ORIGINAL RESEARCH

Prognostic Value of Hepatorenal Function By Modified Model for End-stage Liver Disease (MELD) Score in Patients Undergoing Tricuspid Annuloplasty

Yan Chen, MD; Ying-Xian Liu, MD; Wai-Kay Seto, MD; Mei-Zhen Wu, MD; Yu-Juan Yu, MD; Yui-Ming Lam, MBBS; Wing-Kuk Au, MBBS, FCSHK; Daniel Chan, MBBS, FCSHK; Ko-Yung Sit, MBBS, FCSHK; Lai-Ming Ho, PhD; Hung-Fat Tse, MD, PhD; Kai-Hang Yiu, MD, PhD

***Background*—**The Model for End-stage Liver Disease excluding international normalized ratio (MELD-XI) score and the modified MELD score with albumin replacing international normalized ratio (MELD-Albumin) score, which reflect both liver and renal function, have been reported as predictors of adverse events in liver and heart disease. Nonetheless, their prognostic value in patients undergoing tricuspid annuloplasty has not been addressed.

***Methods and Results*—**A total of 394 patients who underwent tricuspid annuloplasty were evaluated. Baseline clinical, laboratory, and echocardiographic parameters were recorded. Adverse outcome was defined as the occurrence of heart failure requiring admission or all-cause mortality. Patients who underwent tricuspid annuloplasty had a high prevalence of preoperative hepatorenal dysfunction that was more common in patients with severe tricuspid regurgitation than those with mild to moderate tricuspid regurgitation. The MELD-XI and MELD-Albumin scores were excellent predictors of 1-year adverse outcome (area under the curve: 0.69 and 0.75, respectively). Kaplan–Meier survival curve demonstrated that a high score on MELD-XI (≥12.0) and MELD-Albumin (≥10.7) was associated with an increased risk of adverse events. During a median follow-up of 40 months, both MELD-XI and MELD-Albumin scores were significantly associated with adverse outcome, even after adjusting for potential confounding factors. Significant improvement of hepatorenal function at 1 year postoperation was noted only in patients who had no adverse events, not in those who experienced an adverse outcome.

***Conclusions*—**Both MELD-XI score and MELD-Albumin score can provide useful information to predict adverse outcome in patients undergoing tricuspid annuloplasty. The present study supports monitoring of modified MELD score to improve preoperative risk stratification of these patients. **(*J Am Heart Assoc*. 2018;7:e009020. DOI: 10.1161/JAHA.118.009020.)**

Key Words: liver and renal dysfunction • Model for End-stage Liver Disease • outcome • tricuspid annuloplasty • tricuspid regurgitation

Tricuspid regurgitation (TR) is common and associated with a poor prognosis and reduced long-term survival.[1,2] Tricuspid annuloplasty (TA) is currently recommended for the treatment of significant TR[3,4] and has been increasingly performed over the past decade.[5] Although TA has shown a satisfactory outcome in the short term, postoperative residual significant TR and mortality remain high during long-term follow-up.[6,7] Accurate preoperative risk evaluation is essential to identify patients at high risk and improve clinical outcome. Previous studies have demonstrated that TR can cause liver[8,9] and renal dysfunction[10]; nonetheless their prognostic value in patients with TA is largely unknown.

Recently, the Model for End-stage Liver Disease (MELD) score,[11] which reflects liver and renal function and is based on international normalized ratio (INR), total bilirubin, and creatinine, has been widely used as a prognostic predictor in patients with liver and heart diseases.[12–15] Furthermore, the MELD-XI score, a modified MELD score that excludes INR

From the Division of Cardiology, Department of Medicine (Y.C., Y.-X.L., M.-Z.W., Y.-J.Y., Y.-M.L., H.-F.T., K.-H.Y.), Division of Gastroenterology and hepatology, Department of Medicine (W.-K.S.), Department of Surgery (W.-K.A, D.C., K.-Y.S.), University of Hong Kong, Queen Mary Hospital, Hong Kong, China; Division of Cardiology, Department of Medicine, University of Hong Kong Shenzhen Hospital, Hong Kong, China (Y.C., K.-H.Y.); School of Public Health (L.-M.H.), Centre of Heart, Brain, Hormone and Healthy Aging, Li Ka Shing Faculty of Medicine (H.-F.T., K.-H.Y.), University of Hong Kong, China.

