Hepatorenal Dysfunction Predicts Operative Mortality After Triple Valve Surgery: Utility of MELD-Na

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Abstract

Background Despite significant advancements in operative techniques and myocardial protection, triple valve surgery (TVS) remains a formidable operation with a relatively high in-hospital mortality. We evaluated the prognostic value of Model for End-stage Liver Disease score including sodium (MELD-Na) for mortality after TVS and its predictive value when incorporated in the EuroSCORE risk model. Methods We performed a retrospective cohort study of 61 consecutive patients who underwent TVS from November 2005 to June 2016. Demographics, clinical, biochemical, and operative data were collected and analysed. Results Median follow-up duration was 8.0 years. 70.5% of patients suffered from rheumatic heart disease. 86.9% underwent mechanical double valve replacement with tricuspid valve repair. There were six operative deaths (9.84%), with the most common cause of death being multiorgan failure (83.3%). 26.2% had a moderately elevated MELD-Na score of 9 to 15, and 4.9% had a severely elevated score of >15. Patients with a MELD-Na >9 had a higher unadjusted rate of operative mortality, prolonged ventilation, need for dialysis and acute liver failure after TVS. Hierarchical logistic regression was performed using logistic EuroSCORE as the base model. After risk adjustment, each point of MELD-Na score increase was associated with 1.405 times increase in odds of operative mortality. The regression analysis was repeated by incorporating individual components of the MELD-Na score, including bilirubin, sodium, and albumin. All three biochemical parameters were significantly associated with operative mortality Conclusion MELD-Na score as a quantifier of hepatorenal dysfunction is sensitive and specific for mortality after triple valve surgery.

Article title

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Running head

MELD-Na and triple valve surgery

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Glossary of Abbreviations

LV = left ventricle

MELD = Model for End-stage Liver Disease

MELD-Na = MELD score including Na (sodium)

NYHA = New York Heart Association

RV = right ventricle

RVF = right ventricular failure

TVS = triple valve surgery

Abstract

Background

Despite significant advancements in operative techniques and myocardial protection, triple valve surgery (TVS) remains a formidable operation with a relatively high in-hospital mortality. We evaluated the prognostic value of Model for End-stage Liver Disease score including sodium (MELD-Na) for mortality after TVS and its predictive value when incorporated in the EuroSCORE risk model.

Methods

We performed a retrospective cohort study of 61 consecutive patients who underwent TVS from November 2005 to June 2016. Demographics, clinical, biochemical, and operative data were collected and analysed.

Results

Median follow-up duration was 8.0 years. 70.5% of patients suffered from rheumatic heart disease. 86.9% underwent mechanical double valve replacement with tricuspid valve repair. There were six operative deaths (9.84%), with the most common cause of death being multiorgan failure (83.3%).

26.2% had a moderately elevated MELD-Na score of 9 to 15, and 4.9% had a severely elevated score of >15. Patients with a MELD-Na >9 had a higher unadjusted rate of operative mortality, prolonged ventilation, need for dialysis and acute liver failure after TVS.

Hierarchical logistic regression was performed using logistic EuroSCORE as the base model. After risk adjustment, each point of MELD-Na score increase was associated with 1.405 times increase in odds of operative

mortality. The regression analysis was repeated by incorporating individual components of the MELD-Na score, including bilirubin, sodium, and albumin. All three biochemical parameters were significantly associated with operative mortality

Conclusion

MELD-Na score as a quantifier of hepatorenal dysfunction is sensitive and specific for operative mortality after triple valve surgery.

Introduction

In Hong Kong, patients indicated for concomitant poly-valvular surgery were often referred for surgical assessment late in the course of their disease. Severe pulmonary hypertension, impaired biventricular function, and hepatorenal dysfunction were highly prevalent in these patients. Despite significant advancements in operative techniques and myocardial protection, concomitant operations on the trifecta of aortic, mitral and tricuspid valves still mandates a prolonged period of cardiopulmonary bypass and myocardial ischemia, which may overwhelm the limited cardiopulmonary and visceral reserve in these patients.

