# Infective endocarditis and solid organ transplantation: Only worse outcomes during initial transplantation hospitalization

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**Background** The epidemiology, and outcome of infective endocarditis (IE) among solid organ transplant (SOT) recipients is unknown.

**Methods** We used data from the 2013-2018 Nationwide Readmissions Database (NRD). IE- and SOT-associated hospitalizations were identified using diagnosis and procedure codes. Outcomes included inpatient mortality, length of stay, and inpatient costs. Adjusted analyses were performed using weighted regression models.

**Results** A total of 99,052 IE-associated hospitalizations, corresponding to a weighted national estimate of 193,164, were included for analysis. Of these, 794 (weighted $n = 1{,}574$) were associated with transplant history (SOT-IE). Mortality was not significantly different between SOT-IE and non-SOT-IE (17.2% vs. 15.8%, adjusted relative risk [aRR]: 0.86, 95% confidence interval [CI] [0.71, 1.03]), and fewer SOT-IE patients underwent valve repair or replacement than non-SOT-IE (12.5% vs. 16.2%, aRR 0.82, 95% CI [0.71, 0.95]). We then compared outcomes of patients diagnosed with IE during their index transplant hospitalization (index-SOT-IE) to patients without IE during their transplant hospitalization (index-SOT). Index-SOT-IE occurred most frequently among heart transplant recipients (45.1%), and was associated with greater mortality (27.1% vs. 2.3%, aRR 6.07, 95% CI [3.32, 11.11]).

**Conclusion** Dual diagnosis of SOT and IE was associated with worse outcomes among SOT recipients during index hospitalization, but not overall among patients with IE. (Am Heart J 2021;240:63–72.)

Infective endocarditis (IE) is a rare but devastating disease. Despite advances in the diagnosis and treatment of IE, mortality remains high. In addition, rates of IE are increasing.[1,2] The rise in IE in the past decade may be due in part to the opioid epidemic[3], as well as the emergence of new risk factors, including increased healthcare contact and immunosuppression.[2]

With over 30,000 solid organ transplants (SOT) performed annually in the United States alone, there is a growing population of immunocompromised patients at increased risk for infection. The prevalence and impact of IE in the SOT population (SOT-IE), however, is unknown. The existing literature is limited to small case series and single center retrospective studies.[4,5,6] The present study uses a large national administrative database to further address these issues. We present the largest study to date investigating the prevalence of IE in SOT recipients. We compare the risk factors, inpatient cost, and mortality of SOT-IE as compared to non-SOT-IE patients in the US. We also investigate the impact of IE on the outcome of SOT recipients during index transplant hospitalization.

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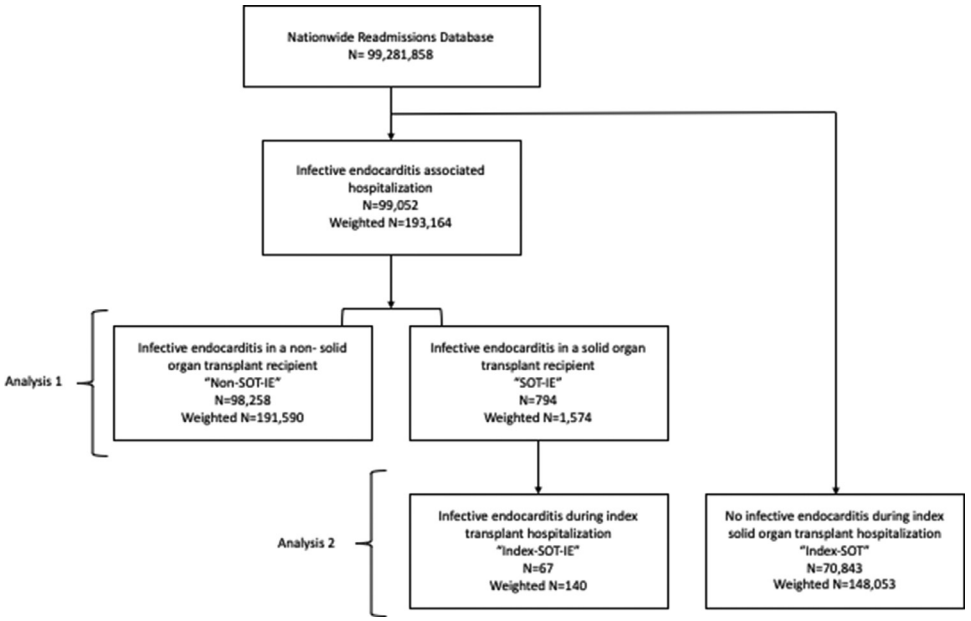
## Methods

### Study design, data source and study population

This retrospective cohort study used data from the 2013-2018 Nationwide Readmissions Database (NRD), Healthcare Cost and Utilization Project, United States Agency for Healthcare Research and Quality. The NRD is an all-payer administrative dataset containing most acute care and short stay hospitalizations from participating

**Figure 1**




Study design: Analysis 1 compares solid organ transplant admissions with endocarditis (SOT-IE) to non-solid organ transplant admissions with endocarditis (non-SOT-IE). Analysis 2 compares index solid organ transplantation admissions complicated by endocarditis (index-SOT-IE) to those index solid organ transplantation admissions that are not complicated by endocarditis (index-SOT).

