# Association Between Surgical Indications, Operative Risk, and Clinical Outcome in Infective Endocarditis

## A Prospective Study From the International Collaboration on Endocarditis

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***Background***—Use of surgery for the treatment of infective endocarditis (IE) as related to surgical indications and operative risk for mortality has not been well defined.

***Methods and Results***—The International Collaboration on Endocarditis–PLUS (ICE-PLUS) is a prospective cohort of consecutively enrolled patients with definite IE from 29 centers in 16 countries. We included patients from ICE-PLUS with definite left-sided, non–cardiac device–related IE who were enrolled between September 1, 2008, and December 31, 2012. A total of 1296 patients with left-sided IE were included. Surgical treatment was performed in 57% of the overall cohort and in 76% of patients with a surgical indication. Reasons for nonsurgical treatment included poor prognosis (33.7%), hemodynamic instability (19.8%), death before surgery (23.3%), stroke (22.7%), and sepsis (21%). Among patients with a surgical indication, surgical treatment was independently associated with the presence of severe aortic regurgitation, abscess, embolization before surgical treatment, and transfer from an outside hospital. Variables associated with nonsurgical treatment were a history of moderate/severe liver disease, stroke before surgical decision, and *Staphyloccus aureus* etiology. The integration of surgical indication, Society of Thoracic Surgeons IE score, and use of surgery was associated with 6-month survival in IE.

***Conclusions***—Surgical decision making in IE is largely consistent with established guidelines, although nearly one quarter of patients with surgical indications do not undergo surgery. Operative risk assessment by Society of Thoracic Surgeons IE score provides prognostic information for survival beyond the operative period. *S aureus* IE was significantly associated with nonsurgical management. **(*Circulation*. 2015;131:131-140. DOI: 10.1161/CIRCULATIONAHA.114.012461.)**

**Key Words:** endocarditis ■ infection ■ mortality ■ surgery ■ valve

The decision to perform surgery in infective endocarditis (IE) remains a challenge because of the potential for acute and life-threatening complications of this disease, uncertain response to antibiotic therapy, and comorbid host conditions. Cardiac surgery is used in combination with antibiotics for the treatment of IE in ≈50% of affected patients.[1–5] Surgical management of IE can optimize source control by removal of infected tissue, reduce morbidity from embolic events,[6] and reduce mortality in the appropriate clinical context.[7–10]

**Editorial see p 121**
**Clinical Perspective on p 140**

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*A complete list of the ICE Investigators can be found in the online-only Data Supplement.

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Consensus guidelines outline specific conditions for which surgery is recommended,[11–14] but clinical application of these recommendations is poorly understood.

Although cardiac surgery can be life-saving, it also carries significant risk for the patient. Risk scoring systems can be a useful tool to aid clinical decision making with respect to surgical treatment of cardiac conditions. Recently, a risk model has been derived from the Society of Thoracic Surgeons (STS) database including 13 617 operations performed for IE among cardiac surgery centers across North America.[15] The STS score model for operative mortality consists of 13 variables and has been internally validated with good discriminatory function. However, the relationship between operative risk and longer-term outcome has not been evaluated.

To better understand surgical treatment of IE, the International Collaboration on Endocarditis (ICE) group designed a prospective study to evaluate factors that influence the use of surgical intervention in IE. The purpose of this study is to evaluate the differences in clinical characteristics between IE patients treated with or without cardiac surgery as related to the presence and timing of IE complications and operative risk and the possible relationship between these factors and outcome. We hypothesized that appropriate use of surgery according to recommended indications as well as operative risk would affect 6-month survival in IE.

## Methods

### Study Population and Clinical Data

The present study cohort was obtained from the ICE-PLUS database. ICE-PLUS contains 2002 patients with definite IE as defined by the modified Duke criteria.[16] Data were prospectively collected from 29 centers in 16 countries between September 1, 2008, and December 31, 2012. A standard case report form with 275 variables was used to collect data on all patients. The background to the ICE collaboration[17,18] has been reported previously. The study was approved by the institutional review board or ethics committee at all participating sites, according to local standards.

Patients who had definite[16] left-sided IE were included in the present study. Patients with right-sided IE only and cardiac device–related IE were excluded. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was used.

### Definitions

Definitions of the standard variables used in the ICE database have been reported previously.[7,19] *Systemic embolization,* termed *embolization* throughout this text, was defined as embolism to any major arterial vessel, excluding stroke. *Persistent positive blood cultures* were defined as blood cultures still positive after 72 hours of adapted antibiotic therapy. *Healthcare-associated IE* consisted of either nosocomial or non-nosocomial acquired infection, where *nosocomial healthcare-associated IE* was defined as IE occurring in a patient hospitalized for >48 hours, and *non-nosocomial healthcare-associated IE* was defined if signs or symptoms consistent with IE developed before hospitalization in patients with extensive out-of-hospital contact with healthcare interventions, including (1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days before the onset of IE; (2) visiting a hospital or hemodialysis clinic or receiving intravenous chemotherapy within the 30 days before the onset of IE; (3) hospitalization in an acute care hospital for ≥2 days in the 90 days before the onset of IE; or (4) residing in a nursing home or long-term care facility.[20] ICE-PLUS included additional variables related specifically to cardiac surgical risk and decision making. S*urgery* was defined as replacement or repair of the affected valve during the initial hospitalization for IE. Indications for surgery included the following: heart failure, embolic event, persistent bacteremia, paravalvular complication, severe valvular regurgitation, vegetation size, and microorganism. Data were collected on the case report form for timing of each IE complication and indication for surgery; surgery consultation and recommendation; timing of surgery; and the reasons for lack of surgery. Surgery was defined as *elective* if the patient's cardiac function had been stable in the days or weeks before the operation, and the procedure could be deferred without increased risk of compromised cardiac outcome; as *urgent* if the surgical procedure was required during the same hospitalization to minimize chance of further clinical deterioration; or as *emergency* if the patient was having ongoing, refractory (difficult, complicated, or unmanageable) unrelenting cardiac compromise, with or without hemodynamic instability, and was not responsive to any form of therapy except cardiac surgery.[15] The risk scoring system (ie, STS-IE score), based on the STS Adult Cardiac Surgery Database, was used to stratify patients according to their risk of death within 30 days of operative management of IE.[15] Additional details regarding the STS-IE score are provided in the online-only Data Supplement.