Risk stratification is one of the cornerstones of modern cardiac surgery.[1] Although a myriad of scoring systems are available for coronary and valvular procedures, both the modern iterations of EuroSCORE and STS risk calculator were designed with coronary or single-valve operations in mind.[2] Neither scoring system took liver function into account.

The Model for End-stage Liver Disease (MELD) is a scoring system originally developed to predict short-term mortality in patients with cirrhosis and trans-jugular intrahepatic portosystemic shunt, first adopted by the United Network for Organ Sharing for prioritizing liver recipients in 2002. It has been demonstrated to predict operative mortality after tricuspid surgery and cardiac surgery in general.[3–7] In this case series, we aim to quantify the impact of hepatorenal dysfunction using MELD and evaluate its ability to predict operative mortality after triple valve surgery (TVS).

Patients and methods

Study design

Between June 2005 and June 2015, a total of 61 patients underwent TVS at the Prince of Wales Hospital, Hong Kong. Local paper and electronic health records were retrospectively reviewed to collect perioperative data. Database lock date was 1st March 2021. Paper and electronic health records were reviewed to determine the occurrence of postoperative complications and cardiac events. The Hong Kong Patient Master Index provided data on vital status. The study was authorized by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and consent was waived in view of its retrospective nature.

Operative technique

Median sternotomy and aorto-bicaval cannulation were the standard surgical approach. Cardioplegic arrest was achieved by administering cold crystalloid cardioplegia into the aortic root in antegrade fashion. Coronary ostia were selectively cannulated and perfused with cardioplegia in patients with aortic regurgitation. Tricuspid valve repair was routinely performed with the heart arrested using a remodeling annuloplasty ring and bicaval snares.

Definition of endpoints

The primary endpoint was operative mortality, which was defined as death within any time interval after the operation if the patient had not been discharged from the hospital or within 30 days of the operation. The secondary endpoint was late cardiac events, which were defined as the occurrence of recurrent congestive heart failure or cardiac death after discharge.

Calculation of EuroSCORE and simplified MELD-Na

Standard EuroSCORE definitions of preoperative risk factors and postoperative adverse events were used. EuroSCORE was calculated by the first author using the EuroSCORE web site (www.euroscore.org).

Most patients had blood sampling multiple times in the months leading up to surgery, usually due to prior hospitalizations for heart failure. In addition, our unit routinely requests an organ function biochemistry panel for all patients on the day prior to surgery. To ensure fair comparison and account for day-to-day fluctuations in creatinine and bilirubin measurements, it was the measurement taken the day prior to surgery that was used in the final calculation.

The following formulas were used for calculation of MELD and MELD-Na:

$$Simplified\ MELD = \ 9.57\ x\ log\,(Creatinine\ in\ mg/dL) + \ 3.78\ x\ log(Bilirubin\ in\ mg/dL)\ + \ 6.43$$

$$Simplified\ MELD\ including\ Na = \ MELD - Na\ in\ mEq/L - [\ 0.025\ x\ MELD\ x\ \ (140 - Na)\ ] + 140$$

International Normalized Ratio (INR) was omitted from the formula because 85.2% of the cohort had atrial fibrillation and 82.0% were on oral anticoagulants preoperatively.

Assessment of right ventricular systolic function

Significant heterogeneity exists when comparing right ventricular systolic function based on echocardiographic data alone. The most common modalities used by referring institutions were tricuspid annular plane systolic excursion (TAPSE) and fractional area change (FAC). Reporting standards vary from one institution to another. Some institutions report both while other institutions report just one parameter. For the purpose of comparison, right ventricular systolic function was classified as normal and abnormal using a TAPSE cut-off of 16mm and FAC cut-off of 35%, based on American Society of Echocardiography guidelines from 2016.[8]

Statistical analysis

Statistical analysis was performed with SPSS version 20.0. Descriptive statistics were reported as mean with standard deviation for continuous variables and as frequencies and percentages for categorical variables.

Univariate analysis was performed to determine risk factors for early and late mortality. For categorical data, the χ^2 test was used to evaluate univariate categorical data when the minimum number of observations in a category was over 5; otherwise, likelihood ratios G-tests were used. For continuous data, simple logistic regression was used. Variables with a p-value less than 0.05 on univariate analysis were considered statistically significant.