states (by 2018, 28 states, comprising 60% of the US population and 58.2% of all hospitalizations). Data included in the NRD consists of basic demographic data, diagnosis and procedure codes, inpatient charges, primary payer, type of hospital, length of stay and discharge disposition. The NRD allows for identification of subsequent hospitalizations for a patient within the same calendar year (e.g., patients discharged in 2013 can be followed for the remainder of 2013) and state within the United States. Same-day inter-hospital transfers are incorporated as a single record (i.e., are not considered a readmission). The database provides weights intended to allow for estimation of national outcomes, and prior studies have utilized the NRD to analyze national epidemiological trends in IE.[3, 7] Using the NRD, we performed two analyses: 1) a comparison of SOT-IE to non-SOT-IE, and 2) a comparison of Index-SOT-IE to Index-SOT **(Figure 1).**

## SOT-IE vs. non-SOT-IE: analysis 1

For the first analysis, patients were eligible for inclusion if they were diagnosed with IE based on the use of Internal Classifications of Diseases 9th edition (ICD-9): 421.*, 112.81 and Internal Classification of Diseases 10th Edition, Clinical Modification (ICD-10-CM): I33* and B37.6. Patients were classified into one of two groups: SOT-IE or non-SOT-IE. Patients with an ICD-9 or ICD-10 diagnosis or procedure code indicating a history of SOT or receipt of SOT during the captured hospitalization were considered as SOT-IE, while all remaining patients with IE were classified as non-SOT-IE (Supplementary Table I). Causative pathogen was determined by presence of an organism specific infection as indicated by ICD-9 and ICD-10 code (Supplementary Table II). Medical comorbidities were determined using the Elixhauser comorbidity index.[3,8]

## IE during index transplant hospitalization: analysis 2

For the second analysis, patients were eligible for inclusion if they were hospitalized and received organ transplantation procedure. Patients were then classified into one of two groups: patients diagnosed with IE (index-SOT-IE) and those who were not diagnosed with IE (index-SOT), based on ICD-9 and ICD-10 diagnosis codes.

## Study outcomes

The primary outcome of interest for both analyses was in-hospital mortality. In-hospital mortality was identified during the patient's first hospitalization meeting the above criteria (the "index hospitalization") and any hospital stays within 60 days of discharge from the index hospitalization. To allow sufficient time for the 60-day follow up, only patients discharged between January and October of each calendar year were included in the study. Secondary outcomes of interest included

intubation/ventilation procedures, extracorporeal membrane oxygenation (ECMO) deployment, occurrence of a thromboembolic event (all identified from ICD-10 diagnosis and procedure codes), total inpatient days, and total inpatient costs (as estimated by total inpatient charges, adjusted by cost-to-charge ratios).

### Statistical analysis

Data were summarized using mean and standard deviation for continuous data and percentages for categorical data. Weighted linear regressions and chi-squared tests were done as appropriate for bivariate tests of association. Multivariate analyses were performed using weighted logistic, Poisson, and gamma / log-link regression models for binary, length of stay, and cost outcomes as appropriate. For the second analysis (outcomes of transplant hospitalizations, evaluating effect of endocarditis diagnosis, we repeated the analysis in subgroups defined by whether the patient had a cardiac transplant or a non-cardiac transplant, since that was felt to be an important potential effect modifier. Because there were only a very small proportion of data missing (<1% for Zip code median household income and primary payer) for most variables, we performed modal value imputation. An exception was made for IE etiologic organism, which was commonly unknown; we instead modeled this variable treating unknown organism as a separate category. Because odds ratios can be difficult to interpret, we converted the adjusted odds ratios from logistic regression to relative risks.[9] A two-sided alpha value of 0.05 was pre-specified to be statistically significant. Data were analyzed in Stata Statistical Software, Version 16.1 (Statacorp, College Station, TX). Given this was a retrospective analysis using an existing limited dataset, it was determined to be exempt from review by the Duke Health Institutional Review Board. Work contained in this manuscript were made possible by the following grants from the National Institutes of Health (K24-AI093969 [VGF]; NIAID (T32-AI100851 [EME]); and TL1-TR002555 [JJF]). Data acquisition was also supported by funding from the Foundation for Women and Girls with Blood Disorders to JJF. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

## Results

### Clinical characteristics of the SOT-IE and non-SOT-IE populations: Analysis 1

Between January-October from 2013-2018, there were a total of 99,052 hospitalizations associated with IE, corresponding to a national weighted estimate of 193,164 admissions. Of these, 794 (weighted $n$ = 1,574) were associated with history of SOT. SOT-IE admissions had higher rates of renal failure, liver disease, and diabetes with chronic complications than non-SOT-IE admissions (79.7% vs. 31.2%, 22.0% vs. 11.3%, and 31.2% vs. 16.0%, $P < 0.001$ respectively) **[Table I]**. SOT-IE admissions had lower rates of comorbid drug abuse than non-SOT-IE admissions (3.4% vs. 21.3%, $P < 0.001$). Among the SOT-IE population, the most common transplanted organ (allowing for multiple organs) was kidney (72.3%), followed by liver (17.0%) and then pancreas (8.0%) **[Figure 2A]**.