### Analytical Plan

Baseline characteristics and clinical events are presented as medians with 25% and 75% percentiles for continuous variables and frequencies with proportions for categorical variables. Statistical significance for comparisons between groups was determined with the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. A 2-sided $P$ value of <0.05 was considered statistically significant. Characteristics of patients undergoing surgery (surgery group) were compared with those of patients who did not undergo surgery during the index hospitalization (no surgery group). Among patients with a surgical indication, multivariable logistic regression was used to identify variables independently predictive of surgical treatment. Variables included in the multivariable model were those that were significant in the bivariate analyses at $P$<0.10 and STS score quintile. The model was reduced by backward elimination, and the final model included variables significant at $P$<0.10, whereas STS quintile was forced to remain. Survival probabilities according to the presence or absence of surgical indications and STS score were estimated in 50-day intervals from admission with the use of the life table method. Cumulative survival probability plots were generated with the use of the Kaplan-Meier method. Statistical analyses were performed with SAS version 9.4 software (SAS Institute, Cary, NC), and plots were generated with Splus 8.1 (TIBCO Software Inc, Palo Alto, CA).

## Results

### Overall Cohort

The study schema is depicted in Figure 1. There were a total of 1296 patients with left-sided, definite IE, including 314 (25%) with prosthetic valve IE. Patients were characterized by

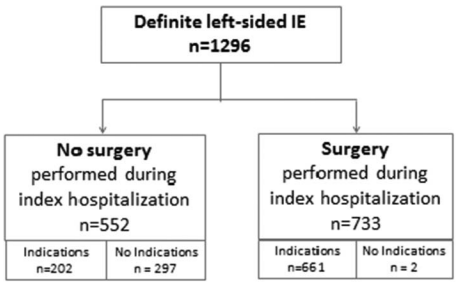



**Figure 1.** Study population. IE indicates infective endocarditis. Data on surgical status are missing in 11 patients. Data on the presence of surgical indications are missing in 53 patients in the no surgery group and 70 patients in the surgery group.