Correspondence to: Kai-Hang Yiu, MD, PhD, Cardiology Division, Department of Medicine, The University of Hong Kong, Room 1929B, Block K, Queen Mary Hospital, Hong Kong. E-mail: khkyiu@hku.hk

Received February 22, 2018; accepted April 28, 2018.

Clinical Perspective

What Is New?

- In this relatively large study, we assessed the clinical prognostic value of the Model for End-stage Liver Disease excluding international normalized ratio (MELD-XI) score and modified MELD score with albumin replacing international normalized ratio (MELD-Albumin) score in patients who underwent tricuspid annuloplasty (TA).
- Our study demonstrated that both MELD-XI and MELD-Albumin scores were significantly associated with adverse outcome in patients undergoing TA.
- Patients with a high preoperative MELD-XI score (≥12.0) and MELD-Albumin score (≥10.7) were at increased risk of an adverse event after TA.

What Are the Clinical Implications?

- The present data extend the usefulness of modified MELD scores to predict adverse outcome in patients who underwent TA.
- The findings in our study suggest that early TA, preferably before the development of liver and renal dysfunction, can improve clinical outcome.
- Further, modified MELD scores can be evaluated continuously before and following TA in order to identify patients who remain at high risk for adverse events.

during calculation because of anticoagulation,[16] has been confirmed to be useful in predicting outcomes of various types of cardiac surgery including heart transplantation,[17,18] Fontan surgery,[19] and transcatheter aortic valve implantation.[20] In addition, the MELD-Albumin score, which includes the serum value of albumin to replace INR, has been shown to be associated with clinical outcome following heart transplantation.[15] Nonetheless, the prognostic value of these 2 modified MELD scores in patients undergoing TA is unknown. The aim of this study was to assess the clinical prognostic value of the MELD-XI score and MELD-Albumin score in patients who underwent TA.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

From February 2007 to December 2016, 415 consecutive patients who underwent elective TA at Queen Mary Hospital were evaluated. Patients with a documented history of congenital heart disease (n=5), known liver disease (n=13), or end-stage renal disease requiring dialysis (n=3) were excluded. A final total of 394 patients were included in this study. Concomitant left heart valvular surgery and coronary artery bypass grafting during TA was documented. Adverse outcome was defined as the occurrence of heart failure requiring admission or all-cause mortality with data retrieved from the interhospital computer medical system. If patients had multiple adverse outcomes, only the first event was coded. The study was part of CVATS (Chinese Valvular Heart Disease Study) to evaluate the pattern of disease, pathophysiology, and clinical outcome of valvular heart disease in Chinese patients.[21] The study was approved by the ethics committee of the West Cluster Hospital Authority of Hong Kong, and all patients gave written informed consent.

Clinical Parameters

Clinical data on preoperative variables were collected from patient records by 1 investigator. Conventional cardiovascular risk factors such as history of diabetes mellitus, hypertension, hyperlipidemia, and smoking status were documented. The etiology of valvular heart disease was recorded as chronic rheumatic heart disease or nonchronic rheumatic heart disease according to the predominant lesion of the valve. New York Heart Association classification was recorded as class I/II or class III/IV, and the status of atrial fibrillation was also retrieved for each patient from Hospital Authority records.

Laboratory Measurements

Preoperative blood data were based on the most recent laboratory analysis before TA. Postoperative blood data were also collected 1-year post-TA according to the TA date in Hospital Authority records. Serum creatinine was recorded in all patients and considered abnormal, according to our institutional normal range, when creatinine level was >1.3 mg/dL. Estimated glomerular filtration rate was calculated using the Modified Diet in Renal Disease Equation[22] and patients with estimated glomerular filtration rate <60 mL/min per 1.73 m^2 were deemed to have chronic kidney disease.[23] Liver function tests were performed for each patient and the cutoff for abnormal values in our hospital were total bilirubin >1.0 mg/dL, albumin <4.1 g/dL, alanine transaminase >40 U/L, and aspartate transaminase >40 U/L.