Using logistic EuroSCORE as the base model, a hierarchical logistic regression model incorporating MELD-Na was used to ascertain the association between MELD-Na and operative mortality and major morbidities.

Survival was estimated using the Kaplan–Meier method. Survival curves were compared using Cox proportional-hazards model. The discriminatory power of MELD-Na and EuroSCORE for in-hospital mortality evaluated using area under the receiver operating characteristic (ROC) curve. The ROC analysis results were interpreted as follows: AUC <0.70, low diagnostic accuracy; AUC in the range of 0.70–0.90, moderate diagnostic accuracy; and AUC [?]0.90, high diagnostic accuracy. Survival curves were generated with MedCalc version 19.4.

Results

Patient demographics and baseline characteristics

Patient demographics and baseline characteristics were shown in Table 1. The mean follow-up duration was 82 months, ranging from 70 to 175 months. None were lost to follow-up. There were 27 men (44.3%) and 34 women (55.7%). Age ranged between 42 and 77 years, with a mean of 58.6 ± 11.0 years. 24.6% had dyspnea with mild exertion or minimal activity, corresponding to New York Heart Association (NYHA) functional class III or IV status. 57.4% had a prior hospitalization for acute decompensated heart failure. 73.8% (n=45) had normal left ventricular ejection fraction. One in four patients had moderate-to-severe pulmonary hypertension, as defined by mean pulmonary arterial pressures.

Data regarding right ventricular systolic function was missing in 15 patients (21.7%) due to institutional database purge of aged data. For the patients with available data, one in five had right ventricular systolic dysfunction.

8.2% of the operations were performed on an urgent basis due to refractory heart failure or repeated hospitalizations for heart failure. 6.6% had prior cardiac surgery.

Operative details

Operative details were shown in Table 2. 86.9% (n=53) had mechanical aortic and mitral valve replacement. All tricuspid valves were successfully repaired. The aetiology of the aortic and mitral valve dysfunction was predominantly rheumatic (70.5%) and degenerative (26.2%). One patient had active aortic and mitral valve endocarditis at the time of surgery. Concomitant CABG was performed in six cases. The crossclamp and cardiopulmonary bypass times were 186 ± 30 and 132 ± 24 minutes, respectively.

Postoperative complications

Postoperative complications were shown in Table 3. 6.6% of patients required resternotomy for haemostasis. Perioperative cerebrovascular events were not uncommon. Four patients had an ischaemic stroke, and one became debilitated as a result; two patients suffered from intracranial haemorrhage which required neurosurgical intervention. None required permanent pacemaker implantation. 13.1% required renal replacement therapy due to acute renal failure, another 13.1% required prolonged ventilation.

Operative mortality and its association with pre-existing hepatorenal dysfunction

The prevalence and severity of hepatorenal dysfunction was shown in Table 4. 27.9% of all patients had at least one biochemical abnormality, namely hyponatremia (defined as plasma sodium less than 135mEq/L), hyperbilirubinemia (total bilirubin [?] 2.0mg/dL), hypoalbuminemia (albumin <3.5g/dL) and elevated serum creatinine (over 200 umol/L or dialysis). One in ten patients had two or more deranged biochemical parameters.

MELD-Na was used as a surrogate measure of the severity of hepatorenal dysfunction. Most patients had a MELD-Na score less than 9 (68.9%), 26.2% had a moderately elevated score of 9 to 15, and 4.9% had a severely elevated score of greater than 15.

There were six operative deaths. One patient died from a perforated peptic ulcer and refractory sepsis. Five deaths can be attributed to multiorgan failure. The most common cause of demise was exacerbation of pre-existing hepatorenal dysfunction by cardiopulmonary bypass, systemic venous congestion, and post-bypass right ventricular dysfunction, culminating in frank multiorgan failure. Despite instititution of intra-aortic counter-pulsation and dialysis to reduce right ventricular afterload and right-sided filling pressures, mortality remained high. Patients who died exhibited more profound pre-existing hepatorenal dysfunction than those who survived, as reflected by a higher MELD-Na,t (61) = 8.91, p < 0.001.