**Table 1. Baseline Characteristics of Patients With Definite Left-Sided IE**

| | Overall (n=1296)* | Surgery (n=733) | No Surgery (n=552) | OR (95% CI) *P* Value |
|---|---|---|---|---|
| Age, median, y (25th,75th percentile) | 62 (47, 72) | 57 (43, 69) | 68 (55, 77) | *P*<0.001 |
| Male | 884 (68.4) | 527 (72.1) | 349 (63.5) | 1.49 (1.17, 1.9) |
| First clinical manifestation <1 mo | 794 (62) | 428 (59) | 357 (65.6) | 0.75 (0.6, 0.96) |
| Prosthetic valve IE | 314 (25.3) | 150 (21.3) | 163 (30.9) | 0.60 (0.46, 0.79) |
| Transfer from other hospital | 670 (52) | 452 (62) | 213 (38.9) | 2.57 (2.03, 3.24) |
| Healthcare-associated IE | 284 (23.6) | 127 (18.9) | 155 (29.5) | *P*<0.001 |
| Medical history | | | | |
| Previous IE | 100 (7.8) | 51 (7) | 48 (8.8) | 0.79 (0.51, 1.22) |
| Coronary artery disease | 202 (16) | 86 (11.9) | 114 (21.6) | 0.49 (0.36, 0.68) |
| COPD | 180 (14.1) | 87 (12.1) | 91 (16.6) | 0.69 (0.49, 0.96) |
| Previous cardiac surgery | 360 (27.9) | 166 (22.8) | 192 (34.8) | 0.55 (0.43, 0.71) |
| Previous coronary artery bypass surgery | 82 (6.4) | 28 (3.8) | 53 (9.7) | 0.37 (0.22, 0.61) |
| Atrial fibrillation/flutter | 212 (18.1) | 88 (13.3) | 123 (24.5) | 0.48 (0.35, 0.65) |
| Previous heart failure | 202 (16.2) | 94 (13.1) | 111 (20.4) | 0.58 (0.43, 0.80) |
| Cerebrovascular disease | 125 (9.8) | 66 (9.1) | 59 (10.8) | 0.83 (0.56, 1.23) |
| History of stroke | 86 (6.6) | 41 (5.6) | 45 (8.2) | 0.67 (0.42, 1.06) |
| Diabetes mellitus | 271 (21.2) | 117 (16.3) | 150 (27.2) | 0.52 (0.39, 0.69) |
| Moderate or severe renal disease | 149 (11.7) | 55 (7.6) | 92 (16.9) | 0.40 (0.28, 0.58) |
| Hemodialysis dependent | 63 (4.9) | 23 (3.1) | 40 (7.2) | 0.41 (0.23, 0.72) |
| Moderate or severe liver disease | 47 (3.7) | 17 (2.4) | 30 (5.5) | 0.42 (0.20, 0.79) |
| Hemiplegia or neurological dysfunction affecting ambulation | 67 (5.2) | 29 (4) | 38 (6.9) | 0.56 (0.33, 0.95) |
| Cancer | 164 (12.9) | 72 (10) | 90 (16.6) | 0.56 (0.39, 0.78) |
| Immunosuppressive therapy | 71 (5.5) | 29 (4) | 41 (7.5) | 0.52 (0.31, 0.86) |
| HIV | 14 (1.1) | 9 (1.3) | 5 (0.9) | 1.38 (0.41, 5.27) |
| Injection drug use | 59 (4.6) | 37 (5.1) | 22 (4.1) | 1.27 (0.72, 2.28) |
| Dementia | 17 (1.3) | 7 (1) | 10 (1.8) | 0.53 (0.17, 1.55) |
| Echocardiography | | | | |
| Vegetation present (any site) | 1296 (100) | 733 (100) | 552 (100) | 0.75 (0.55, 1.02) |
| New moderate or severe mitral regurgitation | 509 (41.2) | 328 (47.1) | 177 (33.4) | 1.78 (1.4, 2.26) |
| New moderate or severe aortic regurgitation | 416 (33.4) | 303 (43.5) | 110 (20.5) | 2.99 (2.29, 3.9) |
| Perforation | 231 (17.9) | 171 (23.6) | 58 (10.5) | 2.61 (1.88, 3.67) |
| Abscess | 234 (20) | 170 (25.9) | 63 (12.6) | 2.43 (1.75, 3.39) |
| Fistula | 32 (2.5) | 23 (3.2) | 9 (1.6) | 1.98 (0.88, 4.91) |
| Dehiscence | 61 (7) | 42 (8.5) | 19 (5.1) | 1.72 (0.96, 3.19) |
| LV ejection fraction | 60 (51, 65) | 60 (53, 65) | 60 (50, 65) | *P*=0.72 |
| Severe mitral regurgitation | 327 (25.5) | 227 (31.4) | 99 (18) | 2.08 (1.58, 2.76) |
| Severe aortic regurgitation | 283 (22.1) | 240 (33.2) | 41 (7.5) | 6.13 (4.27, 8.96) |
| Microbiology | | | | |
| *Staphylococcus aureus* | 275 (21.1) | 128 (17.5) | 145 (26.3) | 0.59 (0.45, 0.78) |
| Coagulase-negative *Staphylococcus* species | 111 (8.6) | 62 (8.5) | 49 (8.9) | 0.95 (0.63, 1.44) |
| *Enterococcus* species | 175 (13.5) | 88 (12) | 85 (15.4) | 0.75 (0.54, 1.05) |
| Viridans group streptococcal species | 222 (17.1) | 135 (18.4) | 85 (15.4) | 1.24 (0.91, 1.69) |
| Gram-negative (including HACEK) | 53 (4.1) | 31 (4.2) | 21 (3.8) | 1.12 (0.61, 2.07) |
| Fungal | 21 (1.6) | 13 (1.8) | 8 (1.4) | 1.23 (0.47, 3.44) |
| Complications before surgical decision | | | | |
| New or worsening heart failure | 420 (34.7) | 331 (48.7) | 86 (16.5) | 4.81 (3.62, 6.42) |
| NYHA class III or IV | 272 (24.2) | 211 (34.8) | 58 (11.5) | 4.13 (2.97, 5.79) |
| Abscess, paravalvular leak, perforation, or dehiscence | 280 (23.4) | 215 (32.6) | 64 (12.1) | 3.50 (2.55, 4.84) |

(*Continued*)

**Table 1. Continued**

| | Overall (n=1296)* | Surgery (n=733) | No Surgery (n=552) | OR (95% CI) *P* Value |
|---|---|---|---|---|
| Persistent bacteremia | 106 (9.6) | 68 (10.9) | 38 (8.2) | 1.38 (0.89, 2.15) |
| Stroke | 248 (19.5) | 144 (19.9) | 100 (18.7) | 1.09 (0.81, 1.46) |
| Embolization | 274 (22.6) | 195 (28.4) | 77 (14.8) | 2.28 (1.69, 3.10) |
| STS-IE score, median (25th, 75th percentile) | 22 (15, 34) | 22 (15, 34) | 22 (15, 32) | *P*=0.74 |
| Outcome | | | | |
| In-hospital death | 252 (19.5) | 108 (14.8) | 143 (26) | 0.50 (0.37, 0.66) |
| Six-month mortality | 303 (23.4) | 128 (17.5) | 173 (31.4) | 0.46 (0.35, 0.61) |

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IE, infective endocarditis; LV, left ventricular; NYHA, New York Heart Association; OR, odds ratio; and STS, Society of Thoracic Surgeons.

*Surgical status missing in 11 patients.

a median age of 62 years (25th, 75th percentiles=47, 72) and a substantial rate of medical comorbidities (Table 1). A previous history of IE was noted in 7.8% of patients, and 27.9% of patients had a history of prior cardiac surgery.

## Comparison of Patients Who Underwent Surgery Versus No Surgery for IE

Surgical treatment for IE was performed in 733 patients, which represented 57% of all patients and 76% of patients with a surgical indication. The median age was 57 years (25th, 75th percentiles=43, 69) for patients who underwent surgery compared with 68 years (25th, 75th percentiles=55, 77) for those who did not undergo surgery ($P<0.001$). Patients who underwent surgery were more likely to be male (odds ratio [OR]=1.49 [1.17, 1.90]) and to have cardiac valvular manifestations of IE such as new moderate or severe mitral regurgitation (OR=1.78 [1.40, 2.26]), new moderate or severe aortic regurgitation (OR=2.99 [2.29, 3.90]), valve perforation (OR=2.61 [1.88, 3.67]), or abscess (OR=2.43 [1.75, 3.39]). Complications such as worsening heart failure (OR=4.81 [3.62, 6.42]), New York Heart Association class III or IV heart failure (OR=4.13 [2.97, 5.79]), paravalvular complications (OR 3.50 [2.55, 4.84]), and embolization (OR=2.28 [1.69, 3.10]) were also associated with surgical treatment.