### Microbial etiology of IE: analysis 1

The microbial etiology of IE in SOT and non-SOT populations is shown in **Figure 3**. While the distribution of causative organisms differed significantly between the two groups ($P < 0.001$), *Staphylococcus aureus* was the leading identifiable cause overall. Among the *S. aureus* IE admissions, methicillin resistant *S. aureus* (MRSA) accounted for 40.2% of the *S. aureus* SOT-IE and 42.9% of the *S. aureus* non-SOT-IE admissions. Fungal IE was rare in both patient populations (SOT-IE: 1.2% vs. non-SOT-IE: 0.8%). A total of 18.6% of cases had an unknown microbial etiology of IE owing to absent ICD coding.

### Outcomes of SOT-IE compared to the non-SOT-IE Population: Analysis 1

Unadjusted outcomes for analysis 1 are described in **Table III.** SOT-IE admissions had lower rates of thromboembolic events (19.2% vs. 32.5%, $P < 0.001$) and lower rate of valve repair or replacement (9.2% vs. 13.2%, $P < 0.001$) than non-SOT-IE admissions. Sixty-day mortality, length of stay and total cost of hospitalization were not significantly different between SOT-IE and non-SOT-IE (17.2% vs. 15.8%, $P = 0.33$; 21.6 days vs. 21.3, $P = 0.73$; and $65,900 vs. $58,400, $P = 0.06$). Outcomes were then adjusted for age, sex, differences in medical comorbidities (using the Elixhauser comorbidity criteria), primary insurer, Zip Code household income quartile, hospital bed size and teaching status, organism causing IE and calendar year. Compared to non-SOT-IE, SOT-IE admissions had a significantly lower adjusted relative risk (aRR) of valve replacement or repair (aRR 0.82, 95% CI [0.71, 0.95]) (**Figure 4A**).

### Comparison of index-SOT-IE to index-SOT: analysis 2

Next, we investigated the impact of IE during initial solid organ transplant procedure hospitalization (index hospitalization). A weighted total of 410 index-SOT-IE and 148,035 index-SOT patients were included for this analysis, based on unweighted sample sizes of 67 and 70,843, respectively. Heart transplants accounted for 45.1% of all index-SOT-IE cases, despite representing only 9.8% of all weighted solid organ transplant procedure admissions in the dataset **(Figure 2B)**. The most common identifiable cause of IE among the index-SOT-IE was MSSA (17.4%) **(Table II)**. Sixty-day mortality was significantly higher in index-SOT-IE patients

**Table I.** Clinical Characteristics of Analysis 1: SOT-IE vs. Non-SOT-IE

| | Overall (Weighted $n$ = 193,164) | SOT-IE (Weighted $n$ = 1,574) | Non-SOT-IE (Weighted N = 191,590) | $P$-value |
|---|---|---|---|---|
| Mean (SD) or N (%) | | | | |
| *Demographics* | | | | |
| Age | 57.5 (19.1) | 58.2 (13.7) | 57.5 (19.1) | 0.23 |
| Female sex | 78,511 (40.6) | 625 (39.7) | 77,886 (40.7) | 0.63 |
| *Primary payor* | | | | <0.001 |
| Medicare | 96,144 (49.9) | 1,196 (76.1) | 94,948 (49.6) | |
| Medicaid | 40,506 (21.0) | 105 (6.7) | 40,401 (21.1) | |
| Private insurance | 36,851 (19.1) | 229 (14.6) | 36,622 (19.1) | |
| Self-pay | * (6.0) | * (0.5) | 11,630 (6.1) | |
| No charge | * (1.0) | * (0.0) | 1,997 (1.0) | |
| Other | 5,728 (3.0) | 33 (2.1) | 5,695 (3.0) | |
| *Median Zip Code household income quartile* | | | | 0.15 |
| 1 (lowest) | 58,576 (30.8) | 414 (26.7) | 58,162 (30.8) | |
| 2 | 51,189 (26.9) | 447 (28.8) | 50,742 (26.9) | |
| 3 | 44,551 (23.4) | 394 (25.4) | 44,158 (23.4) | |
| 4 (highest) | 35,932 (18.9) | 295 (19.0) | 35,637 (18.9) | |
| *Comorbidities* | | | | |
| HIV/AIDS | * (1.2) | * (0.5) | 2,389 (1.2) | 0.06 |
| Renal failure | 61,031 (31.6) | 1,255 (79.7) | 59,777 (31.2) | <0.001 |
| Congestive heart failure | 41,984 (21.7) | 383 (24.3) | 41,601 (21.7) | 0.10 |
| Valvular disease | 46,329 (24.0) | 400 (25.4) | 45,928 (24.0) | 0.37 |
| Peripheral vascular disease | 39,559 (20.5) | 288 (18.3) | 39,271 (20.5) | 0.17 |
| Chronic pulmonary disease | 40,234 (20.8) | 202 (12.8) | 40,032 (20.9) | <0.001 |
| Diabetes without chronic complications | 25,263 (13.1) | 214 (13.6) | 25,049 (13.1) | 0.67 |
| Diabetes with chronic complications | 31,154 (16.1) | 491 (31.2) | 30,663 (16.0) | <0.001 |
| Hypothyroidism | 19,574 (10.1) | 203 (12.9) | 19,371 (10.1) | 0.01 |
| Liver disease | 21,961 (11.4) | 346 (22.0) | 21,616 (11.3) | <0.001 |
| Lymphoma | 2,358 (1.2) | 17 (1.1) | 2,341 (1.2) | 0.77 |
| Metastatic cancer | 3,883 (2.0) | 14 (0.9) | 3,868 (2.0) | 0.01 |
| Solid tumor w/out metastasis | 4,255 (2.2) | 23 (1.5) | 4,232 (2.2) | 0.24 |
| Rheumatoid arthritis/collagen vascular disease | 7,392 (3.8) | 49 (3.1) | 7,344 (3.8) | 0.30 |
| Coagulopathy | 49,436 (25.6) | 403 (25.6) | 49,033 (25.6) | 0.98 |
| Obesity | 27,050 (14.0) | 177 (11.2) | 26,873 (14.0) | 0.05 |
| Alcohol abuse | 11,559 (6.0) | 28 (1.8) | 11,531 (6.0) | <0.001 |
| Drug abuse | 40,883 (21.2) | 53 (3.4) | 40,830 (21.3) | <0.001 |
| Depression | 24,290 (12.6) | 202 (12.9) | 24,087 (12.6) | 0.84 |
| Hypertension | 100,375 (52.0) | 1,127 (71.6) | 99,248 (51.8) | <0.001 |

