Outcomes of Transcatheter Aortic Valve Implantation in Patients with Cirrhosis
A Case Series

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Summary
Cirrhosis is a significant adverse factor of cardiac surgeries. Transcatheter aortic valve implantation (TAVI) has evolved as a less invasive therapy for aortic stenosis, whereas detailed case analysis of TAVI in cirrhotic patients is limited.

Among 444 consecutive patients who underwent TAVI in the Sakakibara Heart Institute between October 2013 and January 2018, we retrospectively reviewed 11 patients (2.5%) with cirrhosis. All outcomes were defined according to the Valve Academic Research Consortium-2 criteria.

The median age of the patients was 82 years, and eight (73%) were female. Seven patients (64%) were Child-Turcotte-Pugh class A, and four patients (36%) were class B. The Model for End-Stage Liver Disease score was 10 (7.0-13). TAVI was performed using Edwards SAPIEN XT/SAPIEN3 in nine patients (82%), and Medtronic CoreValve/Evolut R in two patients (18%), via transfemoral (n=8, 73%) or transapical (n=3, 27%) approach. The device success rate was 100% and no extracorporeal circulation had been inducted. No death, stroke, life-threatening bleeding, and acute kidney injury stage 2 or 3 occurred within 30 days, but three major bleeding events (27%) were documented (two access-site bleeding in transapical approach, and one pulmonary hemorrhage caused by transient mitral regurgitation). During a median follow-up of 493 days, four deaths had occurred, and the mid-term survival rate was 81% and 65% at one and two years each.

TAVI is a promising therapeutic option for patients with cirrhosis. Further study should be needed regarding optimal patient selection and procedures in patients with cirrhosis.

Key words: Transcatheter aortic valve replacement, Aortic stenosis, Hepatic decompensation

Cirrhosis is a consequence of chronic liver injury caused by viral infection, excessive alcohol consumption, inappropriate autoimmunity, obesity, or congestive heart failure. Cirrhotic patients are complicated by liver dysfunction, portal hypertension, and splenomegaly, which lead to pancytopenia, fluid retention, hepatic encephalopathy, gastroesophageal varices, renal failure, and hepatocellular carcinoma. In cardiac surgeries, patients with cirrhosis tend to develop bleeding complication and peri-operative organ failure.1-19 Postoperative survivals, especially in patients with Child-Turcotte-Pugh (CTP) class B or C patients, are extremely unfavorable both at short- and long-term. Transcatheter aortic valve implantation (TAVI) has emerged as a less invasive therapy for severe aortic stenosis,9-11 and generally does not require sternotomy and extracorporeal circulation, which correlates with adverse outcomes following cardiac surgeries.1-2 Reflecting procedural invasiveness, TAVI causes less systemic inflammation than surgical aortic valve replacement (SAVR).12-13 The low invasive nature of TAVI should be useful for patients with cirrhosis, but detailed case series of TAVI in cirrhosis contain limited numbers of patients.14-16 We aimed to describe the outcomes of TAVI in patients with cirrhosis.

Methods
Participants: This study was a retrospective observational study. Among 444 consecutive patients who underwent TAVI at the Sakakibara Heart Institute from October 2013 to January 2018, 11 patients with cirrhosis (2.5%) were retrospectively analyzed. Cirrhosis was diagnosed by an hepatologist based on characteristic findings of cirrhosis in laboratory testing, ultrasound, or computed tomography. This study was approved by the institutional ethical committee. Because the subjects were retrospectively enrolled,
written informed consent was waived.

**Procedure of transcatheter aortic valve implantation:** The indication of TAVI was symptomatic severe aortic stenosis irrespective of etiology. Severe aortic stenosis was defined as fulfilling any one of the following: (1) aortic valve area less than 1.0 cm², (2) peak aortic valve flow more than 4.0 m/s, or (3) mean transvalvular pressure gradients more than 40 mmHg. The multidisciplinary heart team, which consisted of a cardiologist, cardiac surgeon, and anesthesiologist, decided the therapeutic option for each patient. We had considered cirrhosis a high-risk factor of SAVR. TAVI was preferred in most cirrhotic patients, but SAVR was selected in middle-aged patients especially having other indications of cardiac surgery (e.g., extensive coronary artery disease or other valve dysfunction).