Unadjusted operative mortality increased with increasing MELD-Na score, $\chi^2(2) = 23.8$, p = 0.000007. Kendall's tau (τb) was 0.551, indicating a moderate association. Patients with a MELD-Na greater than 9 also suffered from more complications, including postoperative mechanical circulatory support, prolonged ventilation, need for dialysis and acute liver failure after TVS (Table 5).

A scatterplot of the MELD-Na and EuroSCORE values of the cohort segregated into survivors and non-survivors were shown in Figure 1 to facilitate visual comparison. The diagnostic accuracy of MELD-Na was compared with EuroSCORE using area under the receiver operating characteristic (ROC) curves. For MELD-Na score, the AUC was an impressive 0.992 [95% CI 0.925-1.000], indicating high diagnostic accuracy. The Youden Index was 0.982 at a cut-off of 13. For EuroSCORE, the AUC was 0.611 [95% CI 0.477-0.733], indicating low diagnostic accuracy.

Risk-adjusted association of MELD-Na with operative mortality and major morbidities

A hierarchical logistic regression model incorporating MELD-Na was constructed with the logistic EuroSCORE as the base model. EuroSCORE alone is weakly associated with operative mortality with an odds ratio of 1.135 [95% CI 1.016 – 1.268] (p = 0.025). After adjustment for baseline EuroSCORE, the regression model demonstrated continued associations between MELD-Na and operative mortality and morbidities (Table 6). Of note, each point of MELD-Na score increase was associated with 1.405 times increase in the odds of operative mortality (p = 0.015).

The regression analysis was repeated by incorporating individual components of the MELD-Na score, including bilirubin, sodium, and albumin. All three biochemical parameters were significantly associated with operative mortality (Table 7). Creatinine was excluded because it already is a component of the logistic EuroSCORE.

Long-term survival and cardiac events

Using the Kaplan-Meier method, the 5-year overall and event-free survival was 78.6% and 72.1% respectively (figure 2 panel A and B). 12.7% of patients had at least one subsequent hospitalization for congestive heart failure. There were two incidences of late prosthetic valve endocarditis and one patient died from septic shock. One patient suffered from structural valve degeneration of the bioprosthetic aortic valve requiring reoperation.

A total of 20 major bleeding events occurred over 424 person-years of follow-up. The unadjusted rate of bleeding with warfarin was 4.72% per person-year. The most common source of bleeding was from the gastrointestinal tract accounting for half of all bleeding events.

Discussion

In a US Agency for Healthcare Research and Quality database review of 5,234 patients who underwent TVS from 2003 to 2012, operative mortality was 13.9%.[9] The 9.8% operative mortality in our series was similar to previously published studies.[10–17]

The key finding is that MELD-Na correlates well with operative mortality after triple valve surgery and exhibits superior diagnostic accuracy over EuroSCORE. The association remains significant after risk adjustment. A possible explanation is that the key driver of operative mortality was multiorgan failure in the valvular heart failure population; this is in contradistinction to the CABG population, in whom operative mortality was driven by low cardiac output syndrome.[18] Just as EuroSCORE is the *quid pro quo* litmus test of ventricular recovery after cardiopulmonary bypass, MELD-Na may serve the litmus test of organ reserve.

In polyvalvular heart failure, right ventricular function and hepatorenal function are delicately intertwined. Both acute and chronic dysfunctions in one organ can initiate and perpetuate dysfunction in the others through complex neurohormonal feedback systems. This complex system of crosstalks between failing organs is collectively referred to as cardiorenal and cardiohepatic syndromes.[19,20] A key message for cardiac surgeon sis that treating the valvular dysfunction may not necessarily lead to recovery in organ function. In fact, the deleterious effects of prolonged cardiopulmonary bypass may precipitate a potent immunogenic cascade leading to frank multiorgan failure and death.

Due to a substantial portion of missing data regarding right ventricular systolic function, the impact of chronic right ventricular dysfunction on hepatorenal dysfunction cannot be quantified in this study. Using the data available, right ventricular systolic dysfunction did correlate with operative mortality on univariate analysis. Volumetric assessment with MRI, right ventricular dimension, as well as strain imaging may provide more accurate assessment of right ventricular function compared with two-dimensional echocardiography. Nonetheless, we believe this is a promising avenue for future research because strategies to mitigate post-bypass right ventricular dysfunction and ensuing organ failure remain limited.

