Clinical Outcomes of Transcatheter vs Surgical Aortic Valve Replacement in Patients With Chronic Liver Disease: A Systematic Review and Metaanalysis

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Background: Chronic liver disease increases cardiac surgical risk, with 30-day mortality ranging from 9% to 52% in patients with Child-Pugh class A and C, respectively. Data comparing the outcomes of transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) in patients with liver disease are limited.

Methods: We searched PubMed, Cochrane Library, Web of Science, and Google Scholar for relevant studies and assessed risk of bias using the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) Cochrane Collaboration tool.

Results: Five observational studies with 359 TAVR and 1,872 SAVR patients were included in the analysis. Overall, patients undergoing TAVR had a statistically insignificant lower rate of in-hospital mortality (7.2% vs 18.1%; odds ratio [OR] 0.67; 95% confidence interval [CI] 0.25, 1.82; I² = 61%) than patients receiving SAVR. In propensity score–matched cohorts, patients undergoing TAVR had lower rates of in-hospital mortality (7.3% vs 13.2%; OR 0.51; 95% CI 0.27, 0.98; I² = 13%), blood transfusion (27.4% vs 51.1%; OR 0.36; 95% CI 0.21, 0.60; I² = 31%), and hospital length of stay (10.9 vs 15.7 days; mean difference –6.32; 95% CI –10.28, –2.36; I² = 83%) than patients having SAVR. No significant differences between the 2 interventions were detected in the proportion of patients discharged home (65.3% vs 53.9%; OR 1.3; 95% CI 0.56, 3.05; I² = 67%), acute kidney injury (10.4% vs 17.1%; OR 0.55; 95% CI 0.29, 1.07; I² = 0%), or mean cost of hospitalization ($250,386 vs $257,464; standardized mean difference –0.07; 95% CI –0.29, 0.14; I² = 0%).

Conclusion: In patients with chronic liver disease, TAVR may be associated with lower rates of in-hospital mortality, blood transfusion, and hospital length of stay compared with SAVR.

Keywords: Aortic valve stenosis, cirrhosis, end stage liver disease, heart valve diseases, liver diseases, transcatheter aortic valve replacement, treatment outcome