P-values by weighted linear regression for continuous variables and weighted chi$^2$ test for binary/categorical variables

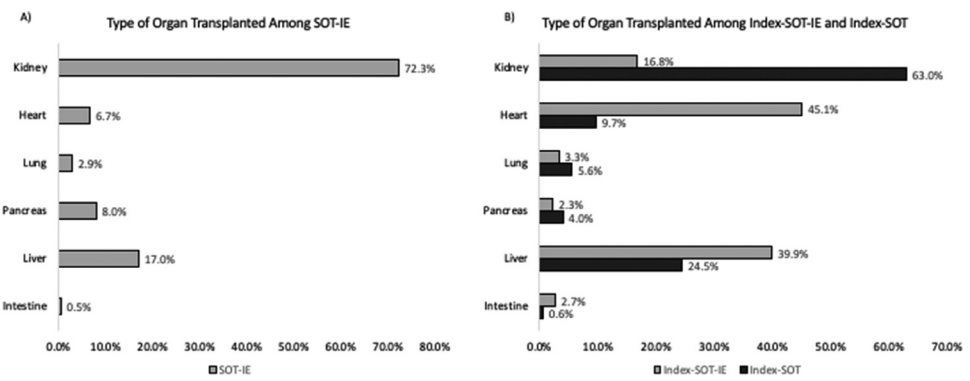
SOT, solid organ transplant; IE, infective endocarditis; SD, standard deviation; N, number; HIV/AIDS, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome.

Missing values in Primary Payor (157 observations) and ZIP Code income quartile (1567 observations)

* N < 10; exact number suppressed to comply with restrictions of data vendor.

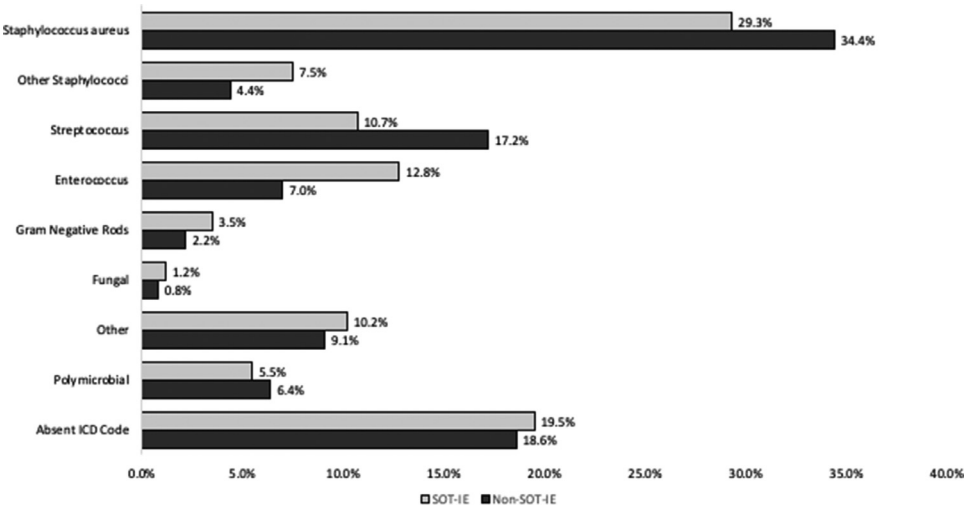
as compared to index-SOT patients (27.1% vs. 2.3%, $P$ <0.001, respectively) (Table IV). Additionally, rates of the following complications occurred more frequently among index-SOT-IE than index-SOT: mechanical ventilation (53.1% vs. 12.2%, $P$<0.001), ECMO deployment (12.7% vs. 2.2%, $P$ <0.001), thromboembolic event (44.6% vs. 7.4%, $P$ <0.001) and valve procedure (8.1% vs. 0.3%, $P$ <0.001). Index-SOT-IE also exhibited significantly longer mean lengths of stay (mean [SD]: 91.8 days [62.8] vs. 19.0 [27.7], $P$ <0.001), and higher total inpatient costs ($516,600 [354.2] vs. $119,600 [132.7], $P$ <0.001) than index-SOT **(Figure 4B).** After adjustment for age, gender, medical comorbidities (using the Elixhauser comorbidity criteria), primary insurer, Zip code income quartile, hospital bed size and teaching status and type of transplant, index-SOT-IE remained significantly associated with 60-day mortality (aRR 6.07, 95% CI [3.32, 11.11]), ventilation (aRR 2.94, 95% CI [1.96, 4.41]), thromboembolic event (aRR 9.39, 95% CI [3.25, 27.16]), valve procedure (aRR 4.00, 95% CI [2.51, 6.37]), longer hospital length of stay (aRR 2.21, 95% CI [1.83, 2.67]), and higher inpatient cost (aRR 2.39, 95% CI [2.00, 2.87]). Effects were overall similar when the analysis was repeated in heart transplant recipients and non-heart

