Received: 6 April 2022 | Accepted: 29 August 2022

DOI: 10.1002/hep4.2094

REVIEW

Approach to the patient with decompensated cirrhosis and aortic stenosis during liver transplantation evaluation

Nikki Duong[1] | **Veronica Nguyen**[2] | **Lorenzo De Marchi**[3] | **Arul Thomas**[2]

[1]Department of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA

[2]MedStar Georgetown University Hospital, Medstar Transplant Hepatology Institute, Washington, DC, USA

[3]Department of Anesthesiology, MedStar Georgetown University Medical Center, Washington, DC, USA

Correspondence
Nikki Duong, Department of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University Medical Center, Richmond, Virginia, USA.
Email: nduong91@gmail.com

Abstract

Aortic stenosis (AS) is the most common valvular disease and is reported to be present in 2%–7% of people over the age of 65. Risk factors for aortic stenosis and NASH overlap; thus, as the population ages, there is an increased likelihood that patients undergoing liver transplantation evaluation may have severe aortic stenosis. There is a high mortality rate associated with cardiac surgeries in patients with cirrhosis. Further, there are no guidelines that assist in the decision making process for patients with cirrhosis and AS. In this review, we highlight key studies that compare transcatheter aortic valve implantation (TAVI) with surgical aortic valve replacement (SAVR) in patients with cirrhosis. We propose an algorithm as to how to approach the patient with aortic stenosis and considerations unique to patients with cirrhosis (i.e., anticoagulation, EGD for variceal assessment; need to determine timing after TAVI before listing).

EPIDEMIOLOGY OF AORTIC STENOSIS, RISK FACTORS, AND ASSOCIATIONS WITH LIVER DISEASE

Epidemiology

Aortic stenosis is the most common valvular disease and is reported to be present in 2%–7% of people over the age of 65.[1] It is an indolent and slowly progressive disease with a high mortality rate once symptoms begin to develop.[2]

Calcific aortic disease comprises a spectrum of pathology that ranges from aortic sclerosis (or leaflet thickening) to aortic stenosis. In the United States and Europe, up to 80% of cases of aortic stenosis are due to calcification.[2] Most patients present in the seventh to eighth decade of life.[2] The calcified valve leads to turbulent flow, which causes damage to the endothelium, and inflammation as well as accumulation of oxidized low-density lipoprotein (LDL).[2] Risk factors include older age, male sex, smoking, hypertension, diabetes, elevated levels of LDL, and C-reactive protein.[1] Other common causes of aortic stenosis include a bicuspid aortic valve and rheumatic heart disease.[3] Bicuspid aortic valve occurs between the fifth and sixth decade of life and is genetically inherited.[4] Rheumatic heart disease was formerly a common cause of aortic stenosis in developing countries but is now less prevalent.[4]

Natural history

The natural history of aortic stenosis involves a steadily increasing afterload, which leads to compensatory

Nikki Duong and Veronica Nguyen contributed equally to this work.

hypertrophy of the left ventricle. As the stenosis progresses, the wall stress becomes too burdensome and the adaptive mechanism of left ventricular hypertrophy fails, leading to deterioration of the systolic function and development of a cardiomyopathy.

In terms of associations, aortic stenosis is commonly identified in patients with coronary artery disease as well as conduction system abnormalities. However, heart block is commonly seen after aortic valve replacement due to periprocedural damage to surrounding structures such as the atrioventricular node.

To date, there is no medical therapy shown to improve survival.[5] Without intervention for symptomatic patients with severe aortic stenosis, the mortality rate can be as high as 75% at 3 years.[5] Thus, prompt recognition and referral for valve replacement is of paramount importance. With surgery, improvement in ejection fraction and symptoms have been noted.[5] According to the 2020 American College of Cardiology (ACC)/American Heart Association guidelines, valve replacement for symptomatic, severe aortic stenosis, and for asymptomatic patients with an ejection fraction of less than 50%, are both Class I recommendations.

Association with liver disease

Cirrhosis results in a hyperdynamic state due to the presence of portosystemic shunts and portal hypertension.[6] As a result, peripheral vasodilation leads to increased cardiac output and higher preload, but because of catecholamine hypersensitivity, patients with cirrhosis have impaired contractility.[6] In aortic stenosis, preload maintains cardiac output; thus, patients with aortic stenosis are preload-dependent. In patients with cirrhosis, the mortality rate associated with cardiac surgeries has been reported to be as high as 100%.[7,8] There are a few cases of combined aortic valve replacement and orthotopic liver transplantation in the literature.[9–11] However, there are no randomized, prospective trials that have evaluated mortality rates in combined aortic valve replacement and orthotopic liver transplantation in the population with cirrhosis. The risk factors for aortic valve calcification are hypertension, diabetes, and elevated cholesterol levels. These are also some of the same risk factors for development of nonalcoholic steatohepatitis (NASH). As the population ages with these risk factors, the incidence of NASH will increase, individuals will live longer, and patients who may present for liver transplant evaluation due to decompensated NASH cirrhosis will have increasing comorbidities such as severe aortic stenosis. At present, there are no consensus guidelines that address this important yet controversial topic.