The TAVI devices used were Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA; seven patients), Edwards SAPIEN 3 (Edwards Lifesciences; two patients), Medtronic CoreValve (Medtronic, Minneapolis, MN, USA; one patient), and Medtronic Evolut R (Medtronic; one patient). In all patients, we performed upper gastrointestinal endoscopy to check the presence of gastrointestinal varices. Contrasted computed tomography of the trunk was conducted to assess the complications of cirrhosis, including gastrointestinal varices, hepatosplenomegaly and ascites, in addition to the anatomy of the aortic valve and surrounding structures. In principle, TAVI procedures were carried out under general anesthesia with transesophageal echocardiography. In cases complicated with gastrointestinal varices, transthoracic echocardiography was used to guide the procedure. Single oral antiplatelet agent or anticoagulant was used during peri-procedural periods. Two units of red blood cells were cross-matched and prepared for use in the procedure. Percutaneous transfemoral approach was primarily used in TAVI, and transapical approach was alternatively selected in cases unsuitable for transfemoral approach. TAVI and exstirpation were performed in the hybrid operating room. After that, the patients were monitored in the intensive care unit for 12-24 hours, and then moved to general wards. The patients underwent comprehensive cardiac rehabilitation for the purpose of home discharge.

**Clinical data and outcome measures:** Data of patient background, laboratory tests, procedures, complications, and outcomes were prospectively input into the institutional database. The severity of liver dysfunction was evaluated using MELD class, MELD Model for End-Stage Liver Disease (MELD) score, and Model for End-Stage Liver Disease excluding INR score. We assessed device success, 30-day combined endpoint, other procedural complications, and long-term survival according to the Valve Academic Research Consortium (VARC)-2 criteria. Device success was defined as meeting all the following criteria: no procedural death, single prosthetic valve at a proper position, and intended performance of the prosthetic heart valve. Thirty-day combined endpoints were comprised of all-cause mortality, all-stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeating the procedure.

**Statistical analysis:** All statistical analyses were conducted using JMP Pro 13 (SAS Institute Inc., Cary, NC, USA). Categorical data were expressed as number with percentage and continuous data as median (interquartile range). Survival after TAVI was analyzed with the Kaplan-Meier curve.

**Results**

The demographic and clinical characteristics of 11 patients are shown in Tables I, II. The age of the patients was 82 (79-86) years, and eight (73%) were female. The etiologies of cirrhosis were hepatitis C virus in four patients (36%), primary biliary cholangitis in three (27%),...
### Table II. Patient Characteristics and Procedural Data