**Figure 2**




A-B. Type of organ transplanted A) Among SOT-IE and B) Among Index-SOT-IE and Index-SOT SOT, solid organ transplant; IE, infective endocarditis.

**Figure 3**




Microbial etiology of IE among SOT and non-SOT recipients. IE, infective endocarditis; SOT, solid organ transplant.

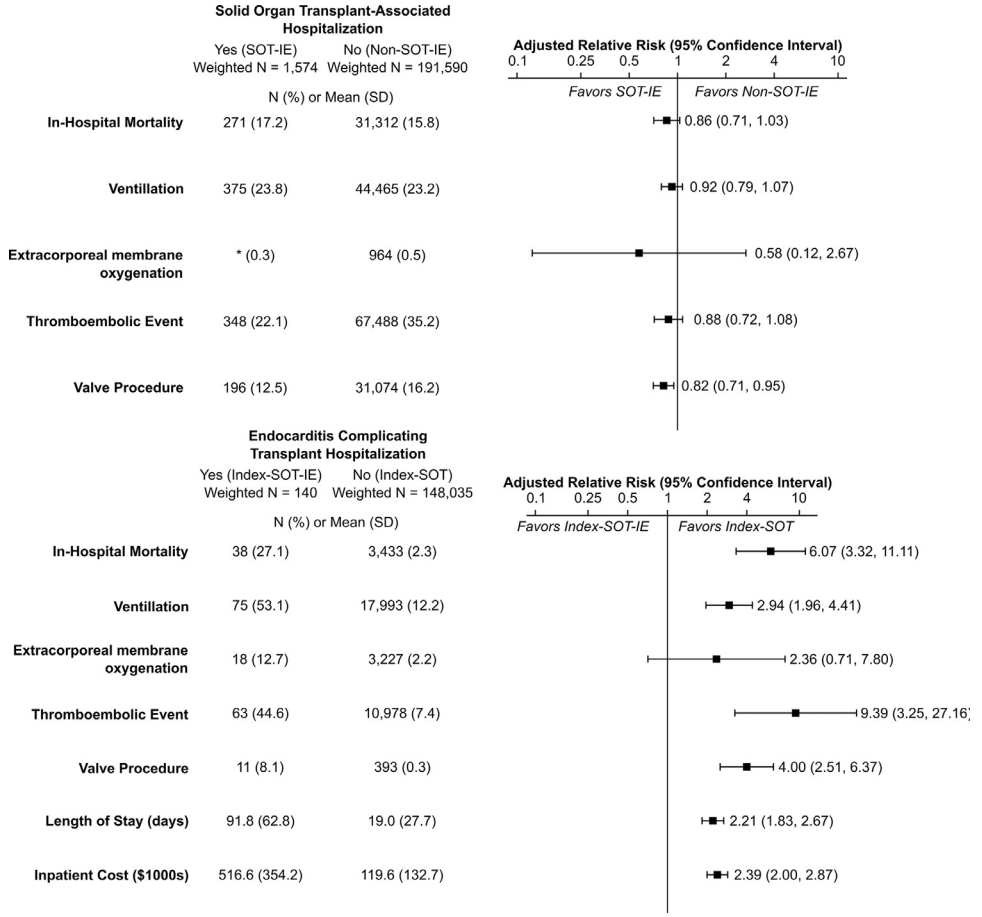
transplant recipients separately (e.g., adjusted relative risk for mortality was 6.49, 95% CI [3.34, 12.60] for heart transplants and 4.27, 95% CI [1.44, 12.72] for non-heart transplants)(Supplementary Table III).

## Discussion

Little is known about the impact of IE in SOT recipients. In the current study, we used a large nationally representative claims database to evaluate the impact and characteristics of IE in patients with SOT. We found that SOT recipients who develop IE do not experience worse outcomes than those who have not received SOT. Next, we found that development of IE during the index hospitalization for solid organ transplantation occurred primarily among heart transplant recipients and significantly increased both mortality and costs as compared to patients who underwent SOT without developing IE.