DEFINING TRANSAORTIC VALVE IMPLANTATION AND SURGICAL AORTIC VALVE REPLACEMENT

For symptomatic patients with severe aortic stenosis, the choice for surgical aortic valve replacement (SAVR) versus transaortic valve implantation (TAVI), formerly known as transaortic valve replacement, involves a multidisciplinary approach that involves consideration of several factors. The first step involves assessment of the patient's life expectancy as well as quality of life after a surgical intervention. If the individual's quality of life is predicted to improve after intervention and the life expectancy is greater than 1 year with valve replacement, then the next step involves a risk assessment score, most commonly being the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM).[12] However, if life expectancy is less than 1 year or quality of life is not expected to improve, then palliative care should be pursued.

By definition, SAVR requires an incision be made in the chest to gain access to the heart and replace the native valve.[5] In contrast, TAVI is a minimally invasive procedure that was first performed in 2002 and shown to have better outcomes and faster recovery times as compared with SAVR.[13] Although TAVI was initially approved for intermediate-risk and high-risk patients, as of August 2019, this procedure has extended to include low-risk patients as well. In fact, the Partner 3 trial demonstrated TAVI superiority to SAVR, while the CoreValve trial demonstrated its noninferiority.[14]

Specifically, the Partner 3 trial suggested that in low-risk patients with aortic stenosis, TAVI was superior to SAVR with regard to 1-year rehospitalization, stroke and mortality rates, with this positive effect noted even at 2-year follow-up.[14] In the CoreValve trial, patients were followed for 5 years, with similar treatment outcomes in patients with high-risk aortic stenosis who underwent TAVI versus SAVR.[15]

TAVI can be performed via a transfemoral, subclavian, transapical, or transaortic approach.[16] Whereas a SAVR replaces the valve entirely, during a TAVI procedure, the new valve is expanded within the native valve.[17] For patients with an STS-PROM-estimated mortality risk above 50% or a contraindication to SAVR (e.g., porcelain aorta or chest pathology that would prohibit a thoracotomy, history of radiation, severe frailty, bicuspid aortic valve), then transfemoral TAVI is recommended. TAVI is also recommended for those at high risk, with an STS-PROM score > 8 and <50% risk of death. Those at intermediate surgical risk, with an STS-PROM score between 4 and 8, can undergo TAVI or SAVR based on individual assessments. In people with the low-risk category (STS-PROM < 4), SAVR is the recommended procedure, based on results from the NOTION trial.[18] This trial concluded that in low-risk

patients (median STS-PROM scores of 3%) undergoing valve replacement, 1-year outcomes were similar after SAVR compared with TAVI. However, patients who underwent TAVI had higher rates of aortic regurgitation and required permanent pacemakers at a higher rate than those who underwent SAVR. The STS-PROM score identifies postprocedural risks and complications based on the procedure performed. The score takes into account extensive demographic, clinical, and laboratory data that include age, gender, race, height, weight, complete blood count, creatinine, presence of hypertension, an immunocompromised state, peripheral artery disease, cerebrovascular disease, mediastinal radiation, cancer, sleep apnea, liver disease, syncope, diabetes, endocarditis, lung disease, drug/alcohol use, pneumonia, home oxygen, history of myocardial infarction, heart failure, atrial flutter or fibrillation, heart block, ventricular tachycardia, use of medications (inotropes, antiplatelet agents, angiotensin-converting enzyme/angiotensin receptor blockers, steroids), and degree of coronary artery and valvular disease.[12] Although the score includes liver disease as a component, the user can only select a binary answer (i.e., the presence or absence of liver disease). This does not account for the presence of cirrhosis, let alone unique clinical features such as frailty, hypoalbuminemia, coagulopathy, and hyponatremia.