INTRODUCTION

The surgical morbidity and mortality of patients with advanced chronic liver disease undergoing heart surgery remain high,1,2 particularly among patients with cirrhosis Child-Pugh class B and C undergoing cardiopulmonary bypass.1,2 The 30-day mortality risk following cardiac surgery is 9% in patients with liver cirrhosis Child-Pugh class A, 37.7% in patients with class B, and 52% in patients with class C.3 Patients with chronic liver disease have pathophysiologic changes that increase their risk of hemorrhage and organ failure. Also, extracorporeal circulation initiates pathophysiological processes that may impair coagulation and organ function in patients with chronic liver disease.1,2 Among patients with severe aortic stenosis, 2% to 5% have liver cirrhosis.4–8 With an increasing prevalence of cirrhosis and an aging population in the United States, the burden of these comorbidities is likely to rise.9 The valvular surgical risk stratification tools commonly used (Society of Thoracic Surgeons [STS] Predicted Risk of Mortality and the European System for Cardiac Operative Risk Evaluation [EuroSCORE II] models) do not include liver disease in their risk stratification.10–12 Data comparing surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) in patients with cirrhosis are limited because these patients are usually excluded from clinical trials. The need exists for a systematic review of available evidence and a metaanalysis to help inform decision making in this patient population. Consequently, the objective of this systematic review was to compare the clinical outcomes of patients with chronic liver disease undergoing TAVR and SAVR.
METHODS
This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations in our protocol, data analysis, and reporting.13
A medical librarian (R.V.) searched the following databases for relevant studies: the Cochrane Library, PubMed, Google Scholar, and the Web of Science from 2009 through May 21, 2018, with no language restrictions. We used medical subject heading terms where available and various combinations of keywords to represent the following concepts: “cirrhosis,” “chronic liver disease,” “transcatheter aortic valve replacement,” “transcatheter aortic valve implantation,” “surgical aortic valve replacement,” and “surgical aortic valve implantation.” We also searched clinicaltrials.gov (May 21, 2018) for ongoing and completed studies.
Studies were considered if they were randomized controlled trials or controlled observational studies and compared TAVR with SAVR in patients with chronic liver disease. We included studies that reported one or more of the following clinical outcomes: mortality, major or life-threatening bleeding, need for blood transfusion, acute kidney injury, length of hospital stay, proportion of patients discharged home, and cost of hospitalization. Two authors (P.N. and S.S.) independently assessed study eligibility, and differences were resolved through discussion or by a third author (Z.F.) when necessary.
Two authors (P.N. and S.S.) independently reviewed all the articles and summarized the study characteristics in a data extraction table adapted from the Cochrane Collaboration data extraction template. The data collected were study design, sample size, patient characteristics and clinical outcomes (death, blood transfusion, periprocedural length of stay, proportion of patients discharged home, acute kidney injury, and cost of hospitalization). The Cochrane Collaboration Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool was used to assess the risk of bias.14
We conducted a qualitative and a quantitative analysis. Effect sizes are presented using the Mantel-Haenszel odds ratio (OR), mean difference, or standardized mean difference with their respective 95% confidence intervals (CIs). The Higgins I-squared (I²) statistic was used to measure heterogeneity. We used a random effects model in all analyses with heterogeneity >25%. Sensitivity analyses were done by removing one study at a time. RevMan v.5.3 was used for metaanalysis.
RESULTS
Search Results and Patient Characteristics
The database search retrieved a total of 89 publications (Figure 1). Five observational studies met the eligibility criteria and were included in the systematic review and metaanalysis.2,4,15-17 Table 1 summarizes the characteristics of the included studies. These studies included a

Table 1. Characteristics of Studies Included in the Metaanalysis

| Study           | Study Type   | Study Population         | Total Patients, n | TAVR, n | SAVR, n | ROBINS-I |
|-----------------|--------------|--------------------------|-------------------|---------|---------|----------|
| Greason et al,2 2013 | Observational | Cirrhosis                | 18                | 6       | 12      | Moderate |
| Thakkar et al,17 2016 | Observational | Cirrhosis                | 129               | 36      | 93      | Moderate |
| Schill et al,16 2017 | Observational | Chronic liver disease   | 35                | 17      | 18      | Unclear  |
| Alqahtani et al,15 2017 | Observational | Cirrhosis                | 1,766             | 174     | 1,592   | Moderate |
| Dhole et al,4 2018   | Observational | Cirrhosis                | 283               | 126     | 157     | Moderate |

ROBINS-I, Risk of Bias in Non-Randomized Studies – of Interventions; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.
Table 2. Patient Clinical Characteristics, Unmatched Cohort

