IE; \(P<0.001\)) and in the propensity-matched cohort (59% S aureus IE versus 68% non-S aureus IE; \(P<0.05\)). Intracardiac abscess (hazard ratio, 2.93; 95% confidence interval, 1.52–5.40; \(P<0.001\)) and left ventricular ejection fraction <40% (odds ratio, 3.01; 95% confidence interval, 1.35–6.04; \(P=0.004\)) were the only independent echocardiographic predictors of in-hospital mortality in S aureus LNVIE. Valve perforation (hazard ratio, 2.16; 95% confidence interval, 1.21–3.68; \(P=0.006\)) and intracardiac abscess (hazard ratio, 2.25; 95% confidence interval, 1.26–3.78; \(P=0.004\)) were the only independent predictors of 1-year mortality.

Conclusions—S aureus is an independent predictor of 1-year mortality in subjects with LNVIE. In S aureus LNVIE, intracardiac abscess and left ventricular ejection fraction <40% independently predicted in-hospital mortality and intracardiac abscess and valve perforation independently predicted 1-year mortality. (Circ Cardiovasc Imaging. 2015;8:e003397. DOI: 10.1161/CIRCIMAGING.114.003397.)

Key Words: echocardiography • endocarditis • odds ratio • risk factors • survival analysis

Staphylococcus aureus is the leading cause of infective endocarditis (IE) in industrialized countries.1,2 In fact, S aureus IE increased at a rate of 1.1% per quarter in the United States from 1999 to 2008.3 This is problematic because S aureus IE is associated with more complications and higher mortality compared with IE due to other pathogens.3,5 However, it remains unknown whether this finding persists when S aureus is compared with a non-S aureus cohort with similar baseline characteristics and if echocardiographic variables can identify patients with increased mortality in S aureus IE.

See Clinical Perspective
See Editorial by Erwin and O’Gara

Received December 2, 2014; accepted June 11, 2015.
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The Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.114.003397/-/DC1
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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org

DOI: 10.1161/CIRCIMAGING.114.003397
Echocardiographic predictors in staphylococcus aureus lnvie

Echocardiographic markers have been studied previously with respect to predicting outcome in IE with discordant results. For example, large or highly mobile vegetations have been studied as potential risk factors for embolic events and mortality.1-3 Yet, studies report discordant results. Gotsman et al4 found staphylococcal infection and vegetation size were independent predictors of embolic events and mortality, whereas Luaces et al5 found vegetation size was independently associated with embolic events, but not mortality.

Similarly, the prognostic role of left ventricular size and systolic function in IE is incompletely defined. For example, Kiefer et al6 found New York Heart Association (NYHA) Class III or IV heart failure was an independent predictor of 1-year mortality in the overall International Collaboration of Infective Endocarditis-Prospective Cohort Study (ICE-PCS) cohort. However, data for left ventricular ejection fraction (LVEF) and LV dimensions were not captured, yet may add incremental prognostic value in IE. Finally, inconsistencies exist about the causative pathogen and risk of tissue destruction, such as fistulas, perforation, or abscess formation.7,8

Using data from the ICE-PCS,1 the main objectives of this study were to determine survival differences for left-sided native valve IE (LN Vie) between S aureus and non-S aureus IE and to identify echocardiographic predictors for adverse outcome in S aureus LN Vie.

Methods

Study Population

This study was approved by each site’s Institutional Review Board or ethics committee. The inclusion criteria of ICE-PCS, a prospective, multicenter, international registry of IE have been reported previously.1 Between January 2000 and September 2006, 5591 unique cases of Duke possible or Duke definite IE10 were enrolled in ICE-PCS. Of these, 1379 comprised the Echo subset derived from 17 sites (9 countries, 3 continents), which prospectively enrolled an average of 81 subjects each. To be eligible for inclusion in ICE-Echo, a completed Echo-specific case report form (CRF) was required for each subject in addition to a completed baseline ICE-PCS CRF. Eligible sites must have completed Echo-specific CRFs on >50% of patients enrolled in ICE-PCS.

To ensure a homogeneous cohort with a comparable pathogenesis, only cases of LN Vie were included. Left-sided infection was defined as echocardiographic evidence of IE exclusively located on the aortic or mitral valves or structures in the left atrium or ventricle. Patients with right-sided IE or both right- and left-sided IE were excluded. Cases associated with any non-native valve or ring were defined as prosthetic and excluded. To evaluate the unique features of S aureus LN Vie, S aureus cases were examined and compared with non-S aureus cases.