If another indication exists for coronary artery bypass graft surgery or another cardiac surgery, then SAVR may be the preferred option. In addition, the use of SAVR is favored in patients who are <75 years, have severe calcification of a bicuspid valve, or will undergo placement of a mechanical valve. TAVI is the preferred procedure when a patient is >75 years, with comorbidities that are not included in the risk-stratification scores such as cirrhosis. Several considerations should be accounted for when contemplating TAVI, such as life expectancy of less than 1 year, severe valvular disease, active endocarditis, myocardial infarction in the past month, bicuspid valve, hypertrophic obstructive cardiomyopathy, ejection fraction <20%, severe pulmonary hypertension, intracardiac mass or thrombus, aortic annulus <18 or >25 mm, severe mitral regurgitation, stroke within the past 6 months, and end-stage renal disease.[5] Cirrhosis is currently not listed by the ACC as a contraindication to valve replacement.

TAVI versus medical therapy for the inoperable patient

The PARTNER trial was a multicenter parallel prospective, randomized, controlled clinical trial that included patients with symptomatic severe aortic stenosis.[16] This study was performed across 21 centers worldwide, with 17 of them being in the United States. Cohort A was deemed high risk and underwent TAVI via the transfemoral or transapical approaches. Cohort B was deemed inoperable by surgeons, and therefore 358 patients were randomized to either undergo transfemoral TAVI or standard medical therapy (balloon valvuloplasty, in which the stenosed valve is widened using a catheter).[16]

At 1-year follow-up, patients who received TAVI had a mortality rate of 30.7% versus 50.7% ($p < 0.001$) for those who received standard medical therapy including valvotomy. Similarly, at the 5-year follow-up, 14% of TAVI patients, compared with 40% of standard therapy patients, had New York Heart Association (NYHA) Class III or IV symptoms. However, the complication rate of developing a stroke was higher in the TAVI group than in the standard therapy group at 1 month (6.7% vs. 1.7% [$p = 0.03$], respectively). Thus, in the inoperable candidate, TAVI is an option with mortality benefit, while also improving symptoms. However, whether having cirrhosis defines a patient as being inoperable still needs clarification and warrants further study.

TAVI versus SAVR

A meta-analysis of randomized trials that compared TAVI versus SAVR for severe aortic stenosis assessed patients with varying degrees of surgical risk and found that patients who underwent TAVI had a lower mortality rate than those who had a SAVR (hazard ratio of 0.87, 95% confidence interval 0.76 to 0.99).[13] More specifically, there was a lower mortality rate in patients receiving a transfemoral (in which the catheter is delivered through the femoral artery) TAVI as compared with transthoracic TAVI.[13] Although TAVI was associated with fewer incidences of acute renal failure, atrial fibrillation, and major bleeding, it was associated with higher rates of vascular complications, new pacemaker implantation, and paravalvular regurgitation.[13]

The following are landmark trials that compare TAVI to SAVR in populations with different risks, as determined by the STS-PROM model.

The CoreValve US Pivotal Trial was a randomized controlled trial of high-risk patients (STS-PROM > 8%) that compared self-expanding transcatheter aortic-valve bioprostheses with surgical aortic-valve replacement; it reported a lower mortality rate in the TAVI group (14.2%) when compared with the SAVR group (19.1%)[14] ($p < 0.001$).[19]

The PARTNER 2A trial of intermediate-risk patients (STS-PROM 4%–8%) undergoing either TAVI, with a balloon-expandable valve, or SAVR found no difference in mortality rate between the two groups (19.3% and 21.1%, respectively; $p = 0.25$).[17] At 1-month follow-up, they reported that TAVI resulted in lower rates of kidney injury, severe bleeding, and new-onset atrial fibrillation, but higher rates of aortic regurgitation and vascular complications.

In terms of patients who are at low risk (STS-PROM < 4%) for surgery, to date, the Nordic Aortic Valve Intervention (NOTION) trial was a randomized trial that compared TAVI with SAVR, but enrolled patients over the age of 70.[18] Of the 280 patients enrolled, they did not find any significant differences in the all-cause mortality between the groups after 1 year. However, patients who underwent TAVI required pacemakers at higher rates, higher rates of paravalvular regurgitation, and were less functional according to the NYHA classification. SAVR patients had higher rates of bleeding, kidney injury, and new-onset atrial fibrillation.[18] Therefore, when comparing TAVI with SAVR, the challenge remains that varying outcomes were used, and even when primary outcomes were similar, the results were mixed.