Kidney transplant recipients accounted for just over 70% of all solid organ transplant patients who developed IE. This finding is likely reflective of the high prevalence of surviving kidney transplant recipients as compared to recipients of other solid organs. Between 2013-2018 there were over 111,000 kidney transplants performed in the United States, accounting for nearly 60%

**Figure 4**




A-B. Adjusted outcomes for IE A) among SOT-IE and non-SOT-IE recipients and B) among Index-SOT-IE. Outcomes were adjusted for age, gender, primary insurer, Zip Code household income quartile, hospital bed size and teaching status, Elixhauser comorbidity criteria, organism causing IE and calendar year; for analysis 1 (panel A), organism causing IE was additionally included in the adjustment, while for analysis 2 (panel B) transplanted organ was additionally included. IE, infective endocarditis; SOT, solid organ transplant; N, number; SD, standard deviation; ECMO, extracorporeal membrane oxygenation.

of all annual SOTs. [10] Additionally, many kidney transplant recipients undergo hemodialysis prior to receiving a kidney transplant. Retained permanent hemodialysis access, such as arterio-venous grafts, may place kidney transplant recipients at increased risk for bacteremia and subsequent complications from bacteremia, including IE.[11] Lastly, calcification of heart valves is common in end stage kidney disease, which in turn leads to increased susceptibility for IE.[12,13]

Importantly, patients with SOT-IE did not experience significantly worse outcomes than patients with non-SOT-IE. We propose a few possible explanations for this key finding. First, it should be noted that there are many factors that determine patients who are 'healthy enough' to undergo transplantation, some of which may not have been captured in our analysis. Despite adjustment, there may be residual confounding factors that we were unable to collect from the NRD that determine patients who are healthy enough to undergo transplant. Second, SOT recipients are in frequent contact with the healthcare system, possibly leading to quicker symptom recognition, diagnosis and treatment of a life-threatening infection. Third, infectious disease consultants are frequently involved in the care of hospitalized transplant patients with infectious complications, a practice which has been shown to decrease mortality and reduce rehospitalization rates.[14] We suspect that early transplant infectious disease consultation may in part account for our findings.

The development of IE during the index SOT hospitalization, however, was associated with significantly worse outcomes including higher mortality, longer duration of stay and higher hospitalization costs. Immunosuppres-

**Table II.** Clinical Characteristics of Analysis 2: Index-SOT-IE vs. Index-SOT

| | Overall (Weighted N = 148,175) | Index-SOT-IE (Weighted *n* = 140) | Index-SOT (Weighted *n* = 148,035) | *P*-value |
|---|---|---|---|---|
| Mean (SD) or N (%) | | | | |
| *Demographics* | | | | |
| Age | 49.9 (15.6) | 46.1 (19.8) | 49.9 (15.6) | 0.33 |
| Female sex | 56,032 (37.8) | 51 (36.3) | 55,981 (37.8) | 0.82 |
| *Primary payor* | | | | 0.16 |
| Medicare | 74,783 (50.8) | 50 (35.3) | 74,734 (50.8) | |
| Medicaid | 12,538 (8.5) | 33 (23.7) | 12,504 (8.5) | |
| Private insurance | 54,764 (37.2) | 49 (34.8) | 54,715 (37.2) | |
| Self-pay | * (0.8) | * (1.5) | 1,174 (0.8) | |
| No charge | * (0.1) | * (0.0) | 130 (0.1) | |
| Other | * (2.6) | * (4.8) | 3,867 (2.6) | |
| *Median ZIP Code household income quartile* | | | | 0.51 |
| 1 (lowest) | 35,408 (24.2) | 22 (16.0) | 35,386 (24.2) | |
| 2 | 38,816 (26.6) | 38 (27.6) | 38,778 (26.6) | |
| 3 | 38,112 (26.1) | 37 (27.1) | 38,074 (26.1) | |
| 4 (highest) | 33,799 (23.1) | 41 (29.4) | 33,758 (23.1) | |
| *Comorbidities* | | | | |
| HIV/AIDS | * (0.6) | * (0.0) | 899 (0.6) | 0.65 |
| Renal failure | 104,471 (70.5) | 57 (40.7) | 104,414 (70.5) | <0.001 |
| Congestive heart failure | 8,142 (5.5) | 12 (8.5) | 8,130 (5.5) | 0.36 |
| Valvular disease | * (4.1) | * (3.1) | 6,086 (4.1) | 0.62 |
| Peripheral vascular disease | 7,662 (5.2) | 13 (9.2) | 7,649 (5.2) | 0.11 |
| Chronic pulmonary disease | * (10.0) | * (5.9) | 14,762 (10.0) | 0.23 |
| Diabetes without chronic complications | 13,223 (8.9) | 11 (7.5) | 13,213 (8.9) | 0.69 |
| Diabetes with chronic complications | 32,484 (21.9) | 15 (11.0) | 32,469 (21.9) | 0.06 |
| Hypothyroidism | * (10.0) | * (6.7) | 14,844 (10.0) | 0.32 |
| Liver disease | 35,692 (24.1) | 42 (30.0) | 35,650 (24.1) | 0.32 |
| Lymphoma | * (0.3) | * (0.0) | 422 (0.3) | 0.73 |
| Metastatic cancer | * (0.2) | * (0.0) | 250 (0.2) | 0.80 |
| Solid tumor w/out metastasis | * (4.7) | * (0.0) | 6,918 (4.7) | 0.17 |
| Rheumatoid arthritis/collagen vascular disease | * (3.6) | * (1.4) | 5,264 (3.6) | 0.33 |
| Coagulopathy | 40,624 (27.4) | 67 (47.7) | 40,557 (27.4) | 0.003 |
| Obesity | 21,906 (14.8) | 10 (7.0) | 21,896 (14.8) | 0.05 |
| Alcohol abuse | 6,376 (4.3) | 10 (7.0) | 6,366 (4.3) | 0.42 |
| Drug abuse | * (1.5) | * (1.0) | 2,289 (1.5) | 0.64 |
| Depression | * (9.0) | * (5.8) | 13,359 (9.0) | 0.31 |
| Hypertension | 34,350 (23.2) | 39 (27.7) | 34,311 (23.2) | 0.52 |
| Microbial etiology of IE | | | | . (.) |
| MRSA | * (4.0) | * (4.0) | . (.) | |
| MSSA | 24 (17.4) | 24 (17.4) | . (.) | |
| Other *Staphylococci* | 11 (7.8) | 11 (7.8) | . (.) | |
| Streptococcus | 13 (9.1) | 13 (9.1) | . (.) | |
| *Enteroccocus* | * (4.4) | * (4.4) | . (.) | |
| Gram Negative Rods | * (1.9) | * (1.9) | . (.) | |
| Fungal | * (3.7) | * (3.7) | . (.) | |
| Other | 31 (21.9) | 31 (21.9) | . (.) | |
| Unknown | 34 (24.4) | 34 (24.4) | . (.) | |
| Polymicrobial | * (5.4) | * (5.4) | . (.) | |