| Characteristic                  | Alqahtani, et al15a | Dhoble, et al4a,b | Thakkar, et al17a,b | Greason, et al2 | Schill, et al16 |
|--------------------------------|---------------------|------------------|---------------------|----------------|----------------|
|                                | TAVR n=174          | SAVR n=1,592     | TAVR n=126          | SAVR n=157     | TAVR n=36      | SAVR n=93      | TAVR n=6       | SAVR n=12      | TAVR n=17      | SAVR n=18      |
| Mean age, years                | 72                  | 64               | 71.7                | 65.3           | 73.4           | 66               | 76               | 68               | 73.8           | 55.1           |
| Male                           | 108 (62.1)          | 1,041 (65.4)     | (58.7)              | (65.6)         | (77.8)         | (67.7)           | 5 (83)           | 10 (83)          | 12 (70.6)       | 12 (66.7)      |
| Mean MELD score                | NA                  | NA               | NA                  | NA             | NA             | 9                | 10               | 10.7             | 11.8           |
| Chronic kidney disease         | 77 (44.3)           | 369 (23.2)       | NA                  | NA             | NA             | NA               | NA               | 1 (5.9)          | 4 (22.2)       |
| Hypertension                   | 124 (71.3)          | 785 (49.3)       | NA                  | NA             | (69.4)         | (66.7)           | NA               | NA               | 15 (88.2)       | 11 (61.1)      |
| Diabetes                       | 88 (50.6)           | 447 (28.1)       | (60.3)              | (47.1)         | (58.3)         | (47.3)           | 3 (50)           | 3 (25)           | 11 (64.7)       | 4 (22.2)       |
| Congestive heart failure       | 21 (12.1)           | 134 (8.4)        | (70.6)              | (49.0)         | 0              | (4.3)            | 6 (100)c         | 6 (50)c          | 15 (88.2)       | 10 (55.6)      |
| Peripheral artery disease      | 48 (27.6)           | 271 (17.0)       | (21.4)              | (10.2)         | (19.4)         | (14.0)           | 4 (66.7)         | 2 (16.7)         | 7 (41.2)        | 1 (5.6)        |
| Atrial fibrillation or flutter | 63 (36.2)           | 659 (41.4)       | NA                  | NA             | NA             | NA               | NA               | NA               | NA             |
| Chronic lung disease           | 55 (31.6)           | 379 (23.8)       | NA                  | NA             | (27.8)         | (32.3)           | 3 (50)           | 3 (25)           | 8 (47.1)        | 7 (38.9)       |

aPropensity score–matched cohort study.
bPatient numbers (n) not provided in the article for the characteristics.
cNew York Heart Association class III-IV only.

Note: Data are presented as n (%) or as (%) unless otherwise indicated.
MELD, Model for End-Stage Liver Disease; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

A total of 2,231 patients, with 359 and 1,872 patients assigned to the TAVR and SAVR arms, respectively. Table 2 summarizes the characteristics of all patients, and Table 3 provides the characteristics of the patients in the propensity score–matched cohorts. In the 5 studies identified for this meta-analysis, bleeding events were either not reported (Dhoble et al4 and Alqahtani et al15) or the reporting was too clinically heterogeneous to be pooled. We therefore did not conduct

Table 3. Patient Clinical Characteristics, Propensity Score–Matched Cohorts

| Characteristic                  | Alqahtani, et al15a | Dhoble, et al4a | Thakkar, et al17a |
|--------------------------------|---------------------|-----------------|------------------|
|                                | TAVR n=134          | SAVR n=134      | TAVR n=55        | SAVR n=55       | TAVR n=30       | SAVR n=30       |
| Mean age, years                | 71                  | 71              | 67.2             | 67              | 71.7            | 70.5            |
| Male                           | 84 (62.7)           | 79 (59)         | (65.5)           | (65.5)          | (73.3)          | (66.7)          |
| Mean MELD score                | NA                  | NA              | NA               | NA              | NA              | NA              |
| Chronic kidney disease         | 52 (38.8)           | 53 (39.6)       | NA               | NA              | NA              | NA              |
| Hypertension                   | 93 (69.4)           | 93 (69.4)       | NA               | NA              | (66.7)          | (73.3)          |
| Diabetes                       | 64 (47.8)           | 59 (44.0)       | (58.2)           | (54.4)          | (53.3)          | (53.3)          |
| Congestive heart failure       | 17 (12.7)           | 13 (9.7)        | (56.4)           | (54.5)          | 0               | (13.3)          |
| Coronary artery disease        | 55 (41.0)           | 56 (41.8)       | (61.8)           | (43.6)          | NA              | NA              |
| Peripheral artery disease      | 31 (23.1)           | 28 (20.9)       | (21.8)           | (10.9)          | (20.0)          | (10.0)          |
| Atrial fibrillation or flutter | 54 (40.3)           | 57 (42.5)       | NA               | NA              | NA              | NA              |
| Chronic lung disease           | 38 (28.4)           | 40 (29.9)       | (23.3)           | (43.3)          |                  |                 |

aPatient numbers (n) not provided in the article for the characteristics.
Note: Data are presented as n (%) or as (%) unless otherwise indicated.
MELD, Model for End-Stage Liver Disease; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.
Transcatheter vs Surgical Aortic Valve Replacement in Liver Disease