In contrast, patients who did not undergo surgical treatment for IE were more likely to have medical comorbidities such as coronary artery disease (OR for surgery=0.49 [0.36, 0.68]), previous heart failure (OR=0.58 [0.43, 0.80]), diabetes mellitus (OR=0.52 [0.39, 0.69]), and moderate/severe renal disease (OR=0.40 [0.28, 0.58]) and to have infection caused by *Staphyloccus aureus* (OR=0.59 [0.45, 0.78]). In-hospital mortality (143 [26%] versus 108 [14.8%]; OR=0.50 [0.37, 0.66]) and 6-month mortality (173 [31.4%] versus 128 [17.5%]; OR=0.46 [0.35, 0.61]) were higher among patients who did not undergo surgery compared with those who did (Table 1).

## Indications for Surgical Treatment of IE

An indication for cardiac surgery was present in 863 patients (74%); 76% (661/863) of these patients underwent surgery. The median time from admission to surgery was 7 days (25th, 75th percentiles=2, 16). Surgical timing was considered urgent in 63%, elective in 28%, and emergency in 9% of cases. Conditions representing a surgical indication that were more common among patients who underwent surgery were severe valvular regurgitation (OR=7.52 [5.74, 9.88]), vegetation size (OR=6.38 [4.78, 8.58]), heart failure (OR=4.63 [3.36, 6.43]), abscess (OR=3.50 [2.34, 5.35]), embolic event (OR=2.72 [1.94, 3.86]), and microorganism (OR=1.75 [1.15, 2.71]). Persistent bacteremia (OR=1.31 [0.86, 2.02]) was the

**Table 2. Indications and Timing of Cardiac Surgery in Infective Endocarditis**

| | Overall (n=863) | Surgery (n=661) | No Surgery (n=202) | OR (95% CI) *P* Value |
|---|---|---|---|---|
| Heart failure | 303 (35.1) | 258 (35.2) | 58 (10.5) | 4.63 (3.36, 6.43) |
| Embolic event | 209 (24.2) | 167 (22.8) | 54 (9.8) | 2.72 (1.94, 3.86) |
| Persistent bacteremia | 98 (11.4) | 68 (9.3) | 40 (7.2) | 1.31 (0.86, 2.02) |
| Abscess | 159 (18.4) | 137 (18.7) | 34 (6.2) | 3.5 (2.34, 5.35) |
| Severe valvular regurgitation | 517 (59.9) | 460 (62.8) | 101 (18.3) | 7.52 (5.74, 9.88) |
| Vegetation size | 404 (46.8) | 370 (50.5) | 76 (13.8) | 6.38 (4.78, 8.58) |
| Microorganism | 115 (13.3) | 82 (11.2) | 37 (6.7) | 1.75 (1.15, 2.71) |
| Timing of cardiac surgery | | | | |
| Admission to surgical indication, median, d (25th, 75th percentiles) | 1 (0, 5) | 0 (0, 4) | 2.5 (0, 8) | <0.001 |
| Admission to surgical consult, median, d (25th, 75th percentiles) | 1 (0, 6) | 1 (0, 5) | 4 (1, 10) | <0.001 |
| Admission to surgery, median, d (25th, 75th percentiles) | | 7 (2, 16) | | |

CI indicates confidence interval; and OR, odds ratio.