P-values by weighted linear regression for continuous variables and weighted chi$^2$ test for binary/categorical variables

SOT, solid organ transplant; IE, infective endocarditis; SD, standard deviation; N, number; HIV/AIDS: Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome; MRSA, methicillin resistant *S. aureus;* MSSA, Methicillin susceptible *S. aureus*

Missing values in Primary Payor (457 observations) and median ZIP code income quartile (1059 observations)

*N < 10; exact number suppressed to comply with restrictions of data vendor.

sion is at its greatest peri-transplant. It is possible that high levels of immunosuppression, such as the T-cell depleting therapies administered at the time of transplant, are detrimental in IE. Unfortunately, due to the nature of the NRD we were unable to determine the individual immunosuppression regimens of infected patients and are therefore limited in our ability to explore this hypothesis, even with large multi-center registries such as the International Collaboration on Endocarditis. We encourage additional studies to test this association. Given the

**Table III.** Unadjusted 60-day Outcomes of Analysis 1: SOT-IE vs. Non-SOT-IE

| | Overall (Weighted $n = 193,164$) | SOT-IE (Weighted $n = 1,574$) | Non-SOT-IE (Weighted $n = 191,590$) | *P*-value |
|---|---|---|---|---|
| Mean (SD) or N (%) | | | | |
| Death | 30,583 (15.8) | 271 (17.2) | 30,312 (15.8) | 0.33 |
| ECMO deployed | * | * | 964 (0.5) | 0.56 |
| Mechanical ventilation | 44,840 (23.2) | 375 (23.8) | 44,465 (23.2) | 0.71 |
| Thromboembolic event | 67,836 (35.1) | 348 (22.1) | 67,488 (35.2) | <0.001 |
| Length of stay (days) | 21.3 (20.3) | 21.6 (21.4) | 21.3 (20.3) | 0.73 |
| Total Costs ($ Thousands) | 58.4 (68.6) | 65.9 (76.0) | 58.4 (68.5) | 0.06 |
| Valve Repair or Replacement | 31,270 (16.2) | 196 (12.5) | 31,074 (16.2) | 0.007 |

P-values by weighted linear regression for continuous variables and weighted chi$^2$ test for binary/categorical variables
SOT, solid organ transplant; IE, infective endocarditis; SD, standard deviation; N, number; ECMO, extracorporeal membrane oxygenation
*N < 10; exact number suppressed to comply with restrictions of data vendor.

**Table IV.** Unadjusted Outcomes for Analysis 2: Index-SOT-IE vs. Index-SOT

| | Overall (Weighted $n = 148,175$) | Index-SOT-IE (Weighted $n = 140$) | Index-SOT (Weighted $n = 148,035$) | *P*-value |
|---|---|---|---|---|
| Mean (SD) or N (%) | | | | |
| Death | 3,471 (2.3) | 38 (27.1) | 3,433 (2.3) | <0.001 |
| ECMO | 3,245 (2.2) | 18 (12.7) | 3,227 (2.2) | <0.001 |
| Mechanical ventilation | 18,068 (12.2) | 75 (53.1) | 17,993 (12.2) | <0.001 |
| Thromboembolic event | 11,041 (7.5) | 63 (44.6) | 10,978 (7.4) | <0.001 |
| Length of stay (days) | 19.1 (27.9) | 91.8 (62.8) | 19.0 (27.7) | <0.001 |
| Total Costs ($ Thousands) | 119.9 (133.5) | 516.6 (354.2) | 119.6 (132.7) | <0.001 |

P-values by weighted linear regression for continuous variables and weighted chi$^2$ test for binary/categorical variables
SOT, solid organ transplant; IE, infective endocarditis; SD, standard deviation; N, number; ECMO, extracorporeal membrane oxygenation

relatively rarity of transplant-associated IE, we believe it likely will be difficult to perform a prospective study in this disease area, but it would likely be possible to use more clinically granular data, such as from combining records from hospitals sharing an electronic medical record platform. This approach would allow access to (among other variables): a) microbiology and other laboratory data, b) determination if infectious diseases was consulted, c) patients home medications and in-hospital therapies, d) imaging results.