We would like to highlight the importance of including hyponatremia in the risk score. Hyponatremia in heart failure is mediated by increased activity of anti-diuretic hormone and activation of the renin-angiotensin-aldosterone system. Aggressive diuresis may also have played a role. As demonstrated in the OPTIMISE-HF registry, hyponatremia in patients hospitalized for heart failure was associated with higher rates of in-hospital and follow-up mortality.[21]Although it is unclear whether hyponatremia contributes to poor prognosis or serves simply as a marker of disease severity, the presence and severity of hyponatremia should alert the surgeon to the severity of the underlying heart failure.[22]

This study was retrospective in nature and suffered from weaknesses inherent to all retrospective studies, including selection bias and confounding. The number of subjects was small. The findings generated were at best hypothesis-generating and would benefit from verification in a sizable regional or national database.

In Papworth's landmark publication regarding the EuroSCORE back in 1999, the authors commented that "the true test of such a system is in its widespread application in the field", and that its use should be routine for all cardiac surgical patients.[2] In the modern era, MELD-Na can be easily calculated by inputting the four biochemical parameters into mobile applications on smartphones and tablet computers. We believe that it is not a stretch to imagine that the adoption of MELD-Na can become widespread and find its rightful place in risk stratifying patients with valvular heart failure.

Conclusion

MELD-Na score as a quantifier of hepatorenal dysfunction is sensitive and specific for operative mortality after triple valve surgery.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

First authorship: KL

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Last authorship: WHL

Concept or design: KL, MJU, WHL

Acquisition of data: KL, MJU, CCY, HYK

Analysis or interpretation of data: KL, HYK, CCY, MJU, WHL

Drafting of the manuscript: KL, MJU, WHL

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Tables

Table 1. Demographics and baseline characteristics.

Variable	n (%)	LR	p-value
Age [a]	58.6 ± 10.9	0.088	0.766
Male	27 (44.3%)	0.088	0.766
NYHA class I & II III & IV	46 (75.4%) 15 (24.6%)	10.488	0.001 *
Hypertension	23 (37.7%)	0.417	0.519
Diabetes mellitus	9 (14.8%)	1.480	0.224
Dyslipidemia	8 (13.1%)	4.182	0.141
Chronic lung disease	10 (16.4%)	0.000361	0.985
Extracardiac arteriopathy	2 (3.3%)	2.201	0.138
Previous cardiac surgery	4 (6.6%)	0.858	0.354
Previous chest irradiation	1 (1.6%)	N/A	N/A
Active endocarditis	1 (1.6%)	N/A	N/A

Variable	n (%)	LR	p-value
Preoperative MCS	1 (1.6%)	N/A	N/A
Urgent operation	4 (6.6%)	3.669	0.055
Atrial fibrillation	52 (85.2%)	2.026	0.155
LV function [b] LVEF [?]50% LVEF 31-49% LVEF 21-30% LVEF [?]20%	45 (73.8%) 12 (19.7%) 4 (6.6%) 0	4.860	0.027 *
RV function Impaired Normal Missing	10 (16.4%) 36 (59.0%) 15 (24.6%)	6.715	0.010 *
Mean pulmonary artery pressure [b] <25mmHg 25-40mmHg 41-55mmHg >55mmHg	15 (24.6%) 31 (50.8%) 12 (19.7%) 3 (4.9%)	0.166	0.684
History of ADHF	35 (57.4%)	2.033	0.154
[a]: Comparison between those older than 60 and those younger than 60 [b]: Comparison between those with LVEF [?]50% and those with LVEF <50% [c]: Comparison between those with mPAP [?] 41mmHg and those [?] 40mmHg	[a]: Comparison between those older than 60 and those younger than 60 [b]: Comparison between those with LVEF [?]50% and those with LVEF <50% [c]: Comparison between those with mPAP [?] 41mmHg and those [?] 40mmHg	[a]: Comparison between those older than 60 and those younger than 60 [b]: Comparison between those with LVEF [?]50% and those with LVEF <50% [c]: Comparison between those with mPAP [?] 41mmHg and those [?] 40mmHg	[a]: Comparison between those older than 60 and those younger than 60 [b]: Comparison between those with LVEF [?]50% and those with LVEF <50% [c]: Comparison between those with mPAP [?] 41mmHg and those [?] 40mmHg

Table 2. Operative details.