OUTCOMES FOR TAVI VERSUS SAVR IN PATIENTS WITH CIRRHOSIS

SAVR in patients with cirrhosis

If left untreated, symptomatic aortic stenosis carries a significant morbidity and mortality burden. Cardiac surgery in a patient with cirrhosis is known to increase mortality, and procedural complications and can lead to increased lengths of stay.[20–22] When undergoing cardiac surgery, single-center trials report mortality rates that range from 15%–70% in patients with cirrhosis.[23] A study by Steffen et al. used the Nationwide Inpatient Sample (NIS), a publicly available claims-based database that quantifies the morbidity, mortality, and cost of SAVR for a patient with cirrhosis. Between 1998 and 2011, there were 423,789 patients who had a valve replacement, 0.7% (2769) of whom carried a diagnosis of cirrhosis. Overall, the mortality rate was 16% for patients with cirrhosis and 5% for those without. There was no significant difference between the rates of stroke, blood transfusion requirements, wound infections, or pneumonia between those with and without cirrhosis. However, patients with cirrhosis experienced higher total in-hospitalization costs, longer length of stays, and were less likely to be discharged home. Thus, the authors concluded that cirrhosis plays a significant role in determining mortality and poses a significant public health and financial burden on those being considered for SAVR.[24] It is important to note that administrative data sets are limited by the lack of physiologic parameters that do not allow for quantification of liver disease severity using scores such as the Model for End-Stage Liver Disease (MELD). Because SAVR is an invasive procedure that requires the use of cardiopulmonary bypass, which leads to the release of endogenous vasoactive and cytotoxic substances, it could be detrimental in cirrhosis where there is already systemic vasodilation.[25–27] Thus, TAVI may be a more viable option.

TAVI in patients with cirrhosis

For high-risk patients with severe symptomatic aortic stenosis, TAVI is now the standard of care, as it is less invasive and avoids the need for general anesthesia and cardiopulmonary bypass.[1,17] Data surrounding patients with liver disease who undergo TAVI are limited to case reports or small series.[28–30] It is considered a minimally invasive technique, and the data have supported that TAVI is superior to SAVR in high-risk individuals.[19] In a study by Adams et al., of the 795 randomized patients, 394 were assigned to TAVI and 401 to SAVR. Of the 394 patients assigned to TAVI, 10 had cirrhosis. Of the 401 patients assigned to SAVR, 7 had cirrhosis. These patients were from 45 centers in the United States. The mortality rate was significantly lower in the TAVI group compared with the SAVR group (14.2% vs. 19.1%; $p < 0.001$).

A study at the University of Pennsylvania between 2007 and 2014 evaluated the outcomes of patients with chronic liver disease (CLD) and severe symptomatic aortic stenosis treated with balloon-expandable TAVI.[29] Their sample size was rather small. Of the 706 patients who were treated with TAVI, only 17 had CLD, of whom 14 and 3 underwent a transfemoral and transapical approach, respectively. The mean STS score was 8.4 and mean MELD was 11.4. One person died in the hospital (5.9%) from a congestive heart failure, and 3 died at 90 days (17.7%). The deaths were due to sepsis and acute liver injury in a liver-transplant patient on immunosuppression with biopsy confirming chronic hepatitis, without further description provided. Another patient died from sepsis and kidney failure at postoperative day 487. The third patient died of unknown causes at postoperative day 1005. No patients experienced major bleeding; no patients required permanent pacemaker implantation; 1 had a myocardial infarction (6%); 1 had a transient ischemic attack (6%); and 5 had postprocedural acute kidney injury (29%). Their study did not mention the postprocedural time frame at which kidney injury had occurred. Of the 17 patients, 14 (82%) had confirmed cirrhosis, and 3 (18%) had chronic hepatitis; there were no patients with MELD scores > 20. In high-risk patients, the use of TAVI was associated with positive outcomes.[1] This study was limited by the small sample size at a single center; however, it was the largest TAVI outcome study in this population. The authors concluded that TAVI is feasible to treat aortic stenosis in mild to moderate CLD with low complication rates.

A propensity score–matched analysis and multicenter study done in Madrid, Spain, by Tirado-Conte et al. of 114 patients with CLD, with a mean MELD of

11.3 and undergoing TAVI, were compared to 1118 patients without liver disease.[31] Of the 114 patients, 83 had cirrhosis (73%). Acute kidney injury was more common in the group with CLD (30.8%) as compared to the group without liver disease (13.5%; $p = 0.01$); in-hospital mortality rates were similar for patients with and without liver disease (7% and 4%; $p = 0.344$); however, at 2 years postoperatively, the noncardiac mortality was significantly higher in the liver disease group (26.4% vs. 14.8%; $p = 0.034$). Thus, the authors concluded that TAVI may be an option as a bridge to transplant or before a definitive cure for the underlying etiology of the liver disease. In the short-term, TAVI was suggested as an option for patients with cirrhosis; however, this study suggested that the long-term outcomes may be dismal.[31]

Poor renal reserve or Child-Turcotte-Pugh Class B or C predicted mortality in this study. Further data are needed on this subgroup of patients, as liver transplant may be the only definite therapy.