To preserve the assumption of independence, only the first episode of LN Vie recorded for an individual patient was included in the analysis.

Clinical Data

Baseline characteristics were collected on the standard ICE-PCS CRF consisting of 275 variables. Data are stored in the ICE database and maintained by the Duke Clinical Research Institute.

Echocardiographic Data

Echocardiograms from the index hospitalization were performed as clinically indicated by expert investigators at each site, in accordance with applicable guidelines. For patients in ICE-Echo, echocardiograms were interpreted by a site expert echocardiographer using a standardized ICE-Echo CRF, consisting of 64 variables, including detailed information on left ventricular (LV) function and diameters, valvular status, vegetation characteristics and intracardiac complications. Echocardiographic data were obtained from a transthoracic echocardiogram or transesophageal echocardiogram. Echocardiographic data for the ICE-Echo cohort have been validated by an echocardiography core laboratory.9

Definitions

The definitions used in the ICE-PCS cohort have been described previously.1 Briefly, definite vegetations were defined as irregularly shaped discrete echogenic masses adherent to, yet distinct from, cardiac surfaces, including valve structures, myocardium, and intracardiac devices. Vegetation size was measured as the maximal linear dimension. Vegetation size was analyzed both as a continuous variable and as a categorical variable using a cut-off value of 10 mm. Highly mobile vegetations were defined as oscillating vegetations remaining within the chamber or prolapsing between 2 chambers during a cardiac cycle. Intracardiac abscess was defined as thickened areas or masses within the myocardium or annular region with a nonhomogeneous echogenic or echoluent appearance. LV ejection fraction was assessed by visual estimate, rounded to the nearest 5%, whereas LV dimensions were obtained from either transthoracic parasternal long axis view or transesophageal transgastric long axis view.

Analytic Plan

The association between S aureus, echocardiographic variables and mortality was assessed. The primary outcomes were in-hospital and 1-year all-cause mortality. Continuous variables were presented as medians with 25th and 75th percentiles. Categorical variables were presented as frequencies and percentages of the specified group. Statistical significance was determined at the 0.05 level. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC) and R for Mac OS X (Version 0.94.105, http://www.R-project.org/).

Univariate and Multivariable Analysis

Univariate comparisons of clinical and echocardiographic characteristics were made with the Wilcoxon rank-sum test or the χ2 test as appropriate. Bivariate logistic regression models were assessed to identify variables predictive of in-hospital and 1-year mortality. Risk estimates for in-hospital mortality are presented as odds ratios (ORs) and 95% confidence intervals (95% CI).

Multivariable logistic regression modeling was performed to determine the factors independently associated with S aureus infection among patients with LN Vie. This model included all clinical and echocardiographic variables considered a priori to be confounders or covariates of interest, including age (<45, 46–60, 61–70, and >70 years), sex, diabetes mellitus, hemodialysis, intravenous drug use, HIV, cancer, native valve predisposition to IE, time because first manifestation of disease, healthcare-associated IE, stroke, embolization, persistent bacteremia, congestive heart failure, persistent positive blood culture, any echocardiographic complication (abscess, fistula, or perforation), LVEF<40%, valvular regurgitation, and vegetation size. LVEF<40% was identified as a cut-off value because of potential alterations in management of subjects with heart failure and reduced LVEF.14,15

Propensity-Matched Cohort

Because of differing baseline and echocardiographic characteristics between S aureus and non-S aureus groups, a propensity-matched cohort was developed.16 The patients’ probabilities of having S aureus as the causative organism, derived from the model described above, were used for matching non-S aureus LN Vie cases with S aureus LN Vie cases in a 1:1 ratio using Greedy next neighbor matching techniques.17 Kaplan–Meier survival analysis with log-rank significance test was performed to estimate overall survival differences. A
stratified Cox Proportional Hazards model was performed to estimate *S. aureus* as an independent predictor of death.18

**Cox Proportional Hazard Models With Inverse Probability of Treatment Weighting**

To evaluate independent echocardiographic factors associated with mortality for *S. aureus* IE, unique Cox Proportional hazard models were fitted for in-hospital and 1-year survival. The multivariate model included clinical and echocardiographic variables identified a priori by an experienced cardiologist. Moderate and severe mitral and aortic valve regurgitation were merged because of few events in each group. To account for immortal time bias, surgery was modeled as a time-dependent factor defined as days from admission to cardiac surgery during admission. These models were further weighted by the inverse probability of treatment weighting using a propensity score for surgery calculated individually.19 The model included baseline variables and clinical characteristics considered associated with cardiac surgery. To address pathogen-specific predictors, a separate Cox model was performed for streptococcal IE, a cohort with a different disease course and prognosis. Similarly, both immortal time bias and treatment bias was taken into account.