| Characteristic                                           | Value                  |
|----------------------------------------------------------|------------------------|
| Age (years)                                              | 82 (79-86)             |
| Male/female                                             | 3 (27) / 8 (73)        |
| Body surface area (m²)                                   | 1.5 (1.0-1.5)          |
| NYHA class 3 or 4                                        | 7 (64)                 |
| Hypertension                                             | 11 (100)               |
| Diabetes mellitus                                        | 6 (55)                 |
| Previous coronary artery bypass grafting                 | 1 (9.1)                |
| Previous stroke                                          | 1 (9.1)                |
| Peripheral artery disease                                | 2 (18)                 |
| Chronic obstructive pulmonary disease                    | 2 (18)                 |
| Carotid artery stenosis                                  | 1 (9.1)                |
| White blood cell (10⁹/L)                                 | 5.4 (4.4-6.7)          |
| Hemoglobin (g/dL)                                        | 11.6 (10.0-12.7)       |
| Platelet (× 10⁹/L)                                       | 112 (100-158)          |
| PT-INR                                                   | 1.0 (1.0-1.5)          |
| Creatinine (mg/dL)                                       | 1.0 (1.0-1.3)          |
| eGFR (mL/minute/1.73m²)                                  | 53 (30-66)             |
| Albumin (g/dL)                                           | 3.3 (3.0-3.8)          |
| Total bilirubin (mg/dL)                                  | 0.7 (0.6-0.9)          |
| Aortic valve area (cm²)                                  | 0.61 (0.50-0.69)       |
| Ejection fraction (%)                                    | 62 (56-65)             |
| Society of Thoracic Surgeons score (%)                  | 5.8 (5.0-9.6)          |
| Etiology of cirrhosis                                    |                        |
| Hepatitis C virus                                        | 4 (36)                 |
| Primary biliary cholangitis                              | 3 (27)                 |
| Alcohol                                                  | 1 (9.1)                |
| Hepatitis B virus                                        | 1 (9.1)                |
| Non-alcoholic steatohepatitis                            | 1 (9.1)                |
| Unknown                                                  | 1 (9.1)                |
| Child-Turcotte-Pugh score                               | 6 (6-7)                |
| Child-Turcotte-Pugh class                                | A: 7 (64), B: 4 (36), C: 0 (0) |
| MELD score                                               | 10 (7.0-13)            |
| MELD-XI score                                            | 7.2 (2.0-11)           |
| Charlson Comorbidity Index                               | 3 (3-5)                |
| Complications of cirrhosis                               |                        |
| Gastroesophageal varix                                   | 2 (18)                 |
| Hepatocellular carcinoma                                | 2 (18)                 |
| Ascites                                                  | 1 (9.1)                |
| Hepatic encephalopathy                                  | 1 (9.1)                |
| Emergent/elective procedure                              | 0 (0) / 11 (100)       |
| General anesthesia                                       | 8 (73)                 |
| Transfemoral/transapical approach                        | 8 (73)/3 (27)          |
| Puncture/cut-down*                                       | 6 (55)/2 (18)          |
| Edwards SAPIEN XT/Edwards SAPIEN 3/ Medtronic CoreValve/Medtronic Evolut R | 7 (64)/2 (18)/1 (9.1)/1 (9.1) |
| Procedural time (minutes)                                | 115 (78-165)           |
| Pre-mean transvalvular pressure gradients (mmHg)         | 43 (42-51)             |
| Post-mean transvalvular pressure gradients (mmHg)        | 9 (6-12)               |
| Red blood cell transfusion (units)                       | 0 (0-0)                |
| Contrast material (mL)                                   | 105 (80-113)           |
| Device success rate**                                    | 11 (100)               |

Data are expressed as number with percentage or median (interquartile range). NYHA indicates New York Heart Association; PT-INR, international normalized ratio of prothrombin time; eGFR, estimated glomerular filtration rate; MELD, Model for End-Stage Liver Disease; and MELD-XI, Model for End-Stage Liver Disease excluding INR. * In patients with transfemoral approach. ** Device success was defined by Valve Academic Research Consortium-2: no procedural death, single prosthetic heart valve at proper position, and intended performance of the prosthetic heart valve.
and alcohol, hepatitis B virus, non-alcoholic steatohepatitis, and unknown in one (9.1%) each. Seven patients (64%) were CTP class A and four (36%) were class B. Two patients (18%) were complicated by hepatocellular carcinoma, and both had been radically treated before TA VI. The indications of TA VI included prohibitive surgical risk in six patients (Cases 1-4, 6, 7) and high surgical risk in the others (Cases 5, 8-11).

TA VI was conducted under general anesthesia in eight patients (73%; Table II). Transfemoral approach was selected in eight patients (73%) and transapical approach in the remaining three (27%). The device success rate was 100%. There was no mortality, emergent cardiac surgery, and use of extracorporeal membrane oxygenation within 30 days (Table III). The rate of 30-day combined endpoint was 0%. Other complications leading to extended hospital stay included major bleeding in three patients (27%; two access-site bleeding in transapical approach and one pulmonary hemorrhage), minor vascular injury in two patients (18%), acute kidney injury stage 1, unstable angina, and hepatic decompensation in one patient (9.1%) each. Pulmonary hemorrhage in Case 7 was caused by transient mitral regurgitation, which developed during valve deployment, and bailed out through a conservative treatment (i.e., blood transfusion, hemostatic drug, and noninvasive positive pressure ventilation). In Case 2, atherosclerotic plaque rupture led to unstable angina three weeks after TAVI, and we performed urgent percutaneous coronary intervention uneventfully.

During a median follow-up period of 493 days, four deaths occurred (Figure). The causes of death were infection in three patients (days 299, 606, and 1092), and liver failure in one patient (day 49). Kaplan-Meier curve showed 81% and 65% survival at one year and two years following TAVI.