MELD-XI Score and MELD-Albumin Score

Based on the standard MELD score formula and previous studies, the MELD-XI and MELD-Albumin scores were calculated according to the formulas that are described in Figure 1.

$$\text{MELD-XI score}^{16} = 5.11\times\ln(\text{TotalBilirubin}) + 11.76\times\ln(\text{Creatinine}) + 9.44$$

$$\text{MELD score}^{12} = 11.2\times\ln(\text{INR}) + 3.78\times\ln(\text{TotalBilirubin}) + 9.57\times\ln(\text{Creatinine}) + 6.43$$

$$\text{MELD-Albumin score}^{*15} = 11.2\times\ln(1) + 3.78\times\ln(\text{TotalBilirubin}) + 9.57\times\ln(\text{Creatinine}) + 6.43$$

$$\text{MELD-Albumin score}^{\#15} = 11.2\times\ln[1 + (4.1 - \text{Albumin})] + 3.78\times\ln(\text{TotalBilirubin}) + 9.57\times\ln(\text{Creatinine}) + 6.43$$

Figure 1. The formulas for calculating Model for End-stage Liver Disease (MELD) score and modified MELD scores. To avoid negative scores, a lower limit of total bilirubin and creatinine was set at 1.0 mg/dL. *MELD-Albumin score was calculated using this formula when serum albumin was ≥4.1 g/dL. #MELD-Albumin score was calculated using this formula when serum albumin was <4.1 g/dL.

Conventional Echocardiography

Detailed transthoracic echocardiography was performed in all patients before cardiac surgery. Left ventricular ejection fraction was measured according to the modified biplane Simpson's rule.[24] TR severity was quantified by a semiquantitative approach using vena contracta width (mild-moderate <7 mm and severe ≥7 mm) and hepatic venous flow pattern according to guidelines.[3] Pulmonary artery systolic pressure was estimated by combining right ventricular systolic pressure, which was calculated from peak TR velocity by continuous-wave Doppler using simplified Bernoulli equation, with the estimated right atrial pressure value: pulmonary artery systolic pressure=4 $(V)^2$+right atrial pressure.[25] Residual significant TR was defined as moderate or severe according to transthoracic echocardiography examination results before discharge after TA surgery.

Statistical Analysis

Data are expressed as mean±SD or median (interquartile range) for continuous variables and frequencies or proportions for categorical variables. Comparisons between groups were performed by Student *t* test and Mann-Whitney *U* test for continuous variables, and Pearson χ^2 for categoric variables. Univariate Cox regression analysis was used to estimate the relationship between potential predictors and adverse outcome at 1-year and long-term follow-up. Considering the large number of candidate variables, multivariable Cox regression with stepwise forward selection was performed to analyze the influence of relevant variables (variables with $P<0.10$ in univariate Cox regression were included) on adverse events. For multivariable analysis, the MELD-XI score and MELD-Albumin score were evaluated separately because of multicollinearity. The proportional hazards assumptions based on Schoenfeld residuals method for the Cox regression models were verified by Stata 14.0 (StataCorp) and deemed valid. Receiver operating characteristic curve and calculation of the area under the curve analyses were used to determine the liver and renal function parameters most associated with adverse events at 1-year follow-up. The optimal cutoff value was defined as the maximized value for the sum of sensitivity and specificity. Kaplan–Meier curve with a log-rank test was constructed to compare the adverse events in patients dichotomized according to MELD-XI score and MELD-Albumin score, respectively, based on the optimal cutoff value from 1-year receiver operating characteristic analysis. The Harrell C index was calculated using Stata 14.0 to estimate the discriminatory power of 2 modified MELD scores and known prognostic factors for long-term adverse events. The higher the Harrell C index, the better the model discriminated the adverse outcome. Gronnesby-Borgan test[26] was performed by the score test with 5 group using Stata 14.0 to assess model calibration (the goodness-of-fit of the model), and a nonsignificant Gronnesby-Borgan test indicates good calibration. All remaining statistical analyses were performed using the statistical package SPSS for Windows (version 22.0, SPSS Inc) and *P* values reported are 2-sided for consistency. $P<0.05$ was considered statistically significant.

Results

Baseline Clinical Characteristics of the Study Population

The baseline clinical characteristics are described in Table 1. Abnormal liver function test results at baseline were noted in 298 (75.6%) patients (including isolated and combined parameters abnormalities) and over 35% had chronic kidney disease. Patients were divided into 2 groups according to TR severity (Table 1). Patients with severe TR were older and had a higher prevalence of liver and renal dysfunction than those with mild to moderate TR. Notably, patients with severe TR had higher MELD-XI and MELD-Albumin scores than patients with mild to moderate TR (11.9 versus 10.3 and 10.1 versus 8.5, respectively). Other clinical and echocardiographic parameters were similar between the 2 groups.