Because patients with cirrhosis are at higher risk of complications after surgery, data from the Cleveland Clinic presented as an abstract at the 2018 American Association on the Study of Liver Diseases Meeting in San, Francisco, California, aimed to identify outcomes after TAVI in patients with cirrhosis using the NIS database from 2011 to 2014.[32] During this time interval, there were 42,214 patients who had undergone TAVI, 691 of whom had cirrhosis. They reported no statistically significant differences between groups, thus concluding that TAVI could be safe in patients with cirrhosis.

TAVI versus SAVR in patients with CLD

A study by Greason et al. from the Mayo Clinic reviewed 18 patients from 2008 to 2012, and compared patients with cirrhosis, of whom 6 received TAVI and 12 received SAVR.[28] Pooled collectively, their STS mortality risk was 3.2% with a mean MELD score of 9. Of the patients receiving TAVI, a transfemoral approach was done in 83%, whereas 17% were approached transapically. None of these patients required mechanical or extracorporeal support, although 5 (83%) needed vasopressors and 4 (67%) required blood products. Their median hospital stay was 5 days, and at 219 days after the procedure, all were alive. In terms of the SAVR group, 8 patients (67%) required vasopressors, 100% of patients needed a blood transfusion, 8 patients (67%) had renal failure as a complication, and 1 (8%) required a pacemaker. Median stay was 6 days. Two patients died during hospitalization, and at 228 days, 5 more patients died. Although their sample size was small, this case series demonstrated that patients who had TAVI required fewer transfusions and experienced less morbidity and mortality than those who had SAVR. The in-hospital mortality rate for TAVI was 0% and 17% for SAVR patients.

Peeraphatdit et al. compared TAVI against SAVR in 105 patients with aortic valve stenosis and cirrhosis between 2008 and 2016.[33] Overall, the median MELD score was 12. There was no difference in terms of in-hospital or 30-day mortality rates between the TAVI and SAVR groups; however, those who underwent TAVI required fewer transfusions and had shorter lengths of stay. Furthermore, in a subgroup analysis of patients with MELD scores of < 12, SAVR was safer with a median survival of 4.4 years, as compared to TAVI with a median survival of 2.8 years. However, in patients with a MELD score > 12, there was no mortality benefit when comparing TAVI or SAVR against standard medical therapy (balloon valvuloplasty). From this study it was concluded that MELD score is a predictor of mortality in patients undergoing TAVI and SAVR. In addition, patients with low MELD scores may perform better with SAVR. More recently, Lak et al. performed a retrospective study reviewing patients from 2015 to 2018 at a single center and identified 32 patients with cirrhosis and severe aortic stenosis who underwent TAVI.[34] This group was compared to the control group with propensity matched analysis, with results revealing patients with severe aortic stenosis and cirrhosis after the TAVI procedure had similar outcomes to the control group for 1-year mortality rate and adverse cardiac and cerebrovascular events.

Alqahtani et al. performed a review of the NIS database to evaluate trends and outcomes in patients with cirrhosis undergoing TAVI and SAVR from 2003 to 2014.[35] They included patients over >65 years and found that in-hospital mortality rates were significantly lower in TAVI than in SAVR patients (8% and 20%, respectively). In addition, patients who had SAVR required more blood transfusions and had higher rates of acute kidney injury, requiring dialysis. They had lengthier hospitalizations and were less likely to be discharged to go home. By using administrative data sets, there are limitations in analysis due to reliance on diagnostic codes rather than actual clinical data. The authors concluded that in select patients, TAVI can avoid the need for cardiopulmonary bypass and reduce morbidity when compared with SAVR.[28,36–38] Based on this report, there still exists a need for a single risk-stratification tool for patients with cirrhosis undergoing major cardiac procedures.

A similar study was conducted by Thakkar et al. using the NIS database from 2011 to 2012 in patients >50 years and included 93 SAVR and 36 TAVI cases.[39] There was no statistically significant difference in terms of in-hospital mortality rates between the two groups (6.7% and 6.7%, respectively); however, SAVR patients had higher mean length of stays (14.3 vs. 6.2 days; $p = 0.006$) and higher rates of vascular complications (63.3% vs. 33.3%, respectively; $p = 0.02$), transfusions

(56.7% vs. 30%, respectively; p = 0.04), and other complications (e.g., cardiac, respiratory, neurological, renal) (80% vs. 60%, respectively). Thus, unlike the Algahtani study, which showed a mortality benefit with TAVI, this study was only able to demonstrate that there were fewer complications associated with TAVI.[35] One limitation to this type of study is the lack of follow-up, which could account for the inability to determine a mortality benefit.