**Table 3. Clinical Characteristics of Patients With Surgical Indications Treated With Surgery Versus No Surgery**

| | Overall (n=863) | Surgery (n=661) | No Surgery (n=202) | OR (95% CI) |
|---|---|---|---|---|
| Age, median, y (25th, 75th percentiles) | 59 (44, 71) | 57 (43, 68) | 63 (52, 77) | *P*<0.001 |
| Male | 606 (70.1) | 468 (71) | 134 (66.7) | 1.23 (0.85, 1.74) |
| First clinical manifestation <1 mo | 525 (61.1) | 390 (59.5) | 132 (66.7) | 0.73 (0.52, 1.04) |
| Prosthetic valve IE | 201 (23.3) | 144 (21.9) | 57 (28.5) | 0.7 (0.48, 1.02) |
| Transfer from other hospital | 503 (58.3) | 414 (63) | 87 (43.3) | 2.23 (1.60, 3.12) |
| Healthcare-associated IE | 165 (20.7) | 102 (16.9) | 62 (32.3) | 0.43 (0.29, 0.63) |
| Medical history | | | | |
| Previous IE | 60 (7) | 47 (7.2) | 13 (6.5) | 1.11 (0.58, 2.29) |
| Coronary artery disease | 124 (14.6) | 82 (12.6) | 41 (21.2) | 0.53 (0.35, 0.83) |
| COPD | 120 (14) | 84 (12.9) | 36 (17.9) | 0.68 (0.44, 1.07) |
| Previous cardiac surgery | 221 (25.5) | 156 (23.7) | 65 (32.2) | 0.65 (0.46, 0.94) |
| Previous coronary bypass surgery | 42 (4.9) | 27 (4.1) | 15 (7.5) | 0.53 (0.26, 1.09) |
| Atrial fibrillation/flutter | 135 (15.7) | 87 (13.3) | 48 (23.9) | 0.49 (0.32, 0.74) |
| Previous heart failure | 141 (16.5) | 89 (13.7) | 52 (26) | 0.45 (0.30, 0.68) |
| Cerebrovascular disease | 84 (9.8) | 59 (9) | 25 (12.4) | 0.70 (0.42, 1.20) |
| History of stroke | 54 (6.2) | 35 (5.3) | 19 (9.4) | 0.54 (0.29, 1.02) |
| Diabetes mellitus | 151 (17.7) | 101 (15.6) | 49 (24.3) | 0.58 (0.39, 0.87) |
| Moderate or severe renal disease | 79 (9.3) | 49 (7.5) | 29 (14.8) | 0.47 (0.28, 0.80) |
| Hemodialysis dependent | 34 (3.9) | 22 (3.3) | 12 (5.9) | 0.55 (0.25, 1.23) |
| Moderate or severe liver disease | 23 (2.7) | 13 (2) | 10 (5) | 0.39 (0.16, 1.01) |
| Hemiplegia or neurological dysfunction affecting ambulation | 43 (5) | 28 (4.3) | 15 (7.4) | 0.56 (0.28, 1.15) |
| Cancer | 96 (11.3) | 66 (10.2) | 29 (14.8) | 0.65 (0.4, 1.08) |
| Immunosuppressive therapy | 38 (4.4) | 27 (4.1) | 10 (5) | 0.82 (0.38, 1.94) |
| HIV | 13 (1.6) | 9 (1.4) | 4 (2.1) | 0.68 (0.19, 3.08) |
| Injection drug use | 42 (4.9) | 32 (4.9) | 10 (5) | 0.97 (0.45, 2.25) |
| Dementia | 8 (0.9) | 6 (0.9) | 2 (1) | 0.93 (0.16, 9.45) |
| Echocardiography | | | | |
| Vegetation present (any site) | 868 (100) | 661 (100) | 202 (100) | 0.6 (0.39, 0.93) |
| New moderate or severe mitral regurgitation | 415 (50.8) | 321 (51.4) | 90 (47.9) | 1.15 (0.82, 1.62) |
| New moderate or severe aortic regurgitation | 348 (42.3) | 295 (47.2) | 51 (26.4) | 2.49 (1.72, 3.63) |
| Perforation | 177 (20.6) | 141 (21.6) | 34 (16.9) | 1.35 (0.88, 2.11) |
| Abscess | 214 (24.9) | 170 (26.1) | 43 (21.4) | 1.3 (0.88, 1.94) |
| Fistula | 29 (3.4) | 21 (3.2) | 8 (4) | 0.81 (0.34, 2.14) |
| Dehiscence | 49 (7.8) | 39 (8) | 10 (7.1) | 1.14 (0.54, 2.64) |
| LV ejection fraction | 60 (51, 65) | 60 (52, 65) | 60 (50, 65) | *P*=0.73 |
| Severe mitral regurgitation | 263 (30.7) | 199 (30.6) | 63 (31.2) | 0.97 (0.68, 1.39) |
| Severe aortic regurgitation | 244 (28.5) | 214 (32.9) | 28 (14) | 3.01 (1.93, 4.81) |
| Microbiology | | | | |
| *Staphylococcus aureus* | 182 (21) | 116 (17.5) | 65 (32.2) | 0.45 (0.31, 0.65) |
| Coagulase-negative *Staphylococcus* species | 81 (9.3) | 60 (9.1) | 21 (10.4) | 0.86 (0.5, 1.53) |
| *Enterococcus* species | 103 (11.9) | 80 (12.1) | 23 (11.4) | 1.07 (0.64, 1.84) |
| Viridans group streptococcal species | 139 (16) | 115 (17.4) | 22 (10.9) | 1.72 (1.05, 2.94) |
| Gram-negative (including HACEK) | 37 (4.3) | 29 (4.4) | 7 (3.5) | 1.28 (0.54, 3.51) |
| Fungal | 17 (2) | 13 (2) | 4 (2) | 0.99 (0.30,4.23) |
| Complications | | | | |
| New or worsening heart failure | 378 (47) | 314 (51.3) | 61 (32.6) | 2.18 (1.52, 3.13) |
| NYHA class III or IV | 248 (34) | 202 (36.8) | 43 (24.4) | 1.8 (1.21, 2.71) |

(*Continued*)

**Table 3. Continued**

| | Overall (n=863) | Surgery (n=661) | No Surgery (n=202) | OR (95% CI) |
|---|---|---|---|---|
| Abscess, paravalvular leak, perforation, or dehiscence | 215 (27.5) | 175 (29.8) | 39 (20.4) | 1.66 (1.10, 2.52) |
| Persistent bacteremia | 87 (10.9) | 61 (10) | 36 (14.4) | 0.66 (0.40, 1.13) |
| Stroke | 186 (21.9) | 129 (19.8) | 55 (28.5) | 0.62 (0.42, 0.92) |
| Embolization | 221 (27.3) | 181 (29.4) | 39 (20.5) | 1.61 (1.08, 2.45) |
| STS-IE score, median (25th, 75th percentiles) | 24 (15,36) | 22 (16,36) | 27 (15, 37) | *P*=0.07 |
| Outcome | | | | |
| In hospital death | 196 (22.7) | 97 (14.7) | 99 (49.3) | 0.18 (0.12, 0.26) |
| Six-month mortality | 228 (26.4) | 117 (17.8) | 111 (55.2) | 0.18 (0.12, 0.25) |

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IE, infective endocarditis; LV, left ventricular; NYHA, New York Heart Association; OR, odds ratio; and STS, Society of Thoracic Surgeons.

only indication that was not significantly associated with surgical management (Table 2).