**Results**

**Baseline Clinical and Echocardiographic Features**

A total of 1379 patients were included in the ICE-Echo cohort from January 2000 to September 2006. Of these, 727 cases with LNVIE (202 with *S. aureus* and 525 without *S. aureus*) met eligibility criteria for this study. Baseline clinical and echocardiographic characteristics of the overall study population are shown in Table 1. Most comorbidities were significantly more common in patients with *S. aureus* IE. However, those subjects with non-*S. aureus* IE were more likely to have a history of a native valve predisposition (40% versus 24%; *P*<0.0001) and were more likely to undergo cardiac surgery during admission (55% versus 38%; *P*<0.0001) compared with those subjects with *S. aureus* IE (Table 1). Echocardiographic variables associated with non-*S. aureus* IE were LV enlargement, moderate or severe aortic regurgitation, and vegetation presence and mobility (Table 1). Mean vegetation size did not differ between groups (12 mm versus 13 mm; *P*=0.47).

**Propensity-Matched Cohort**

The propensity-matched cohort consisted of matched cases of *S. aureus* LNVIE (n=187) and non-*S. aureus* LNVIE (n=187). Fifteen cases of *S. aureus* LNVIE were not included in the propensity-matched cohort because of random missing variables. Importantly, there were no significant differences in baseline characteristics in the matched *S. aureus* LNVIE cohort (n=187) as compared with the overall *S. aureus* LNVIE cohort (n=202). The matched non-*S. aureus* LNVIE cohort included the following microorganisms: streptococci (n=77), enterococci (n=40), coagulase negative staphylococci (n=33), fungi (n=3), HACEK (n=1), Gram-negative (n=14), and culture negative (n=19) microorganisms.

**Survival Data**

In-hospital survival rates were significantly lower for *S. aureus* than for non-*S. aureus* in the overall LNVIE cohort (72% versus 88%, respectively; 95% CI, 0.08–0.23; *P*<0.0001), but not in the propensity-matched cohort (74% versus 79%, respectively; 95% CI, −0.04 to 0.14; *P*=0.26). One-year survival rates were significantly lower for *S. aureus* IE in both the overall cohort (Figure 1A; 57% versus 80%; 95% CI, 0.15–0.31; *P*<0.0001) and the propensity-matched cohort (Figure 1B; 59% versus 68%; *P*<0.05). Survival rates for matched non-*S. aureus* IE were significantly lower than unmatched non-*S. aureus* IE in the LNVIE cohort (Figure 1B; 68% versus 86%; *P*<0.001). In a multivariate Cox proportional hazards model adjusted for age, sex, comorbidities, and echocardiographic variables, *S. aureus* was independently associated with 1-year mortality in the overall, nonmatched cohort (Figure 1C). Furthermore, in a multivariate stratified Cox proportional hazards model adjusted for age, sex, comorbidities, and echocardiographic variables, *S. aureus* remained independently associated with 1-year mortality in the propensity-matched cohort (Figure 1D).