Although heart transplant recipients account for less than 10% of all SOTs each year [10] they accounted for 45% of cases in which IE developed during the hospitalization to undergo transplantation. There are a few possible reasons for this observation. First, retained fragments of cardiac implantable electrical devices (CIED) such as permanent pacemakers or implantable cardioverter defibrillators may place heart transplant patients at increased risk for infection at the time of transplant.[15] These CIED are routinely implanted for end stage heart failure, and CIED fragments remain in up to 42% of heart transplant recipients.[16] Although CIED fragment retention may pose a risk factor for IE, the extent of this risk is unresolved.[17-19] A second possible reason for the higher rate of heart transplant index-SOT-IE cases is the presence of left-ventricular assist devices (LVAD) in these patients. Recurrent bacteremia and chronic LVAD infection are frequent adverse events among this population,[20-22] potentially predisposing patients to bloodstream infection and IE at the time of heart transplant. Because IE is an exceedingly rare indication for heart transplant, we do not believe that the high incidence of index-SOT-IE among heart transplant recipients is due to a pre-transplant diagnosis of IE.[23] We encourage further studies to determine risk factors for IE among heart transplant patients, particularly at the time of their transplant.

The most frequently identifiable cause of IE in both the non-SOT-IE and SOT-IE groups was *S. aureus*. Previously published temporal trends indicate that *S. aureus* is increasingly the most common cause of IE.[24, 25] This finding is also consistent with some of the limited published data on SOT-IE, including a 1998 case series of 46 cases of SOT-IE[4] and a retrospective registry based study in Spain and France reporting on 18 SOT-IE cases over an 11 year period.[26] In contrast, a recent report of 14 cases of IE in SOT recipients over a seven-year period found that *Enterococcus* was the most common etiologic agent.[5] In our study, fungal IE was the least common cause of IE, accounting for 0.8% of all cases of SOT-IE. This finding agrees with some,[5, 27] but not all,[4] previous reports. We suspect that the high incidence of *S. aureus* IE in our SOT-IE group is a direct consequence of their healthcare

contact[25] and their likelihood of having central venous access catheters.[5]

### Limitations

Our study was limited by the fact that clinically detailed data including source of infection, presence of indwelling central venous catheters, underlying indication for SOT, immunosuppression regimens and antimicrobial treatment information were unavailable through the NRD. We were also unable to determine the causative organism in approximately 19% of all patients in the study. Our study used ICD-9 and ICD-10 codes which may be associated with false positive and false negative findings,[28] and the ICD codes for IE and SOT have not been validated in this dataset. Specifically, given the constraints of the NRD, we were unable to validate the diagnosis of IE using standard clinical criteria such as the modified Duke Criteria, and because our analysis intentionally included a relatively broad definition of IE based on diagnosis codes to capture as many cases as possible, this may have led to the erroneous inclusion of non-IE related hospitalizations in both the SOT and non-SOT groups. Yet, our study provides incremental value over the currently limited data in this field, and helps move forward further investigations on this poorly understood topic. We encourage future studies to investigate incidence of IE among SOT recipients to supplement our findings with granular patient data.

## Conclusion

We present the largest study to date of SOT-IE. By using a large, contemporary sample comprised of over one-half of all US hospitalizations, we produced nationally representative data of IE in SOT recipients. This study suggests that SOT recipients with IE do not experience worse outcomes than non-SOT recipients with IE, but that contracting IE during index transplant hospitalization leads to greater complications and substantially higher mortality than SOT without IE.

## Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplemental materials.

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## Disclosures

The authors of this manuscript have conflicts of interest to disclose. VGF reports personal fees from Novartis, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Basilea, Affinergy, Janssen, xBiotech, Contrafect, Regeneron, Basilea, Destiny, Amphliphi Biosciences. Integrated Biotherapeutics; C3J, grants from NIH, MedImmune, Cerexa/Forest/Actavis/Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Cubist/Merck; Medical Biosurfaces; Locus; Affinergy; Contrafect; Karius; Genentech, Regeneron, Basilea, Janssen, from Green Cross, Cubist, Cerexa, Durata, Theravance; Debiopharm, Royalties from UpToDate; and a patent for sepsis diagnostics pending.

## Conflict of Interest

VGF reports personal fees from Novartis, Novadigm, Durata, Debiopharm, Genentech, Achaogen, Affinium, Medicines Co., Cerexa, Tetraphase, Trius, MedImmune, Bayer, Theravance, Basilea, Affinergy, Janssen, xBiotech, Contrafect, Regeneron, Basilea, Destiny, Amphliphi Biosciences. Integrated Biotherapeutics; C3J, grants from NIH, MedImmune, Cerexa/Forest/Actavis/Allergan, Pfizer, Advanced Liquid Logics, Theravance, Novartis, Cubist/Merck; Medical Biosurfaces; Locus; Affinergy; Contrafect; Karius; Genentech, Regeneron, Basilea, Janssen, from Green Cross, Cubist, Cerexa, Durata, Theravance; Debiopharm, Royalties from UpToDate; and a patent for sepsis diagnostics pending.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.06.007.

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