Table 1. Baseline Characteristics of Patients Undergoing TA

Variable	All Patients (N=394)	Mild-Moderate TR (n=228)	Severe TR (n=166)	*P* Value
Age, y	63.1±9.9	61.9±10.3	64.8±9.1	<0.01
Male, No. (%)	153 (38.8)	95 (41.7)	58 (34.9)	0.18
Diabetes mellitus, No. (%)	79 (20.1)	40 (17.5)	39 (23.5)	0.15
Hypertension, No. (%)	79 (20.1)	45 (19.7)	34 (20.5)	0.86
Hyperlipidemia, No. (%)	72 (18.3)	51 (22.4)	21 (12.7)	0.01
Smoking, No. (%)	46 (11.7)	24 (10.5)	22 (13.3)	0.41
Atrial fibrillation, No. (%)	295 (74.9)	163 (71.5)	132 (79.5)	0.07
NYHA class III/IV, No. (%)	176 (44.7)	93 (40.8)	83 (50.0)	0.07
CRHD, No. (%)	252 (64.0)	135 (59.2)	117 (70.5)	0.02
LVEF, %	57.1±9.8	57.3±9.7	56.7±10.0	0.53
PASP, mm Hg	49.0±13.4	48.8±12.6	49.2±14.4	0.75
Residual significant TR after TA, No. (%)	39 (9.9)	17 (7.5)	22 (13.3)	0.06
Laboratory examination				
eGFR, mL/min per 1.73 m^2	67.9±20.9	70.4±19.0	64.5±22.8	<0.01
CKD, eGFR <60 mL/min per 1.73 m^2, No. (%)	140 (35.5)	65 (28.5)	75 (45.2)	<0.01
Creatinine, median (IQR), mg/dL	0.96 (0.42)	0.95 (0.38)	0.98 (0.42)	<0.05
Elevated (>1.3 mg/dL), No. (%)	63 (16.0)	30 (13.2)	33 (19.9)	0.07
Total bilirubin, median (IQR), mg/dL	0.99 (0.84)	0.94 (0.63)	1.17 (1.05)	<0.01
Elevated (>1.0 mg/dL), No. (%)	193 (49.0)	95 (41.7)	98 (59.0)	<0.01
Albumin, median (IQR), g/dL	4.1 (0.6)	4.2 (0.5)	4.0 (0.7)	0.07
Decreased (<4.1 g/dL), No. (%)	171 (43.4)	87 (38.2)	84 (50.6)	0.01
ALT, median (IQR), U/L	21 (13)	21 (14)	21 (12)	0.28
Elevated (>40 U/L), No. (%)	45 (11.4)	28 (12.3)	17 (10.2)	0.53
AST, median (IQR), U/L	31 (13)	29 (14)	34 (15)	<0.01
Elevated (>40 U/L), No. (%)	86 (21.8)	41 (18.0)	45 (27.1)	0.03
MELD-XI score, median (IQR)	11.0 (3.9)	10.3 (3.1)	11.9 (3.0)	<0.01
MELD-Albumin score, median (IQR)	8.8 (5.1)	8.5 (3.8)	10.1 (6.6)	<0.01
Valvular surgery detail, No. (%)				
Mitral valve repair with TA	122 (31.0)	78 (34.2)	44 (26.5)	0.10
Mitral valve replacement with TA	116 (29.4)	71 (31.1)	45 (27.1)	0.39
Aortic valve replacement with TA	32 (8.1)	12 (5.3)	20 (12.0)	0.02
Dual valvular surgery with TA	84 (21.3)	62 (27.2)	22 (13.3)	<0.01
Isolated TA	40 (10.2)	5 (2.2)	35 (21.1)	<0.01
Concomitant CABG with TA, No. (%)	33 (8.4)	23 (10.1)	10 (6.0)	0.15

Values are mean±SD, median (interquartile range, IQR), or number (percentage). ALT indicates alanine transaminase; AST, aspartate transaminase; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CRHD, chronic rheumatic heart disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MELD-Albumin, Model for End-stage Liver Disease with albumin replacing international normalized ratio; MELD-XI, Model for End-stage Liver Disease excluding international normalized ratio; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; TA, tricuspid annuloplasty; TR, tricuspid regurgitation.