Among patients with an indication for surgery, clinical differences between patients who underwent surgery versus those receiving medical therapy alone are shown in Table 3. In multivariable modeling (C statistic=0.76), independent variables associated with surgical treatment were severe aortic regurgitation (OR=2.38 [1.30, 4.20]), abscess (OR=1.95 [1.15, 3.29]), embolization before surgical treatment (OR=1.70 [1.01, 2.86]), and transfer from an outside hospital (OR=2.70 [1.75, 4.15]). In contrast, significant predictors of nonsurgical treatment were a history of moderate/severe liver disease (OR=0.16 [0.04, 0.64]), stroke before surgical decision (OR=0.54 [0.32, 0.90]), and *S aureus* etiology (OR=0.50 [0.30, 0.85]). STS score by quintile was not significantly associated with surgical treatment (Table 4). When geographic region was included in the model, these clinical variables remained independently associated with surgery, but region was not.

**Table 4. Multivariable Model* Predicting Surgery Among Patients With Surgical Indications**

| Variable | OR (95% CI) |
|---|---|
| History of COPD | 0.57 (0.31–1.05) |
| History of heart failure | 0.61 (0.35–1.06) |
| History of cancer | 0.54 (0.29–1.02) |
| History of moderate/severe liver disease | 0.16 (0.04–0.64) |
| Transfer from another hospital | 2.70 (1.75–4.15) |
| Severe aortic regurgitation | 2.38 (1.30–4.20) |
| *Staphylococcus aureus* etiology | 0.50 (0.30–0.85) |
| New heart failure, NYHA class III or IV | 1.59 (0.96–2.64) |
| Abscess before surgical decision | 1.95 (1.15–3.29) |
| Stroke before surgical decision | 0.54 (0.32–0.90) |
| Embolization before surgical decision | 1.70 (1.01–2.86) |
| STS quintile 2 | 1.36 (0.66–2.78) |
| STS quintile 3 | 0.59 (0.30–1.18) |
| STS quintile 4 | 0.83 (0.41–1.66) |
| STS quintile 5 | 0.93 (0.46–1.89) |

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; OR, odds ratio; and STS, Society of Thoracic Surgeons.

*C statistic 0.76.

## Reasons for Lack of Surgery

The reasons for lack of surgery were available for 181 patients (90%) who had surgical indications but were treated with medical therapy only (Table 5). The most common reason for lack of surgery was having a poor prognosis regardless of treatment (33.7%). Hemodynamic instability (19.8%), death before surgery (23.3%), stroke (22.7%), and sepsis (21.0%) were other common medical reasons for nonsurgical treatment. Future surgery was planned for 26% of these 181 patients.

Because *S aureus* was associated with medical treatment of IE alone, we examined reasons for nonsurgical management in this subgroup. Sepsis was the single factor associated with nonsurgical management of *S aureus* IE compared with other microbiological causes (Table 5). Furthermore, the median STS-IE score for *S aureus* patients was 32 (25th, 75th percentiles=20, 39) compared with 24 (25th, 75th percentiles=15, 35) in non–*S aureus* patients ($P<0.001$).

## Relationship Between Surgical Indications, Operative Risk, and Outcome

The median STS-IE score among all patients with a surgical indication was 24 (25th, 75th percentiles=15, 36). STS-IE score by quintile was associated with 6-month survival when surgical indications were present, independent of surgical intervention (Figure 2). Furthermore, in patients with an indication for surgery, surgical intervention was found to be associated with higher 6-month survival than no surgery. Patients with higher operative risk who underwent surgery had survival similar to patients with lower operative risk treated without surgery, whereas patients with higher operative risk who did not undergo surgery had very low survival (Figure 3).

# Discussion

Despite advances in the diagnosis and management of IE, the mortality of this disease has remained high and largely unchanged.[1,21–25] Surgery can be life-saving in patients with complications of IE unlikely to be cured or improved by medical therapy alone; however, the interplay between surgical indications, acute clinical status, surgical decision making, and expected outcome is complex and poorly understood. In

**Table 5. Reasons for Lack of Surgery Among Patients With Surgical Indications**

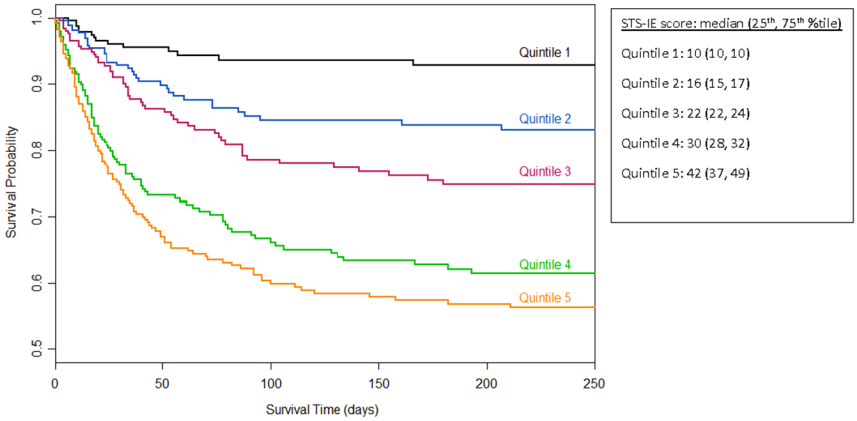
| Reason for Lack of Surgery | Overall (n=181)* | Staphylococcus aureus (n=61) | Non–S aureus (n=120) | OR (95% CI) *P* Value |
|---|---|---|---|---|
| Stroke† | 37 (22.7) | 15 (30) | 22 (19.5) | 1.77 (0.76–4.04) |
| Intracranial hemorrhage | 24 (15.2) | 6 (13.3) | 18 (15.9) | 0.81 (0.25–2.35) |
| Heart failure | 18 (11.7) | 6 (13.3) | 12 (11) | 1.24 (0.36–3.89) |
| Sepsis | 33 (21) | 16 (32.7) | 17 (15.7) | 2.60 (1.08–6.14) |
| Hemodynamic instability | 40 (19.8) | 14 (21.5) | 26 (19) | 1.17 (0.52–2.56) |
| Prognosis poor regardless of treatment | 55 (33.7) | 21 (44.7) | 34 (29.3) | 1.95 (0.91–4.15) |
| Patient refused | 23 (15) | 13 (26.5) | 17 (15.9) | 0.79 (0.24–2.32) |
| Patient died before surgery | 37 (23.3) | 4 (9.5) | 24 (21.8) | 1.29 (0.54–2.99) |
| Resources not available | 8 (5.5) | 12 (26.1) | 4 (3.8) | 2.63 (0.46–14.78) |
| Surgeon declined to operate | 40 (25.8) | 10 (24.4) | 28 (25.7) | 1.02 (0.42–2.37) |
| Other | 46 (32.6) | 12 (25.5) | 36 (36) | 0.57 (0.22–1.38) |
| Future surgery anticipated or scheduled | 39 (26) | 12 (25.5) | 27 (26.2) | 0.97 (0.40–2.20) |
| STS-IE score, median (25th, 75th percentiles) | 27 (15, 37) | 32 (20, 39) | 24 (15, 35) | *P*=0.01 |