**Echocardiographic Predictors of Mortality in LNVIE**

Echocardiographic data were obtained from a transthoracic echocardiogram in 59 of 202 cases (29%) and transesophageal echocardiogram in 143 of 202 cases (71%). In a bivariate logistic model for 202 cases of *S. aureus* LNVIE adjusted for surgery, multiple variables were significantly associated with in-hospital or 1-year mortality (Table 2). In-hospital mortality was associated with LVEF <40% (OR, 2.28; 95% CI, 0.97–4.57; *P*=0.06), moderate or severe mitral stenosis (OR, 7.66; 95% CI, 3.80–14.8; *P*<0.0001), moderate or severe aortic stenosis (OR, 2.51; 95% CI, 1.38–4.25; *P*<0.01), abscess (OR, 2.74; 95% CI, 1.44–4.82; *P*<0.001), presence of a vegetation (OR, 3.40; 95% CI, 1.69–8.00; *P*<0.01), vegetation >10 mm (OR, 1.88; 95% CI, 1.11–3.39; *P*<0.05), and vegetation with moderate or severe mobility (OR, 2.27; 95% CI, 1.47–3.52; *P*<0.0001). One-year mortality was associated with LVEF <40% (OR, 2.61; 95% CI, 1.33–4.62; *P*<0.01), moderate or severe mitral stenosis (OR, 9.57; 95% CI, 5.21–16.9; *P*<0.0001), moderate or severe aortic stenosis (OR, 2.04; 95% CI, 1.18–3.31; *P*<0.01), abscess (OR, 2.09; 95% CI, 1.15–3.54; *P*<0.01), and presence of perforation of left-sided valves (OR, 1.82; 95% CI, 1.13–2.80; *P*<0.01). There were no significant differences for geographical region (North America versus Europe, Asia or South America; OR, 1.46; 95% CI, 0.92–2.29; *P*=0.10; Table 2).

To evaluate independent echocardiographic variables associated with mortality for *S. aureus* IE, unique Cox Proportional hazard models were made for in-hospital and 1-year survival. To account for both immortal time bias and treatment bias, surgery was both modeled as a time-dependent factor and included as a weight (Figure 2). When surgery was taken into account in the multivariate model, the risk of in-hospital mortality was 3× higher with the presence of LVEF <40% (OR, 3.01; 95% CI, 1.35–6.04) or an abscess (OR, 2.93; 95% CI, 1.52–5.42). One-year mortality was 2× higher with the presence of mitral or aortic valve perforation (OR, 2.16; 95% CI, 1.21–3.68) or abscess (OR, 2.25; 95% CI, 1.25–3.78). Moderate or severe valvular regurgitation was found in 70 cases. Perforation was found in 20 cases and was associated with moderate or severe valvular regurgitation (moderate aortic regurgitation in 4/20 cases [20%], severe aortic regurgitation in 13/20 cases [65%], and both severe mitral and aortic regurgitation in 3/20 cases [15%]).
The presence of a vegetation and vegetation size >10 mm were associated with in-hospital mortality in the bivariate models but did not predict mortality within the subset of *S aureus* IE in the multivariate models. Vegetation size, when assessed as a continuous variable, was also not independently predictive of mortality in *S aureus* IE.

Furthermore, to compare echocardiographic factors associated with mortality for microorganisms with varying pathogenesis, unique Cox Proportional hazard models with the same covariates as models for *S aureus* LNVIE were generated for 1-year survival in streptococcal IE only, as <10 in-hospital deaths occurred in streptococcal IE. Abscess formation was an

### Table 1. Baseline Characteristics, Complications, and Echocardiographic Findings for Duke Definite Left-Sided Native Valve Infective Endocarditis (n=727)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort (n=727)</th>
<th>Staphylococcus aureus (n=202)</th>
<th>Non S aureus (n=525)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, median (range)</td>
<td>56 (45–69)</td>
<td>57 (44–69)</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>132 (65)</td>
<td>370 (70)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Symptom to admission &lt; 1 mo</td>
<td>194 (97)</td>
<td>347 (69)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>53 (26)</td>
<td>34 (6)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>71 (35)</td>
<td>88 (17)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>11 (5)</td>
<td>8 (2)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Current intravenous drug use</td>
<td>38 (18)</td>
<td>37 (7)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>24 (12)</td>
<td>59 (11)</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Native valve predisposition*</td>
<td>48 (24)</td>
<td>206 (40)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Healthcare-associated IE</td>
<td>88 (45)</td>
<td>78 (16)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Previous IE</td>
<td>7 (3)</td>
<td>25 (5)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>14 (7)</td>
<td>57 (11)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>62 (31)</td>
<td>119 (23)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Peripheral embolization</td>
<td>92 (46)</td>
<td>172 (33)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Persistent bacteremia</td>
<td>55 (27)</td>
<td>41 (8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>New onset heart failure</td>
<td>74 (36)</td>
<td>206 (39)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>NYHA class III–IV</td>
<td>45 (24)</td>
<td>130 (27)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Mycotic aneurysm</td>
<td>7 (3)</td>
<td>18 (3)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>8 (4)</td>
<td>10 (2)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>78 (38)</td>
<td>286 (55)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiographic findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>15 (8)</td>
<td>44 (10)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>LVESD &gt;40 mm</td>
<td>19 (15)</td>
<td>103 (28)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LVESD &gt;60 mm</td>
<td>16 (12)</td>
<td>90 (23)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation (moderate or severe)</td>
<td>87 (43)</td>
<td>258 (50)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation (moderate or severe)</td>
<td>54 (27)</td>
<td>247 (48)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis (moderate or severe)</td>
<td>14 (7)</td>
<td>38 (7)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis (moderate or severe)</td>
<td>3 (2)</td>
<td>18 (4)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>20 (10)</td>
<td>182 (15)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>18 (9)</td>
<td>57 (11)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Vegetation present</td>
<td>168 (82)</td>
<td>483 (91)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Maximal dimension (median, IQR)</td>
<td>12 (8–18)</td>
<td>13 (8–18)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Vegetation &gt;10 mm</td>
<td>101 (67)</td>
<td>310 (70)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Mobile vegetation</td>
<td>100 (49)</td>
<td>350 (66)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe mobility</td>
<td>62 (30)</td>
<td>249 (47)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