MELD-XI Score and MELD-Albumin Score Were Significant Predictors of 1-Year Adverse Outcome

A total of 52 adverse events (31 heart failure and 21 deaths) occurred at 1-year follow-up. Predictors of 1-year adverse outcome were assessed by Cox regression analysis (Table 2). Univariate analysis revealed that age, sex, MELD-XI score, MELD-Albumin score, and other known clinical risk factors were associated with 1-year adverse events. To avoid bias from multicollinearity, multivariable Cox regression analysis

Table 2. Factors Associated With 1-Year Adverse Events in All Patients Using Cox Regression Analysis

	Univariate		Multivariable (MELD-XI Score Model)		Multivariable (MELD-Albumin Score Model)	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.05 (1.02–1.08)	<0.01	1.05 (1.02–1.08)	<0.01		NS
Male	2.26 (1.31–3.92)	<0.01	1.90 (1.05–3.45)	0.03		NS
Diabetes mellitus	2.45 (1.39–4.31)	0.02		NS	1.93 (1.09–3.40)	0.02
Hypertension	2.02 (1.13–3.61)	0.02		NS		NS
Hyperlipidemia	0.68 (0.40–1.50)	0.33				
Smoking	2.10 (1.08–3.08)	0.03		NS		NS
Atrial fibrillation	0.67 (0.37–1.19)	0.17				
NYHA class III/IV	2.52 (1.42–4.45)	<0.01	2.17 (1.20–3.94)	0.01	2.26 (1.24–4.09)	<0.01
CRHD	0.63 (0.37–1.09)	0.10				
LVEF	0.96 (0.94–0.99)	<0.01		NS		NS
PASP	1.00 (0.98–1.02)	0.96				
Residual significant TR	1.54 (0.69–3.41)	0.29				
eGFR	0.98 (0.96–0.99)	<0.01		NS		NS
ALT	1.00 (0.98–1.02)	0.76				
AST	1.00 (0.99–1.01)	0.67				
MELD-XI score	1.13 (1.07–1.19)	<0.01	1.13 (1.06–1.21)	<0.01		*
MELD-Albumin score	1.11 (1.07–1.15)	<0.01		*	1.13 (1.07–1.20)	<0.01
Mitral valve repair with TA	1.11 (0.64–1.95)	0.71				
Mitral valve replacement with TA	0.71 (0.37–1.35)	0.29				
Aortic valve replacement with TA	1.57 (0.79–3.12)	0.20				
Dual valvular surgery with TA	0.80 (0.39–1.64)	0.54				
Isolated TA	2.28 (1.15–4.55)	0.02	3.46 (1.67–7.18)	<0.01	2.70 (1.33–5.52)	<0.01
Concomitant CABG	3.75 (1.97–7.16)	<0.01		NS	2.34 (1.20–4.58)	0.01

ALT indicates alanine transaminase; AST, aspartate transaminase; CABG, coronary artery bypass grafting; CI, confidence interval; CRHD, chronic rheumatic heart disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; NS, not statistically significant; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; TA, tricuspid annuloplasty; TR, tricuspid regurgitation.

*Model for End-stage Liver Disease excluding international normalized ratio (MELD-XI) and Model for End-stage Liver Disease with albumin replacing international normalized ratio (MELD-Albumin) scores were not entered into the same multivariable analysis because of collinearity (r=0.78).

was, respectively, performed for MELD-XI score model and MELD-Albumin score model to determine significant predictors associated with 1-year adverse events. Upon multivariable adjustment, both MELD-XI score and MELD-Albumin score remained significantly predictive of 1-year adverse outcome. All proportional hazards assumptions for the Cox regression models were met (P=0.43 for MELD-XI score model and P=0.76 for MELD-Albumin score model).

A receiver operating characteristic curve was generated to determine the accuracy of baseline liver and renal function parameters most associated with adverse events at 1-year follow-up. As shown in Figure 2, both MELD-XI score (area under the curve=0.69, P<0.01) and MELD-Albumin score (area under the curve=0.75, P<0.01) were significantly associated with 1-year outcome, and thus were used to calculate optimal cutoff values for the prediction of adverse events. The best cutoff value was 12.0 (sensitivity 67.3%, specificity 66.4%) for MELD-XI score, and 10.7 (sensitivity 71.2%, specificity 72.5%) for MELD-Albumin score. Importantly, our results found that both modified MELD scores showed good calibration to predict 1-year outcome according to Gronnesby-Borgan test (χ^2 3.02, P=0.55 for MELD-XI score model and χ^2 1.31, P=0.86 for MELD-Albumin score model, respectively).