Lee et al.[40] reviewed the NIS database from 2011 to 2017 for patients who underwent TAVI and SAVR with CLD, comparing case–control propensity score matching with 1353 and 4059 with and without CLD who underwent SAVR, and 606 and 1818 with and without CLD who underwent TAVI. Their study showed no difference in mortality, length of stay, or complications between patients with and without CLD. However, within the SAVR group, patients with CLD had higher mortality, length of stay, and costs as well as respiratory and bleeding complications.

ANTITHROMBOTIC THERAPY

Current recommendations for post-TAVI management includes antithrombotic therapy.[41] The general approach for selection of antithrombotic regimen is dependent on whether the patient has a concurrent indication for anticoagulation, such as atrial fibrillation, or indication for antiplatelet agent, such as recent coronary stent placement. In patients without an additional indication for either antiplatelet or anticoagulation, a single antiplatelet agent is recommended following TAVI, typically aspirin (75–100 mg). In patients with an indication for dual antiplatelet therapy, the duration of dual therapy is dictated by the concurrent indication. For patients with an indication for therapeutic anticoagulation without concurrent antiplatelet indication, patients can be treated with vitamin K antagonist or direct oral anticoagulation without the addition of antiplatelet agents.[42]

These recommendations are further corroborated by the POPular TAVI trial, which demonstrated that oral anticoagulation alone was associated with a reduced risk of all causes of bleeding as well as procedural-related bleeding, as compared with anticoagulation plus clopidogrel.[43]

Importantly, it should be noted that triple antithrombotic therapy is ill-advised due to higher mortality rates.[44] These recommendations pose an interesting dilemma for patients with CLD, especially in those awaiting liver transplantation. It is well described that patients with CLD have chronic pancytopenia, which poses a challenge for maintaining these patients on antiplatelet or anticoagulation therapy. Additionally, when TAVI is performed in the patients with CLD awaiting liver transplantation, the perioperative management of antithrombotic therapy needs to be weighed against the risk of bleeding.

CONCLUSIONS

Calcific aortic disease is a progressive and indolent process that can ultimately lead to severe, symptomatic aortic stenosis and lead to death if left untreated. At present, the options for treatment include standard therapy (balloon valvuloplasty), aortic valve repair with a surgical or transcatheter approach, or palliation. The type of treatment should involve a multidisciplinary approach that centers around the patient's desires, their medical comorbidities, and prognosis. Certain scoring algorithms have been validated in the surgical literature. The most widely used risk stratification tool is the STS-PROM, which considers demographical, laboratory, and historical clinical data points. This score does not explicitly incorporate CLD. In patients with CLD, especially those with indications for liver transplantation, aortic stenosis can be routinely diagnosed via pretransplant cardiac testing. Currently, cirrhosis is not a contraindication to TAVI or SAVR. Due to the hemodynamics, and coagulopathy unique to cirrhosis, TAVI is likely the preferred option; however, when compared with SAVR, higher rates of vascular complications and new-onset paravalvular regurgitation have been reported after TAVI. The ultimate risk in the patient with cirrhosis remains unknown. Because TAVI avoids the need for cardiopulmonary bypass and prolonged anesthesia, it is a preferred option to SAVR, but there are only case reports and case series that support this opinion. In the short term, patients with cirrhosis who receive TAVI perform well, but long-term mortality rates are dismal. This may suggest that TAVI could serve as a bridge to liver transplant. Lee et al. describes no difference in mortality and complication rates in patients who undergo TAVI with or without CLD; however, it is unclear the degree of liver disease in the CLD cohort.[40] The Greason study from the Mayo Clinic compared SAVR to TAVI in patients with cirrhosis and found that the in-hospital mortality rates in the TAVI group were significantly lower, and these patients required fewer transfusions and had shorter lengths of stay.[28] However, their study participants had a mean MELD score of 9 and STS-PROM score of 3.2%; thus, they were overall low-risk and did not have severe decompensated cirrhosis. The current literature of symptomatic patients with aortic stenosis does not include patients with high MELD scores. These are the patients who require liver transplant to survive. There is a need for further data regarding the optimal timing of pursuing a TAVI procedure and the listing of the patient for transplantation. The

questions remains whether TAVI should be considered a requirement before liver transplant evaluation and potential listing. Perhaps the optimal timing would be related to when post-TAVI patients can safely hold antithrombotic therapy in anticipation of transplantation.