Figure 2. Comparison of in-hospital mortality in (A) all patients with chronic liver disease who underwent transcatheter aortic valve replacement (TAVR) vs those who underwent surgical aortic valve replacement (SAVR) and in (B) propensity score–matched patients. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

a metaanalysis on bleeding events. Most studies, however, reported blood transfusion, and those data were pooled for reporting.

In the assessment using the ROBINS-I tool, 4 studies had a moderate risk of bias,2,4,15,17 and 1 study had an unclear risk of bias because of limited information.16

Four studies included patients with a diagnosis of liver cirrhosis undergoing either TAVR or isolated SAVR for aortic stenosis.2,4,15,17 The studies excluded patients <50 years of age, those with incomplete records, and patients who concomitantly underwent other cardiac procedures such as valve replacement or coronary artery bypass surgery. The study by Schill et al included patients with liver disease as defined by the STS criteria (cirrhosis, viral hepatitis, portal hypertension, alcohol dependence, or congestive hepatopathy).16

Outcomes

Overall, patients undergoing TAVR had a statistically insignificant lower rate of in-hospital mortality (7.2% vs 18.1%; OR 0.67; 95% CI 0.25, 1.82; P=0.44; I²=61%) compared to the SAVR group (Figure 2A). However, propensity score matching showed significantly lower rates of in-hospital mortality in the TAVR group than the SAVR group (7.3% vs 13.2%; OR 0.51; 95% CI 0.27, 0.98; P=0.04; I²=13%) (Figure 2B).

The other outcomes are reported only for the propensity score–matched cohorts. Compared with SAVR patients, TAVR patients had a lower rate of blood transfusion (51.1% vs 27.4%; OR 0.36; 95% CI 0.21, 0.60; P<0.0001; I²=31%) (Figure 3A) and lower mean periprocedural length of hospital stay (15.7 vs 10.9 days; mean difference −6.32; 95% CI −10.28, −2.36; P=0.002; I²=83%) (Figure 3B).

No significant differences were seen between the TAVR and SAVR groups in the proportion of patients discharged home (65.3% vs 53.9%; OR 1.3; 95% CI 0.56, 3.05; P=0.54; I²=67%) (Figure 3C), development of acute kidney injury (10.4% vs 17.1%; OR 0.55; 95% CI 0.29, 1.07; P=0.08; I²=0%) (Figure 3D), or mean cost of hospitalization ($250,386 vs $257,464; standardized mean difference −0.07; 95% CI −0.29, 0.14; P=0.51; I²=0%) (Figure 4).

DISCUSSION

In this systematic review and metaanalysis, we pooled data comparing clinical outcomes of patients with chronic liver disease undergoing TAVR and SAVR. In the propensity score–matched cohorts, we found significantly lower pooled odds of in-hospital mortality, blood transfusion, and periprocedural hospital length of stay in patients receiving TAVR, and no difference in the proportion of patients discharged home, the cost of hospitalization following the index procedure, and acute kidney injury between the 2 interventions.

Ample data elucidate the risk of cardiac surgery, including SAVR, in patients with chronic liver disease.18-21 However, little data are available comparing TAVR and SAVR in patients with chronic liver disease.2,4,15,16,17 We did not find a systematic review and metaanalysis on this topic in our literature search. The available studies have small sample
Figure 3. Comparison of (A) need for blood transfusion and (B) periprocedural length of stay in propensity score–matched patients with chronic liver disease who underwent transcatheter aortic valve replacement (TAVR) vs those who underwent surgical aortic valve replacement (SAVR). CI, confidence interval; df, degrees of freedom; IV, inverse variance; M-H, Mantel-Haenszel.