Impact of Dichotomized MELD-XI and MELD-Albumin Scores

The Kaplan–Meier survival curves to compare the incidence of adverse events in patients dichotomized according to their

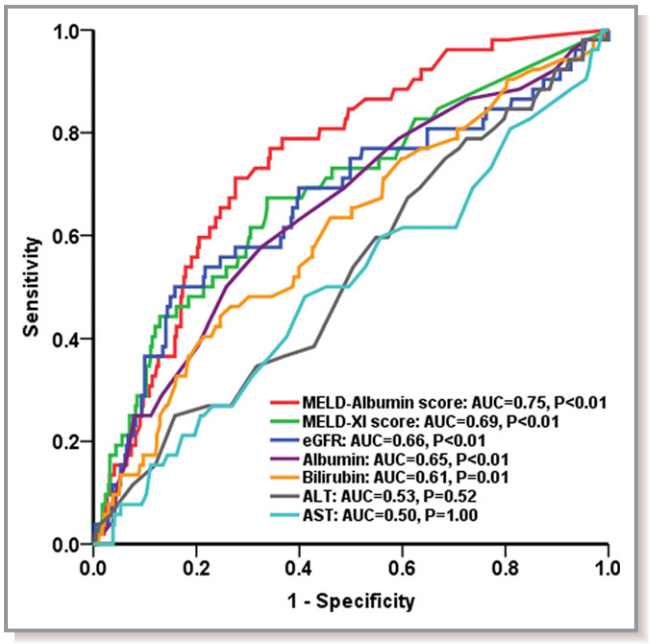

Figure 2. Receiver operating characteristic curves to determine the accuracy of baseline liver and renal function parameters most associated with adverse events at 1-year follow-up. ALT indicates alanine transaminase; AST, aspartate transaminase; AUC, area under the curve; eGFR, estimated glomerular filtration rate; MELD-Albumin, Model for End-stage Liver Disease with albumin replacing international normalized ratio; MELD-XI, Model for End-stage Liver Disease excluding international normalized ratio.

MELD-XI score and MELD-Albumin score are shown in Figure 3. Patients with a high MELD-XI (≥12.0) score had significantly worse 1- and 3-year adverse outcome (1-year survival: 81.7% versus 93.8%; 3-year survival: 69.5% versus 84.9% [P<0.01]). Similarly, patients with a high MELD-Albumin score (≥10.7) had a significantly worse adverse outcome (1-year survival: 77.4% versus 95.0%; 3-year survival: 62.6% versus 87.2% [P<0.01]).

Long-Term Adverse Outcome

The median follow-up after TA was 40 months (range, 1–120 months). A total of 112 adverse events occurred during the follow-up period: 76 patients developed heart failure and required hospital admission and 36 patients died. Table 3 describes the clinical parameters associated with long-term adverse events in all patients. Univariate Cox regression analysis revealed that age, sex, MELD-XI score, MELD-Albumin score, and other known clinical risk factors were associated with long-term adverse events. Multivariable adjustment demonstrated that both MELD-XI score and MELD-Albumin score were significant predictors of long-term adverse outcome. All proportional hazards assumptions for the Cox regression models were met (P=0.37 for MELD-XI score model and P=0.44 for MELD-Albumin score model). The Harrell C indexes at long-term follow-up for these significant predictors and known prognostic factors were as follows: MELD-XI score 0.64, MELD-Albumin score 0.69, age 0.65, diabetes mellitus 0.58, New York Heart Association class III/IV 0.57, combined aortic valve replacement 0.54, isolated TA 0.54, and residual significant TR 0.54. Based on the Harrell C index, the MELD-Albumin score was the best predictor of long-term adverse events among all models, followed by the MELD-XI score. Furthermore, our results also found that both modified MELD scores showed good calibration to predict long-term outcome according to Gronnesby-Borgan test (χ^2 2.69 [P=0.61 for MELD-XI score model] and χ^2 2.16 [P=0.71 for MELD-Albumin score model], respectively).

Liver and Renal Function Progression at 1-Year Follow-Up

Table 4 describes the liver and renal function progression at 1-year follow-up after TA. In patients who were free of adverse events, there was a significant improvement in estimated glomerular filtration rate, total bilirubin, aspartate transaminase, MELD-XI score, and MELD-Albumin score. Nonetheless, in patients who developed heart failure, there was no significant change in liver or renal function.