IE indicates infective endocarditis; IQR, interquartile range; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; and NYHA, New York Heart Association.

*Native valve predisposition includes moderate mitral or aortic regurgitation or stenosis.
independent predictor for 1-year mortality in both streptococcal IE (OR, 3.32; 95% CI, 1.55–6.77) and  

**Discussion**

There are 2 major novel findings in this study. First, *S aureus* infection was identified as an independent predictor of late death in LNVIE, even when compared with a non-*S aureus* cohort matched by the likelihood of having *S aureus* infection from baseline characteristics. Second, in-hospital and 1-year prognostic echocardiographic variables for *S aureus* LNVIE were identified. Once accounting for survival bias and surgery, *S aureus* IE had a 3-fold higher risk of in-hospital mortality with the presence of LVEF<40% or abscess. One-year mortality was 2× higher with the presence of mitral or aortic valve perforation or abscess.

In the ICE-echo cohort, *S aureus* LNVIE was associated with more baseline comorbidities and complications as compared with other pathogens. *S aureus* IE was less likely to affect patients with pre-existing valvular disease as compared with non-*S aureus* LNVIE. These baseline differences between the *S aureus* and non-*S aureus* LNVIE cohorts are similar to those previously described in the overall ICE-PCS cohort, as well as other studies. Some baseline differences, such as increased ventricular dimensions and more moderate and severe aortic regurgitation in non-*S aureus* LNVIE may be due, in part, to the more acute onset of symptoms in *S aureus* LNVIE as compared with non-*S aureus* LNVIE.

*S aureus* LNVIE has higher mortality as compared with non-*S aureus* LNVIE. This finding is similar to previous studies with some important caveats. For example, our finding of increased mortality in *S aureus* as compared with non-*S aureus* is similar to a previous study by Hasbun et al who identified that *S aureus* infection was independently associated with increased 6-month mortality (OR, 3.56; 95% CI, 1.54–6.79; *P*=0.004) in 75 cases of *S aureus* LNVIE from Connecticut. Although this study corroborates the findings of Hasbun et al, some important distinctions should be noted. The current series is larger, prospectively collected, and international with a longer follow-up duration. Taken together, these distinctions attest to the generalizability of our results. Similarly, our finding is concordant with a European multicenter study that found that the presence of *S aureus* infection increased the relative risk of 1-year mortality significantly (RR, 1.9; 95% CI, 1.16–3.14) in 384 Duke definite IE cases. In the latter study, results were derived from multivariate models in heterogeneous cohorts, including native and prosthetic infections and right- and left-sided infections, whereas in this study, only LNVIE cases were included to ensure a homogenous cohort.

In addition, our study goes beyond others by generating a novel propensity-matched cohort. Interestingly, despite propensity matching for *S aureus*, *S aureus* remained
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independently associated with 1-year mortality. Of note, the propensity-matched non-\textit{S} \textit{aureus} cohort had significantly lower survival rates in comparison with the nonmatched, non-\textit{S} \textit{aureus} LNVIE cohort, indicating that when matching 1:1 with baseline characteristics similar to \textit{S} \textit{aureus}, cases of non-\textit{S} \textit{aureus} with the worst prognosis were selected. The remaining difference in outcome for the matched \textit{S} \textit{aureus} LNVIE cohort may, in part, reflect the increased virulence of \textit{S} \textit{aureus}.