### Discussion

We retrospectively analyzed the clinical outcomes of TAVI in 11 patients with cirrhosis. There was no death and VARC-2-defined combined endpoint at 30 days. TAVI is the preferable alternative for patients with cirrhosis.

**Cirrhosis and cardiac surgeries:** The prevalence of cirrhosis among cardiac surgical candidates is relatively low, and cirrhosis is not included in common surgical risk scores such as the EuroSCORE and Society of Thoracic Surgeons score. However, several reports have suggested that cirrhosis is the major adverse factor in cardiac surgeries, and management of cirrhotic patients with cardiac disease is one of the challenging clinical issues. Modi, et al. reviewed nine studies of cardiac surgeries in patients with cirrhosis. Mortality was 5.2% in CTP class A patients, increasing to 35% in class B and to 70% in class C patients. Because dysfunctions due to cirrhosis may extend to different organs, the postoperative complications range widely as infection (19% to 60%), renal dysfunction (9.4% to 53%), respiratory failure (22% to 28%), bleeding (17% to 28%), gastrointestinal dysfunction (15% to 18%), and liver failure (11%). In our series, three major bleeding complications and one hepatic decompensation following TAVI should be mainly attributable to comorbid cirrhosis. Three of these complications had occurred with transapical approach. Transapical TAVI is related to more systemic inflammatory response syndrome and bleeding complication than transfemoral TAVI. At the time of TAVI in cases 2, 3, and 6, we had no option other than transapical approach in patients who were unsuitable for transfemoral approach. Trans-subclavian or transaortic approach might have been more preferable than transapical approach in these cases.

Long-term outcome following cardiac surgeries is also poor as short-term outcome. Jacob, et al. reviewed the long-term mortality of 19 studies performed until

| Table III. Outcomes of Transcatheter Aortic Valve Implantation |
|-----------------|-----------------|
| **n = 11**      | **n = 11**      |
| Thirty-day mortality | 0 (0) |
| Stroke | 0 (0) |
| Bleeding complications | 1 (9.1)/3 (27)/0 (0) |
| Minor/major/life-threatening | 1 (9.1)/0 (0)/0 (0) |
| Acute kidney injury | 0 (0) |
| Coronary artery obstruction requiring intervention | 0 (0) |
| Vascular complications | 3 (27)/0 (0) |
| Valve-related dysfunction requiring repeat procedure | 0 (0) |
| Combined endpoint* | 0 (0) |
| Myocardial infarction | 0 (0) |
| Prosthesis-patient mismatch | 0 (0) |
| New-onset atrial fibrillation | 0 (0) |
| Pacemaker implantation | 0 (0) |
| Postoperative hospital stay (days) | 16 (8-28) |

Data are expressed as number with percentage or median (interquartile range). *Combined endpoint was defined by Valve Academic Research Consortium-2: all-cause mortality, all-stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeating the procedure.
Survival curves following transcatheter aortic valve implantation. The one- and two-year survival rates were 81% and 65% each.

Table IV: Clinical Series Regarding Transcatheter Aortic Valve Implantation in Patients with Cirrhosis

|                     | Greason et al.14 (n = 6) | Shah et al.15 (n = 17) | Wendi16 (n = 11) | This study (n = 11) |
|---------------------|--------------------------|------------------------|------------------|---------------------|
| Age (years)         | 76 (NA)                  | 77 ± 9                 | 73 ± 9           | 82 (79-86)         |
| Male                | 5 (83)                   | 10 (59)                | 7 (64)           | 3 (27)             |
| Society of Thoracic Surgeons score (%) | NA                      | 8.4 ± 6.1              | 8.9 ± 4.6        | 5.8 (5.0-9.6)      |
| Child-Turcotte-Pugh | NA                      |                        |                  |                     |
| Class A             | 11 (65)                  | 2 (18)                 |                  | 7 (64)             |
| Class B             | 6 (35)                   | 6 (55)                 |                  | 4 (36)             |
| Class C             | 0 (0)                    | 3 (27)                 |                  | 0 (0)              |
| MELD score          | 9 (NA)                   | 11.4 ± 3.9             | 16.8 ± 6.2       | 10 (7.0-12.5)      |
| Approach            | Transfemoral             | 5 (83)                 |                  | 8 (73)             |
|                     | Transapical              | 1 (17)                 |                  | 3 (27)             |
| Transcatheter heart valve |                      |                        |                  | NA                 |
| Edwards SAPIEN      | 3 (50)                   | 15 (88)                |                  | 0 (0)              |
| Edwards SAPIEN XT   | 3 (50)                   | 2 (12)                 |                  | 7 (64)             |
| Edwards SAPIEN 3    | 0 (0)                    | 0 (0)                  |                  | 2 (18)             |
| Medtronic CoreValve | 0 (0)                    | 0 (0)                  |                  | 1 (9.1)            |
| Medtronic Evolut R  | 0 (0)                    | 0 (0)                  |                  | 1 (9.1)            |
| Thirty-day mortality| 0 (0)                    | 2 (12)                 | 1 (9.1)          | 0 (0)              |