Discussion

Liver and renal abnormalities are closely related to and have a strong impact on prognosis in patients with cardiac disease. The present study demonstrated that a significant proportion of patients who underwent TA had preoperative liver and renal dysfunction that was more common in those with severe TR than in those with mild to moderate TR. This study is the first to show that high MELD-XI and MELD-Albumin scores, beyond standard clinical and demographic parameters, are significantly associated with adverse outcome in patients who undergo TA. Longitudinal assessment of liver and renal function also demonstrated that a significant improvement in MELD-XI and MELD-Albumin scores occurred only in patients who were free of adverse events, not in those who developed adverse events 1 year following TA. The present data extend the usefulness of modified MELD scores to predict adverse outcome in patients who undergo TA.

Similar to the well-recognized “cardiorenal syndrome,” an interaction between the heart and the liver, termed *cardiohepatic syndrome*, has received increasing attention.[27] There are typically 2 types of liver injury in cardiac disease: (1) acute cardiogenic liver injury in patients with cardiogenic shock; and (2) congestive hepatopathy associated with transmission of elevated right-sided filling pressures to the hepatic venous system and present at various stages along a continuum. One

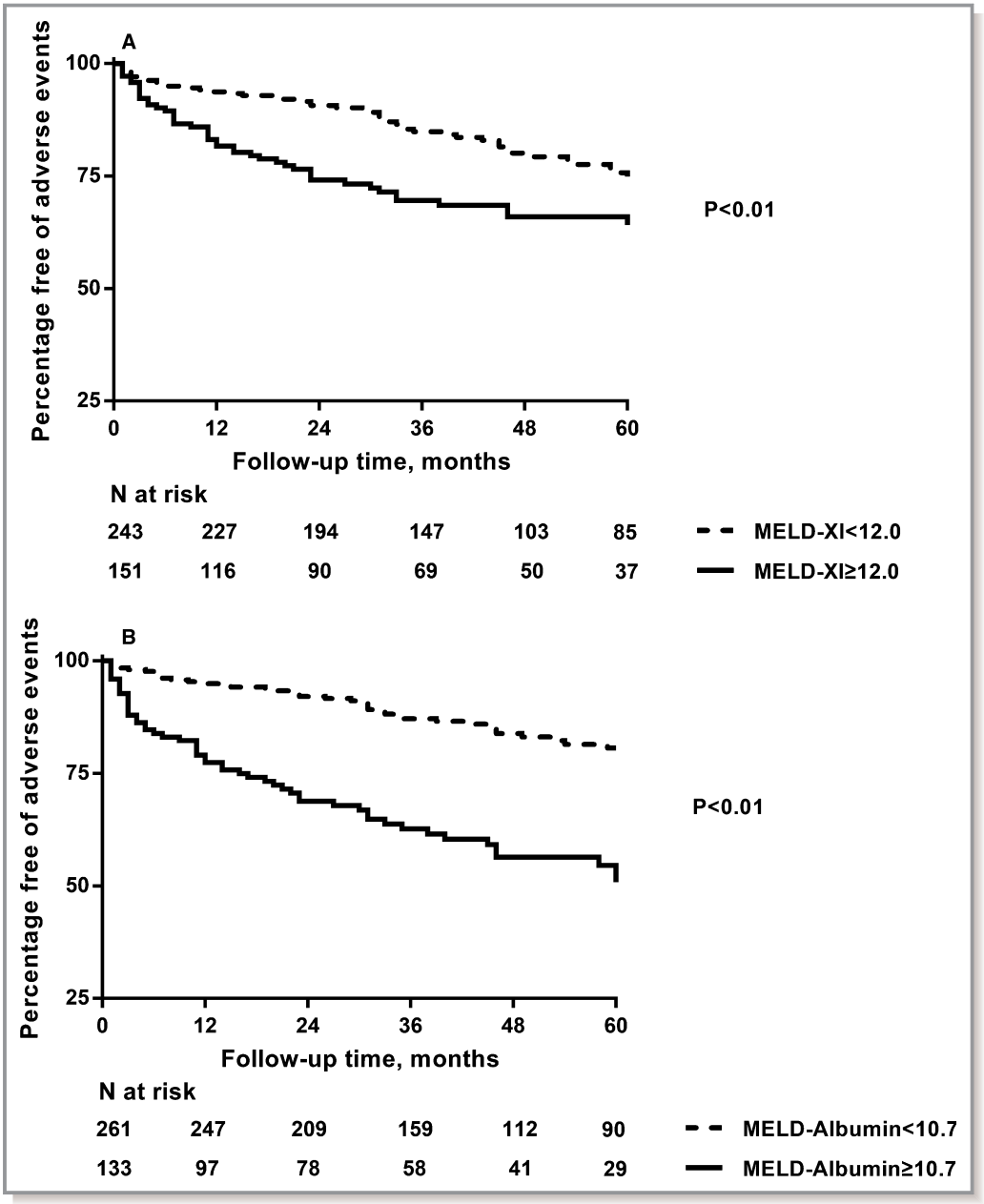

Figure 3. Kaplan–Meier curves for adverse events according to Model for End-stage Liver Disease excluding international normalized ratio (MELD-XI) score groups (A) and Model for End-stage Liver Disease with albumin replacing international normalized ratio (MELD-Albumin) score groups (B) based on the optimal cutoff value from the 1-year receiver operating characteristic curve analysis.

of the key attributes of hepatopathy secondary to chronic congestion is elevated central venous pressure that is transmitted through the hepatic veins and subsequently to hepatic venules. Biochemically, congestive hepatopathy is characterized by alteration of cholestasis biomarkers, although the exact mechanism is uncertain and likely multifactorial. Indeed, the prevalence of abnormal cholestasis biomarkers is high in patients with cardiac disease. In a study that evaluated patients with acute decompensated heart failure, 36.1% had an elevated bilirubin level.