B. Length of Stay

| Study or Subgroup | TAVR | SAVR | Odds Ratio M-H, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------|------|-------------------------------|----------------------------------|
|                   | Mean | SD   | Total | Mean | SD | Total | Weight |
| Alqahtani 2017    | 16   | 0.85 | 134   | 16   | 134 | 134   | 43.2%  | -4.00 [-7.11, -0.89] |
| Thakkar 2016      | 6.18 | 0.85 | 134   | 14.26 | 2.62 | 30   | 56.8%  | -8.08 [-9.07, -7.09] |
| Total (95% CI)    | 164  |      | 164   |      |     | 164   | 100.0% | -6.32 [-10.28, -2.36] |

Heterogeneity: Tau² = 6.94; Chi² = 6.00, df = 1 (P = 0.01); I² = 83%
Test for overall effect: Z = 3.13 (P = 0.002)

A study by Tirado-Conte comparing TAVR in patients with and without cirrhosis showed no difference in in-hospital and 30-day mortality, stroke, major vascular complications, bleeding complications, and new pacemaker implantation. However, patients with cirrhosis had a higher rate of acute kidney injury. In an analysis of the 2-year outcomes of the PARTNER (Placement of AoRTic TranScatheTER Valve) trial, the presence of liver disease was predictive of mortality in patients undergoing SAVR but not TAVR.

Patients with cirrhosis have pathophysiologic states that predispose them to surgical complications. These patients are more prone to bleeding, fluid and electrolyte imbalance, infection, and organ failure such as hepatic encephalopathy, hepatorenal syndrome, and liver failure. Evidence indicates that extracorporeal circulation leads to an increase in the production of vasoactive substances and cytokines that interfere with coagulation, vascular resistance and permeability, the immune system, and other organ functions. A study by Hayashida et al suggested a benefit in avoiding extracorporeal circulation in patients with cirrhosis undergoing cardiac surgery. A study by Marui et al showed 3-fold lower mortality on off-pump coronary artery bypass graft surgery compared to on-pump surgery in patients with cirrhosis, even though the difference did not reach statistical significance (P = 0.29). This underlying pathophysiology of extracorporeal circulation during SAVR in patients with liver disease and the less-invasive nature of TAVR might explain the better outcomes suggested by this metaanalysis. The lack of a significant difference between TAVR and SAVR for the proportion of patients discharged home, cost of hospitalization, and acute kidney injury might be related to lower power attributable to the small size of the metaanalysis. Furthermore, outcomes of TAVR prior to 2014 were worse than they are currently, so powered contemporary studies may find a difference between the 2 interventions in the outcomes for which this metaanalysis did not find significant differences.

Cardiac surgical risk prediction scores do not include liver disease in the risk stratification and therefore may be inadequate for evaluating patients with chronic liver disease. Studies have evaluated prognostic factors in patients with chronic liver disease undergoing cardiac surgery. Thielmann et al reported that the Model for End-Stage Liver Disease (MELD) score was the most reliable predictor of mortality in patients with cirrhosis undergoing open heart surgery compared with Child–Pugh score and EuroSCORE. Arif et al identified MELD score and EuroSCORE as predictive of 30-day mortality in patients with cirrhosis undergoing cardiac surgery with extracorporeal circulation. Arai et al compared the different risk prediction tools in patients with liver disease undergoing TAVR and reported that the Model for End-Stage Liver Disease eXcluding International Normalized Ratio (MELD-XI) score more accurately predicted 6-month mortality after TAVR (area under the receiver operating characteristic curve = 0.67) compared with the STS score, EuroSCORE, and EuroSCORE II (area under the curve = 0.60, 0.58, and 0.57 respectively).
A. Patients Discharged Home