Thus, TAVI should be considered in these patients, as this is one of the only viable options to optimize their transplant candidacy with regard to aortic stenosis. Future studies of high-risk patients with aortic stenosis should include patients with cirrhosis. There exists a need for prospective, randomized clinical trials that follow the long-term outcomes of this patient population who undergo TAVI and their outcomes after liver transplantation. This review reaffirms the ongoing need for transplant hepatologists, cardiologists, anesthesiologists, and transplant surgeons to work in a multidisciplinary fashion while evaluating a patient with cirrhosis with severe aortic stenosis for liver transplant.

CONFLICT OF INTEREST

No conflicts of interest.

ORCID

Lorenzo De Marchi https://orcid.org/0000-0002-9399-9524

REFERENCES

1. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol. 1997;29:630–4.
2. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. Eur Heart J. 2003;24:1231–43.
3. O'Brien KD. Pathogenesis of calcific aortic valve disease: a disease process comes of age (and a good deal more). Arterioscler Thromb Vasc Biol. 2006;26:1721–8.
4. Roberts WC. Anatomically isolated aortic valvular disease. The case against its being of rheumatic etiology. Am J Med. 1970;49:151–9.
5. Sharma UC, Barenbrug P, Pokharel S, Dassen WRM, Pinto YM, Maessen JG. Systematic review of the outcome of aortic valve replacement in patients with aortic stenosis. Ann Thorac Surg. 2004;78:90–5.
6. Morris J, Hellman C, Gawey B, Ramsay MA, Valek TR, Gunning TC, et al. Three patients requiring both coronary artery by- pass surgery and orthotopic liver transplantation. J Cardiothorac Vasc Anesth. 1995;9:322–32.
7. An Y, Xiao Y, Zhong Q. Open-heart surgery in patients with liver cirrhosis. Eu J Cardio Thorac. 2007;31:1094–7.
8. Segura I, Herrero J, Martín A, Saénz de Buruaga JD, Quiroga J, Latorre G, et al. Aortic valve replacement with bioprostheses in liver transplant recipients. J Heart Valve Dis. 2000;9:370–3.
9. Parker B, Mayes J, Henderson J, Savage R. Combined aortic valve replacement and orthotopic liver transplantation. J Cardiothorac Vasc Anesth. 2001;15:474–6.
10. Eckhoff D, Frenette L, Sellers M, McGuire B, Contreras JL, Bynon JS, et al. Combined cardiac surgery and liver transplantation. Liver Transpl. 2001;7:60–1.
11. DeStephano C, Harrison B, Mordecai M, Crawford CC, TSJ S, Hewitt WR, et al. Anesthesia for combined cardiac surgery and liver transplant. J Cardiothorac Vas Anesth. 2010;24:285–92.
12. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60:1438–54.
13. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J. 2016;37:3503–12.
14. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695–705.
15. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. J Am Coll Cardiol. 2018;72:2687–96.
16. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol. 2014;63:1972–81.
17. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597–607.
18. Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol. 2015;65:2184–94.
19. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;370:1790–8.
20. Schwarz F, Baumann P, Manthey J, Hoffmann M, Schuler G, Mehmel HC, et al. The effect of aortic valve replacement on survival. Circulation. 1982;66:1105–10.
21. Brown J, O'Brien S, Wu C, Sikora J, Griffith B, Gammie J. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg. 2009;137:82–90.
22. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. J Am Coll Cardiol. 2011;58:2151–62.
23. Gopaldas R, Chu D, Cornwell L, Dao T, Lemaire S, Coselli J, et al. Cirrhosis as a moderator of outcomes in coronary artery bypass grafting and off-pump coronary artery bypass operations: a 12- year population-based study. Ann Thorac Surg. 2013;96:1310–5.
24. Steffen RJ, Bakaeen FG, Vargo PR, Kindzelski BA, Johnston DR, Roselli EE, et al. Impact of cirrhosis in patients who underwent surgical aortic valve replacement. Am J Cardiol. 2017;120:648–54.
25. Downing SW, Edmunds LH Jr. Release of vasoactive substances during cardiopulmonary bypass. Ann Thorac Surg. 1992;54:1236–43.
26. Casey LC. Role of cytokines in the pathogenesis of cardiopulmonary-induced multisystem organ failure. Ann Thorac Surg. 1993;56(5 Suppl):S92–6.
27. Okano N, Miyoshi S, Owada R, Fujita N, Kadoi Y, Saito S, et al. Impairment of hepatos- planchnic oxygenation and increase of