Data are expressed as number with percentage, median (interquartile range), or mean ± standard deviation. NA indicates not available; and MELD, Model for End-Stage Liver Disease.

The short-term mortality was 9.0%, 38%, and 52% in CTP class A, B, and C, respectively (19% overall). The one-year mortality was 27%, 66%, and 79%, respectively (42% overall). CTP classification and MELD score are useful for predicting mortality.1-6 Several laboratory tests are also associated with outcomes following cardiac surgeries (e.g., preoperative hemoglobin level, platelet count, international normalized ratio of prothrombin time, cholinesterase, bilirubin, and albumin level).3-5,7

TAVI in patients with cirrhosis (Table IV): Although previous studies based on the national database included a comparatively large number of patients with cirrhosis, information regarding individual patient detail or mid- to long-term data following discharge remain scarce.20,22 In managing a cirrhotic patient with aortic stenosis, knowledge from case series is very beneficial on clinical
decision-making. Greason, et al. reported the outcomes of aortic valve replacement in 18 patients (TAVI in 6 cases, SAVR in 12 cases). There was no postoperative death in the TAVI group, but there were two deaths (17%) in the SAVR group. Procedural complications were observed in two patients (17%) in the TAVI group and in eight (67%) in the SAVR group. Shah, et al. reported 17 patients with cirrhosis who underwent TAVI. The in-hospital mortality was 5.9% (one of 17 patients) and the 90-day mortality was 18% (3 patients). Procedural complications consisted of renal failure in five (29%) and hepatic decompensation in one (5.9%), but no bleeding and vascular complication was observed following TAVI. Our eleven patients were elderly, with a median age of 82 years, and most of them were female. The demographic characteristics in the present study are different from those of previous studies. Taking into account other differences, such as severity of cirrhosis, therapeutic device, and definition of outcomes, it is difficult to compare our experience with that of previous reports. However, we achieved 100% device success rate, and the rates of short-term mortality, bleeding events, and renal dysfunction are better than those reported previously. Cardiopulmonary bypass, which was found to correlate with adverse outcomes following cardiac surgeries, was not required in our series. The low invasiveness of TAVI is one of the reasons for the favorable outcomes. Because most candidates of TAVI were the elderly with any frailty, we generally used single antiplatelet or anticoagulant during peri-procedural periods. It may also be associated with less bleeding complication. Second-generation transcatheter heart valve (e.g., Edwards SAPIEN 3, Medtronic Evolut R) was used in only three patients, but such a new device leads to less bleeding, vascular complication, and perivalvular leakage. From the results of the present study, TAVI appears to be the preferred modality over SAVR for elderly patients with cirrhosis. However, for middle-aged patients, the durability of transcatheter heart valve and longevity of each patient should also be considered.

**Limitation:** Firstly, the number of patients included was small. However, there is still paucity of knowledge about TAVI in patients with cirrhosis, and the follow-up duration in our study is one of the longest in the literatures. Moreover, former studies had not utilized the latest universal definition of outcome, VARCH-2 criteria. Second, the majority of our patients had non-advanced cirrhosis. The prognosis of advanced cirrhosis is poor due to cirrhosis itself, and careful considerations should be given in deciding the therapeutic option in such cases.

**Conclusion**

TAVI is a potentially promising therapeutic option in patients with cirrhosis. Further investigations with more patients are warranted.

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**Disclosures**

**Conflicts of interest:** Dr. Tobaru is proctor of Edwards Lifesciences and Medtronic. The other authors have no potential conflicts of interest to state herein.

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