Variable	n (%) or Mean ± SD
Mitral valve procedure Repair Tissue valve Mechanical valve	3 (4.9%) 5 (8.2%) 53 (86.9%)
Aortic valve procedure Tissue valve Mechanical valve	7 (11.5%) 54 (88.5%)
Tricuspid valve procedure Repair Tissue valve Mechanical valve	61 (100%) 0 0
Etiology Rheumatic Degenerative Endocarditis	43 (70.5%) 16 (26.2%) 2 (3.3%)
Concomitant CABG	6 (9.8%)
Crossclamp time (min)	132 ± 24 min
Cardiopulmonary bypass time (min)	186 ± 30 min

Table 3. Postoperative complications.

Complications	n (%)
Death Multiorgan failure Perforated peptic ulcer with refractory sepsis	5 (8.2%) 1 (1.6%)
Mechanical circulatory support Extracorporeal membrane oxygenation Intra-aortic balloon pump	1 (1.6%) 4 (6.6%)
Prolonged ventilation	8 (13.1%)
Dialysis	8 (13.1%)
Acute liver failure	4 (6.6%)
Permanent pacemaker implantation	0
Resternotomy for bleeding	4 (6.6%)

Complications	**n (%)**
Sternal dehiscence	1 (1.6%)
Permanent stroke	4 (6.6%)
Intracranial haemorrhage	2 (3.3%)

Table 4. Biochemical disturbances and relative risk of operative mortality.

Variable	**n (%)**	**LR**	**p-value**
Renal function Normal Creatinine over 200 umol/L ESRF on dialysis	58 (95.1%) 2 (3.3%) 1 (1.6%)	7.336	0.026 *
Total bilirubin (mg/dL) < 2.0 mg/dL 2.0 – 3.0 mg/dL > 3.0 mg/dL	53 (86.9%) 5 (8.2%) 3 (4.9%)	11.096	0.001 *
Sodium (mEq/L) [?]135 mEq/L <135 mEq/L	53 (86.9%) 8 (13.1%)	11.096	0.001 *
Albumin (g/dL) [?]3.5g/dL <3.5g/dL	53 (86.9%) 8 (13.1%)	9.966	0.002 *

Table 5. Unadjusted short-term outcomes between MELD-Na subgroups.

Complications	**MELD-Na [?] 9** (n = 42)	**MELD-Na >9** (n = 19)	**p-value**
Operative mortality	0	6 (31.6%)	0.00008 *
Postoperative MCS	2 (4.76%)	4 (21.1%)	0.058 *
Prolonged ventilation	2 (4.76%)	6 (31.6%)	0.006 *
Dialysis	1 (2.4%)	7 (36.8%)	0.0003 *
Acute liver failure	0	4 (21.1%)	0.002 *

Table 6. Hierarchical logistic regression analysis of associations between MELD-Na and operative mortality and morbidities.

Complications	**Adjusted OR**	**95% CI**	**p-value**
Operative mortality	1.405	1.069 – 1.846	0.015 *
Postoperative MCS	2.051	1.258 – 3.344	0.004 *
Prolonged ventilation	1.921	1.101 – 3.350	0.022 *
Dialysis	5.677	1.003 – 32.13	0.050 *
Acute liver failure	1.763	1.119 – 2.779	0.015 *

Table 7. Hierarchical logistic regression analysis of associations between MELD-Na components and operative mortality.

MELD-Na component	Adjusted OR	95% CI	p-value
Bilirubin	2.466	1.060 – 5.738	0.036 *
Sodium	0.037	0.575 – 0.982	0.037 *
Albumin	0.806	0.660 – 0.985	0.035 *
Creatinine	1.006	0.997 – 1.016	0.189

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- `table.pdf` available at https://authorea.com/users/407871/articles/518060-hepatorenal-dysfunction-predicts-operative-mortality-after-triple-valve-surgery-utility-of-meld-na