In this study, we investigated whether echocardiographic markers could predict in-hospital and 1-year mortality in \textit{S} \textit{aureus} LNVIE. Our finding that large vegetations were not independently associated with an increased risk of mortality agreed with those of Luaces et al\textsuperscript{6} who found that vegetation size was not independently associated with an increased risk of death, but not with others who found that vegetation size was an independent predictor of mortality.\textsuperscript{5,7,8} Possible reasons why our results were not concordant with others were differing study designs (retrospective, single-center study\textsuperscript{8} versus larger, prospective, multicenter, and international), multiple pathogens,\textsuperscript{5,7,8} and different patient populations.\textsuperscript{5,8}

\begin{table}
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\begin{tabular}{llllll}
\hline
\textbf{Characteristic} & \multicolumn{2}{c}{\textbf{In-Hospital Mortality}} & \multicolumn{2}{c}{\textbf{1-Y Mortality}} \\
 & HR (95\% CI) & \textbf{P Value} & HR (95\% CI) & \textbf{P Value} \\
\hline
Age, y, median (range) & 1.01 (1.01–1.02) & <0.05 & 1.01 (1.01–1.03) & <0.05 \\
Men & 0.68 (0.44–1.04) & 0.07 & 0.66 (0.47–0.94) & <0.05 \\
Symptom to admission <1 mo & 0.90 (0.21–2.54) & 0.87 & 2.71 (1.27–5.06) & <0.01 \\
Geographic region: North America & 1.46 (0.92–2.29) & 0.10 & 1.09 (0.76–1.54) & 0.65 \\
Geographic region: Other & 0.97 (0.06–4.33) & 0.97 & 0.61 (0.11–1.88) & 0.47 \\
Hemodialysis & 2.72 (1.74–4.19) & <0.0001 & 2.77 (1.94–3.93) & <0.0001 \\
Diabetes mellitus & 3.06 (2.00–4.68) & <0.0001 & 2.01 (1.41–2.85) & <0.0001 \\
HIV positive & NA & 0.98 & 0.42 (0.14–0.93) & 0.05 \\
Current intravenous drug use & 0.41 (0.20–0.74) & <0.01 & 0.40 (0.23–0.66) & <0.001 \\
Cancer & 0.59 (0.23–1.24) & 0.21 & 1.29 (0.75–2.12) & 0.33 \\
Native valve predisposition* & 1.78 (1.14–2.75) & <0.001 & 1.94 (1.35–2.76) & <0.001 \\
Healthcare-associated IE & 1.81 (1.18–2.79) & <0.01 & 1.72 (1.22–2.42) & <0.01 \\
Previous IE & 0.34 (0.03–1.37) & 0.23 & 0.76 (0.23–1.82) & 0.59 \\
Congenital heart disease & 0.99 (0.47–1.90) & 0.99 & 1.51 (0.88–2.44) & 0.11 \\
\hline
\textbf{Complications} & & & & \\
Stroke & 2.81 (1.83–4.34) & <0.0001 & 2.09 (1.47–2.96) & <0.0001 \\
Peripheral embolization & 1.13 (0.73–1.77) & 0.58 & 0.92 (0.65–1.29) & 0.62 \\
Persistant bacteremia & 1.75 (1.10–2.72) & <0.01 & 2.19 (1.51–3.13) & <0.0001 \\
New onset heart failure & 0.95 (0.63–1.53) & 0.95 & 1.42 (1.01–2.00) & <0.05 \\
NYHA class III–IV & 1.31 (0.97–2.33) & 0.06 & 1.83 (1.28–2.58) & <0.001 \\
Mycotic aneurysm & 1.01 (0.31–2.47) & 0.98 & 1.21 (0.39–2.82) & 0.70 \\
Shock & 6.18 (3.43–10.5) & <0.0001 & 4.47 (2.53–7.34) & <0.0001 \\
\hline
\textbf{Echocardiographic findings} & & & & \\
LVEF <40\% & 2.28 (0.97–4.57) & 0.06 & 2.61 (1.33–4.62) & <0.01 \\
LVEDD >40 mm & 2.16 (0.90–4.41) & 0.05 & 1.31 (0.60–2.47) & 0.45 \\
LVEDD >60 mm & 2.15 (0.87–4.42) & 0.06 & 1.54 (0.69–2.95) & 0.23 \\
Mitral regurgitation (moderate/severe) & 0.93 (0.60–1.43) & 0.75 & 1.06 (0.75–1.51) & 0.73 \\
Aortic regurgitation (moderate/severe) & 1.29 (0.82–2.01) & 0.26 & 1.40 (0.95–1.01) & 0.08 \\
Mitral stenosis (moderate/severe) & 7.66 (3.80–14.8) & <0.0001 & 9.57 (5.21–16.9) & <0.0001 \\
Aortic stenosis (moderate/severe) & 2.51 (1.38–4.25) & <0.01 & 2.04 (1.18–3.31) & <0.01 \\
Abscess & 2.74 (1.44–4.82) & <0.001 & 2.09 (1.15–3.54) & <0.01 \\
Perforation & 1.33 (0.71–2.31) & 0.33 & 1.82 (1.13–2.80) & <0.01 \\
Vegetation present & 3.40 (1.69–6.00) & <0.01 & 1.23 (0.81–1.94) & 0.34 \\
Vegetation >10 mm & 1.88 (1.11–3.39) & <0.05 & 1.45 (0.93–2.32) & 0.11 \\
Vegetation with moderate/severe mobility & 2.27 (1.47–3.52) & <0.001 & 1.51 (1.05–2.15) & <0.05 \\
\hline
\end{tabular}
\caption{Bivariate Model of Clinical and Echocardiographic Predictors Associated With In-Hospital and 1-Year Mortality for \textit{Staphylococcus aureus} Left-Sided Native Valve IE (n=202) Adjusted for Surgery}