CI indicates confidence interval; IE, infective endocarditis; OR, odds ratio; and STS, Society of Thoracic Surgeons.
*Data on "reasons for lack of surgery" available in 90% (181/202) of patients.
†17/37 patients (46%) with hemorrhagic stroke.

this large, contemporary, prospective observational study, we found that surgery is appropriately performed in the majority of patients with IE and surgical indications, yet one quarter of patients with these indications are treated with medical therapy alone during the initial hospitalization. Host factors related to poor prognosis and *S aureus* etiology were strongly related to lack of surgery in these cases. Although operative risk was generally high in these patients, it was not independently associated with surgical intervention but did relate to 6-month survival.

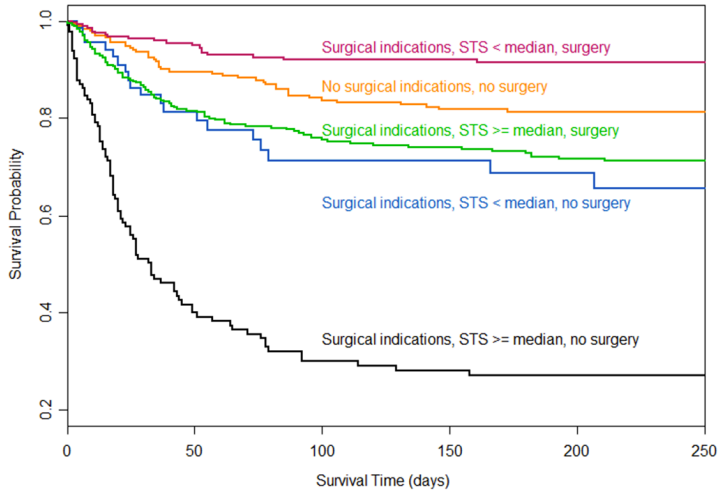
Few prospective studies have evaluated clinical decision making for surgery in IE.[26] Other studies have shown that appropriate, guideline-based use of surgery in IE is associated with lower mortality compared with historical control groups but did not report specific indications or operative risk.[27,28] Our results confirm that guideline-based recommendations for surgery in IE[11,13] (namely, in the setting of severe valvular regurgitation, abscess, and embolic event) were significantly and appropriately associated with surgical intervention. Furthermore, surgery for these indications was associated with higher 6-month survival compared with medical treatment alone.

On the other hand, 24% of patients with surgical indications did not undergo intervention. Although persistent bacteremia and *S aureus* etiology are guideline-based surgical indications, they were associated with a lower likelihood of surgery. This is an unexpected finding because surgery is recommended for IE caused by highly resistant or difficult-to-treat organisms such as *S aureus*,[11,13] and an observational study found lower in-hospital mortality in patients with *S aureus* IE treated with surgery.[7] *S aureus* has been strongly associated with healthcare-associated infection, particularly hemodialysis.[29]




| STS-IE Quintile | Day 0 - 49 | | Day 50 - 99 | | Day 100 - 149 | | Day 150 - 199 | | Day 200 - 250 | | Day >250 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # at risk | # died | # at risk | # died | # at risk | # died | # at risk | # died | # at risk | # died | # at risk | # died |
| 1 | 131 | 5 | 101 | 2 | 89 | 0 | 81 | 1 | 67 | 0 | 30 | 0 |
| 2 | 154 | 15 | 110 | 6 | 93 | 0 | 83 | 1 | 68 | 1 | 30 | 1 |
| 3 | 132 | 17 | 99 | 9 | 84 | 1 | 70 | 2 | 54 | 0 | 24 | 0 |
| 4 | 160 | 50 | 96 | 8 | 78 | 2 | 70 | 3 | 60 | 0 | 29 | 2 |
| 5 | 210 | 78 | 114 | 14 | 92 | 4 | 80 | 2 | 68 | 1 | 32 | 1 |

**Figure 2.** Survival by Society of Thoracic Surgeons (STS)–infective endocarditis (IE) quintile among IE patients with surgical indications.




| Surgery Subgroup | Day 0 - 49 | | Day 50 - 99 | | Day 100- 149 | | Day 150 - 199 | | Day 200 - 250 | | Day >250 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | # at risk | # died | # at risk | # died | # at risk | # died | # at risk | # died | # at risk | # died | # at risk | # died |
| Indication/ STS<22/ Surgery | 246 | 13 | 186 | 6 | 164 | 0 | 148 | 1 | 123 | 0 | 55 | 0 |
| No indication/ No surgery | 266 | 28 | 200 | 12 | 178 | 5 | 157 | 1 | 134 | 0 | 62 | 0 |
| Indication/ STS≥22/ Surgery | 346 | 65 | 244 | 17 | 208 | 5 | 183 | 6 | 152 | 1 | 70 | 1 |
| Indication/ STS<22/ No surgery | 62 | 12 | 42 | 5 | 32 | 0 | 28 | 1 | 22 | 1 | 10 | 0 |
| Indication/ STS≥22/ No surgery | 126 | 75 | 44 | 11 | 30 | 2 | 24 | 1 | 18 | 0 | 10 | 2 |

**Figure 3.** Survival according to presence of surgical indication, Society of Thoracic Surgeons (STS)–infective endocarditis (IE) score, and surgical treatment.