serum hyaluronate during normothermic and mild hypothermic cardiopulmonary bypass. Anesth Analg. 2002;95:278–86.
28. Greason K, Mathew V, Wiesner RH, Suri R, Rihal CS. Transcatheter aortic valve replacement in patients with cirrhosis. J Cardiovasc Surg (Torino). 2013;28:492–5.
29. Shah AM, Ogbara J, Herrmann HC, Fox Z, Kadakia M, Anwaruddin S, et al. Outcomes of transcatheter aortic valve replacement in patients with chronic liver disease. Catheter Cardiovasc Interv. 2015;86:888–94.
30. Pascual I, Muñoz-García AJ, López-Otero D, Avanzas P, Alonso-Briales JH, Morís C. Long-term outcome of cirrhotic patients with severe aortic stenosis treated with transcatheter aortic valve implantation. Rev Esp Cardiol (Engl Ed). 2015;68:353–4.
31. Tirado-Conte G, Rodés-Cabau J, Rodríguez-Olivares R, Barbanti M, Lhermusier T, Amat-Santos I, et al. Clinical outcomes and prognosis markers of patients with liver disease undergoing transcatheter aortic valve replacement: a propensity score-matched analysis. Circ Cardiovasc Interv. 2018;11:e005727.
32. Sarmini M, Asfari M, Al-Khadra Y, Dasarathy S, McCullough A. The safety of transcutaneous aortic valve replacement in cirrhotic patients. In: Proceedings of the AASLD Meeting, San Francisco, CA, USA. Hoboken: Wiley; 2018. Abstract 2334.
33. Peeraphatdit TB, Nkomo VT, Naksuk N, Simonetto DA, Thakral N, Spears GM, et al. Long-term outcomes after transcatheter and surgical aortic valve replacement in patients with cirrhosis: a guide for the hepatologist. Hepatology. 2020;72:1735–46.
34. Lak HM, Chawla S, Gajulapalli RD, Verma BR, Vural AF, Gad M, et al. Outcomes after transfemoral transcatheter aortic valve implantation with a SAPIEN 3 valve in patients with cirrhosis of the liver (a tertiary care center experience). Am J Cardiol. 2021;160:75–82.
35. Alqahtani F, Aljohani S, Ghabra A, Alahdab F, Kawsara A, Holmes DR, et al. Outcomes of transcatheter versus surgical aortic valve implantation for aortic stenosis in patients with hepatic cirrhosis. Am J Cardiol. 2017;120:1193–7.
36. Peterss S, Beckmann E, Bhandari R, Hadem J, Hagl C, Khaladj N, et al. Aortic valve replacement in patients with end-stage liver disease: a modified perfusion concept in high-risk patients. J Heart Valve Dis. 2015;24:302–9.
37. Gundling F, Seidl H, Gansera L, Schuster T, Hoffmann E, Kemkes BM, et al. Early and late outcomes of cardiac operations in patients with cirrhosis: a retrospective survival-rate analysis of 47 patients over 8 years. Eur J Gastroenterol Hepatol. 2010;22:1466–73.
38. Arif R, Seppelt P, Schwill S, Kojic D, Ghodsizad A, Ruhparwar A, et al. Predictive risk factors for patients with cirrhosis undergoing heart surgery. Ann Thorac Surg. 2012;94:1947–52.
39. Thakkar B, Patel A, Mohamad B, Patel NJ, Bhatt P, Bhimani R, et al. Transcatheter aortic valve replacement versus surgical aortic valve replacement in patients with cirrhosis. Catheter Cardiovasc Interv. 2016;87:955.e962.
40. Lee DU, Han J, Fan GH, Hastie DJ, Kwon J, Lee KJ, et al. The clinical impact of chronic liver disease in patients undergoing transcatheter and surgical aortic valve replacement: systematic analysis of the 2011–2017 US hospital database. Catheter Cardiovasc Interv. 2021;98:E1044–57.
41. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2021;143:e229]. Circulation. 2021;143:e72–e227.
42. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. J Am Coll Cardiol. 2020;76:2492–516.
43. Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med. 2020;383:1447–57.
44. Kuno T, Takagi H, Sugiyama T, Ando T, Miyashita S, Valentin N, et al. Antithrombotic strategies after transcatheter aortic valve implantation: Insights from a network meta-analysis. Catheter Cardiovasc Interv. 2020;96:E177–86.

How to cite this article: Duong N, Nguyen V, De Marchi L, Thomas A. Approach to the patient with decompensated cirrhosis and aortic stenosis during liver transplantation evaluation. Hepatol Commun. 2022;6:3291–3298. https://doi.org/10.1002/hep4.2094