\textit{CI} indicates confidence interval; HR, hazard ratio; IE, infective endocarditis; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-systolic diameter; NA, not applicable; and NYHA, New York Heart Association.

*Native valve predisposition includes moderate mitral or aortic regurgitation or stenosis.
which highlights the pathogen and native valve-specific nature of our findings, is the study performed by Thuny et al.\textsuperscript{5} Thuny et al\textsuperscript{5} performed an elegant, prospective, multicenter analysis on 384 consecutive patients with IE from multiple pathogens to assess transesophageal echocardiographic characteristics associated with embolic events and death. In this study, vegetation length \textgreater{} 15 mm was a predictor of 1-year mortality. Together with our findings, these data imply that the prognostic value of vegetation size for mortality may be pathogen and native/prosthetic valve specific.

While heart failure, as a clinical diagnosis, is a major complication associated with adverse outcome in IE,\textsuperscript{9,23} correlation with LVEF may provide additive prognostic information. In this study, we identified LVEF\textless{}40\% as an independent predictor of in-hospital death in \textit{S aureus} LNVIE regardless of NYHA class status or valvular disease. Knowledge of patient LVEF may be useful because treatment strategies differ for subjects with LVEF\textless{}40\% as compared with those with LVEF\textgreater{}40\%.\textsuperscript{24,25}

Extensive tissue destruction is an indication for early surgery in IE.\textsuperscript{10} Even when surgery was accounted for in our multivariable model, the presence of an abscess was associated with in-hospital death and both valve perforation and abscess were associated with 1-year mortality in \textit{S aureus} LNVIE and streptococcal LNVIE. The finding that perforation is an independent marker of mortality concurs with a study conducted by Bachour et al\textsuperscript{11} who found that a valve perforation complicating LNVIE is associated with high mortality in a retrospective review of 123 LNVIE cases. Abscess is a life-threatening complication that cannot be cured with antibiotic therapy alone. The association between extensive cardiac infection and adverse outcome may be related to uncontrolled infection or enhanced virulence of \textit{S aureus}. Unfortunately, the design of this study does not allow for further clarification.