Such host-related factors may influence both operative risk, as evidenced by higher STS-IE score, and longer-term outcome. Furthermore, sepsis, which was more commonly cited as a reason for lack of surgery in *S aureus* IE, may result in hemodynamic or end-organ complications that increase surgical risk. Taken together, our results suggest that a combination of patient-related factors and clinical complications leads to a lower rate of surgery among patients with *S aureus* IE.

Stroke before surgical decision was also inversely associated with surgery during the index hospitalization, likely reflecting the uncertain timing and safety of surgery in patients with IE complicated by stroke.[30–33] The majority of stroke in IE occurs at the time of presentation,[34] before or soon after the initiation of antibiotic therapy.[35] Nearly one half of strokes in patients who did not have surgery despite an indication were hemorrhagic. Although ischemic stroke without major neurological deficit is not a contraindication to cardiac surgery in IE, delay in surgery has been recommended for patients with major ischemic or any hemorrhagic stroke because of concerns for further deterioration.[36]

The risk of operative mortality has been estimated and validated in large, observational registries. Recently, scoring systems to determine operative risk have been developed specifically for patients with IE[15,37] and found to have better discrimination than more general risk scores.[38] The median STS-IE score in our study population was high because of adverse patient characteristics compared with the STS database of patients who all underwent surgery. Importantly, the patients in our study had surgery performed during the active stage of IE, and a high proportion of surgeries were deemed urgent in priority. These variables were strongly associated with increased operative mortality in STS-IE.[15] In addition, although STS-IE score was previously validated for predicting operative mortality,[15] it was also found to be strongly associated with 6-month mortality in our study. It is likely that many of the STS-IE score variables influence survival beyond the operative period. Finally, surgery was associated with a reduction in 6-month mortality, even among patients with higher operative risk.

This study has several limitations. The multicenter ICE collaboration is largely composed of tertiary care centers that specialize in IE, and therefore the data are subject to referral bias. Although the inclusion of multiple centers worldwide contributes to the generalizability of the results, this study does not address regional differences in the presentation and surgical management of IE. The observational nature of this study and treatment selection bias limit any causative determination between surgical treatment and outcome among patients with different STS scores. The presence of surgical indications was determined by site investigators rather than central adjudication. However, the investigators involved in this study are highly experienced in the research and management of IE, and the definitions of these indications and their timing were prespecified in the study protocol.

In conclusion, nearly one quarter of patients with indications for surgery in IE do not undergo surgery during the initial hospitalization because of sepsis or other poor prognostic factors. Operative risk assessment by STS-IE score provides prognostic information for survival after the operative period, but predicted survival is improved when surgery is performed for standard indications. In patients with *S aureus* IE, which is the most common cause of IE in the United States and a recommended indication for surgery in recent guidelines,[13] predicted operative risk is even higher, and surgery is less often

performed. Because *S aureus* is the most common cause of IE in the current era, a better understanding of the role and timing of surgery in these patients is needed.

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## CLINICAL PERSPECTIVE

Infective endocarditis (IE) is a potentially life-threatening disease that is treated with antimicrobial therapy alone or in combination with surgery. Surgical management of IE can optimize source control by removal of infected tissue, reduce morbidity from embolic events, and reduce mortality in the appropriate clinical context. Nevertheless, surgical management of IE is not indicated in all cases of IE. Consensus guidelines outline specific conditions for which surgery is recommended, but clinical application of these recommendations is unclear. In the present study, we found that an indication for surgery was present in the majority (74%) of IE patients; however, surgical therapy was performed for only 76% of patients with a surgical indication. Among patients with a surgical indication, surgical treatment was independently associated with the presence of severe aortic regurgitation, abscess, and embolization before surgical treatment, confirming that clinical practice is consistent with guideline-based recommendations for surgery. On the other hand, factors associated with nonsurgical treatment were a history of moderate/severe liver disease, stroke before surgical decision, and *Staphyloccus aureus* etiology. Finally, operative risk assessment by the Society of Thoracic Surgeons IE score in this cohort provided prognostic information for survival 6 months beyond the operative period. Thus, in a large, multicenter, multinational cohort, we found that surgical decision making is largely consistent with the established guidelines and that the Society of Thoracic Surgeons IE score can provide prognostic information in IE beyond the operative period.

## SUPPLEMENTAL MATERIAL

### Supplemental Methods

The Society of Thoracic Surgeons (STS)-IE score ranges from 0 – 110 points and consists of the following variables: prior coronary artery bypass graft, urgent or emergency status (without cardiogenic shock); urgent, emergency, salvage, or cardiogenic shock status; pre-operative intra-aortic balloon pump or inotropes; multiple valve procedure; prior valve surgery; insulin-dependent diabetes mellitus; non-insulin-dependent diabetes mellitus; hypertension; chronic lung disease; active endocarditis; renal failure or Cr >2.0; and arrhythmia. According to this model, a patient with a pre-operative score of 35 would have an operative risk of at least 10% mortality.[1]

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# Association Between Surgical Indications, Operative Risk, and Clinical Outcome in Infective Endocarditis: A Prospective Study From the International Collaboration on Endocarditis

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