| Study or Subgroup | TAVR Events | Total | SAVR Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-------------|-------|-------------|-------|--------|--------------------------------|--------------------------------|
| Alqahtani 2017    | 97          | 134   | 71          | 134   | 43.4%  | 2.33 [1.40, 3.87]              |                                |
| Dhoble 2018       | 42          | 55    | 39          | 55    | 33.9%  | 1.33 [0.57, 3.11]              |                                |
| Thakkar 2016      | 4           | 30    | 8           | 30    | 22.8%  | 0.42 [0.11, 1.60]              |                                |
| Total (95% CI)    | 219         | 100%  | 219         | 100%  |        | 1.30 [0.56, 3.05]              |                                |
| Total events      | 143         |       | 118         |       |        |                                |                                |

Heterogeneity: Tau² = 0.36, Chi² = 6.01, df = 2 (P = 0.05); I² = 67%
Test for overall effect: Z = 0.61 (P = 0.54)

B. Acute Kidney Injury

| Study or Subgroup | TAVR Events | Total | SAVR Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-------------|-------|-------------|-------|--------|--------------------------------|--------------------------------|
| Alqahtani 2017    | 11          | 134   | 19          | 134   | 70.8%  | 0.54 [0.25, 1.19]              |                                |
| Thakkar 2016      | 6           | 30    | 9           | 30    | 29.2%  | 0.58 [0.18, 1.91]              |                                |
| Total (95% CI)    | 164         | 100%  | 164         | 100%  |        | 0.55 [0.29, 1.07]              |                                |
| Total events      | 17          |       | 28          |       |        |                                |                                |

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)

C. Cost of Hospitalization

| Study or Subgroup | TAVR Mean | SD | Total | SAVR Mean | SD | Total | Weight |
|-------------------|-----------|----|-------|-----------|----|-------|--------|
| Alqahtani 2017    | 292,134   | 234,032 | 134 | 297,360   | 253,888 | 134 | 81.9% | -0.02 [-0.26, 0.22] |
| Thakkar 2016      | 63,913    | 30,251 | 30  | 79,263    | 63,629 | 30  | 18.1% | -0.30 [-0.81, 0.21] |
| Total (95% CI)    | 164       | 100%  | 164 | 100%      |        |      |        |                     |

Heterogeneity: Chi² = 0.97, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)

Figure 4. Comparison of (A) proportion of patients discharged home, (B) patients who developed acute kidney injury, and (C) mean cost of hospitalization in propensity score–matched patients with chronic liver disease who underwent transcatheter aortic valve replacement (TAVR) vs those who underwent surgical aortic valve replacement (SAVR). CI, confidence interval; df, degrees of freedom; IV, inverse variance; M-H, Mantel-Haenszel.

Our metaanalysis has limitations. Three of the included studies were based on National Inpatient Sample data that are derived from administrative data and therefore have the limitations of such a database.4,15,17 Serum bilirubin, MELD scores, or Child-Pugh stages that would measure the severity of liver disease were not available for these 3 studies because the database did not include that data. Also, studies were limited to in-hospital outcomes. Many of the TAVR patients included in our analysis had the procedure done between 2003-2014, so findings may not reflect current procedural outcomes. TAVR valves have improved significantly since then, with smaller sheath sizes leading to lower vascular complications, improved pacemaker rate, and decreased length of stay with the newer generation devices. These improvements have led to significant improvement in the cost effectiveness of TAVR in patients with higher risk profiles. Also, the study by Schill is a conference abstract, so the data may be preliminary.16 Despite pooling data from these studies, the sample size remained low.

CONCLUSION

This analysis suggests that in patients with chronic liver disease and severe aortic stenosis, TAVR is associated with lower rates of in-hospital mortality, blood transfusion, and shorter length of hospital stay compared to SAVR. There may not be a difference in the proportion of patients discharged home, hospitalization costs, and acute kidney injury between the 2 interventions.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

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