Other issues should be considered in the interpretation of these findings. Data quality was dependent on the accuracy and completeness of documentation and abstraction in ICE-PCS and ICE-Echo registries. Echocardiograms were performed as clinically indicated by expert investigators at each site in accordance with then applicable guidelines, thus transesophageal echocardiograms were only performed in addition to transthoracic echocardiography in 70\% of \textit{S aureus} LNVIE cases. Furthermore, variation in image quality and echocardiographic imaging systems did exist. The Core Laboratory validated echocardiographic data and did find substantial or almost perfect intra- and interobserver agreement for all echocardiographic variables.\textsuperscript{13} Furthermore, some potential confounders, such as heart failure status and cardiac complications had missing data. Nonetheless, distribution of missing values was scrutinized and occurred at random as previously described.\textsuperscript{19} Furthermore, this was a PCS, and observed differences in survival between \textit{S aureus} and non-\textit{S aureus} LNVIE may have resulted from residual and unmeasured confounding. However, we were able to match cohorts by several robust baseline characteristics. Finally, cases of LNVIE were reported from hospitals within each region that are referral centers with cardiac surgery programs. Therefore, the results
of this study may not be generalizable to patients receiving care at nontertiary referral medical centers.

Conclusions

*S. aureus* infection is an independent predictor of 1-year mortality in subjects with LNVE. When surgery and clinically prognostic indicators were taken into account, intracardiac abscess and LVEF<40% independently predicted in-hospital mortality in *S. aureus* LNVE. Furthermore, intracardiac abscess and valve perforation independently predicted 1-year mortality in *S. aureus* LNVE. Ideally, identifying these independent echocardiographic markers should lead to more aggressive patient management in patients with *S. aureus* LNVE. Future research on microorganism and host-specific factors is desirable to better elucidate the virulence of *S. aureus* bacteremia in LNVE.

Sources of Funding

Dr Lauridsen was supported by a Fulbright scholarship and grants from the Danish Heart Foundation. Dr Bayer was supported by grant NIH-NIAID-R01AI039108-16. Dr Fowler was supported by Grants K24-AI093969 and R01AI68804 from the National Institutes of Health. Dr Tong is an Australian National Health and Medical Research Council Career Development Fellow (1065736).

Disclosures

Dr Bayer has received grant support from Cubist, ContraFect, and Theravance. Dr Chu has received grant support from Boston Scientific. Dr Corey has received grant support from American Heart Association and Merck. Dr Samad has received grant support from Boston Scientific. Drs. Brunner and Cesari have received grant support from Novartis, Pfizer, and Roche. Dr Fowler is a chair of V710 Scientific Advisory Committee Pharma and he received grant support from Novartis, Pfizer, and Afib. Dr Bruun is a paid consultant to Leo Theravance. Dr Chu has received grant support from American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Dr Fowler was supported by Grants KIA0007959 and KIA0008959 from the National Institutes of Health. Dr Tong is an Australian National Health and Medical Research Council Career Development Fellow (1065736).

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References


Echocardiographic Predictors in Staphylococcus aureus LNVIE


**CLINICAL PERSPECTIVE**

*Staphylococcus aureus* bacteremia is associated with adverse outcome in left-sided native valve infective endocarditis. It is uncertain whether the increased mortality is because of the increased virulence of the pathogen or host-specific factors. We undertook this study to investigate whether *S. aureus* remained an independent predictor of mortality in a non-*S. aureus* cohort with similar baseline characteristics. In this propensity-matched cohort of 187 matched cases, *S. aureus* remained an independent predictor of both in-hospital and 1-year mortality. Because of the adverse prognosis in left-sided, native valve infective endocarditis, independent prognostic echocardiographic variables associated with *S. aureus* left-sided native valve infective endocarditis were identified. After accounting for survival bias and surgery, those with *S. aureus* IE had a 3-fold higher risk of in-hospital mortality when the left ventricular ejection fraction was <40% or when an abscess was present. Mitral or aortic valve perforation or an abscess conferred a 2-fold increase in mortality at 1 year. Thus, specific echocardiographic findings identify patients at high-risk for mortality in *S. aureus* left-sided native valve infective endocarditis, which can then inform clinical management of these patients.
Echocardiographic Findings Predict In-Hospital and 1-Year Mortality in Left-Sided Native Valve *Staphylococcus aureus* Endocarditis: Analysis From the International Collaboration on Endocarditis-Prospective Echo Cohort Study


*Circ Cardiovasc Imaging*. 2015;8:
doi: 10.1161/CIRCIMAGING.114.003397

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/8/7/e003397

Data Supplement (unedited) at:
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