[28] In another study that involved ambulatory patients with heart failure, bilirubin was elevated in 15.2% of patients.[29] Although it is conceivable that the prevalence of ductal enzyme elevation varies in different cardiac conditions, our study revealed that almost half of the patients with TR awaiting TA had an elevated bilirubin level (49%). The reason for this high prevalence of abnormal ductal enzyme in these patients can be explained by an earlier study that showed degree of TR to be correlated with ductal enzyme level, including bilirubin.[8] Together with our previous report that demonstrated a close

Table 3. Factors Associated With Long-Term Adverse Events in All Patients Using Cox Regression Analysis

	Univariate		Multivariable (MELD-XI Score Model)		Multivariable (MELD-Albumin Score Model)	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.06 (1.04–1.08)	<0.01	1.06 (1.03–1.08)	<0.01	1.05 (1.03–1.07)	<0.01
Male	1.44 (0.99–2.09)	0.06		NS		NS
Diabetes mellitus	2.48 (1.67–3.67)	<0.01	1.91 (1.27–2.88)	<0.01	1.83 (1.22–2.75)	<0.01
Hypertension	1.94 (1.28–2.93)	<0.01		NS		NS
Hyperlipidemia	1.20 (0.77–1.86)	0.42				
Smoking	1.12 (0.64–1.96)	0.70				
Atrial fibrillation	1.11 (0.71–1.74)	0.64				
NYHA class III/IV	1.63 (1.12–2.37)	0.01		NS	1.53 (1.03–2.27)	0.04
CRHD	0.91 (0.62–1.35)	0.65				
LVEF	0.97 (0.96–0.99)	<0.01		NS		NS
PASP	1.00 (0.99–1.02)	0.54				
Residual significant TR	2.27 (1.40–3.68)	<0.01		NS	1.81 (1.10–2.98)	0.02
eGFR	0.98 (0.97–0.99)	<0.01		NS		NS
ALT	0.99 (0.98–1.01)	0.36				
AST	1.00 (0.99–1.00)	0.97				
MELD-XI score	1.11 (1.06–1.15)	<0.01	1.14 (1.08–1.20)	<0.01		*
MELD-Albumin score	1.10 (1.06–1.13)	<0.01		*	1.13 (1.08–1.17)	<0.01
Mitral valve repair with TA	0.91 (0.60–1.36)	0.64				
Mitral valve replacement with TA	0.72 (0.47–1.10)	0.13				
Aortic valve replacement with TA	2.79 (1.65–4.70)	<0.01	2.88 (1.68–4.94)	<0.01	3.39 (1.94–5.91)	<0.01
Dual valvular surgery with TA	0.64 (0.38–1.08)	0.10				
Isolated TA	1.96 (1.15–3.35)	0.01	2.73 (1.57–4.75)	<0.01	2.82 (1.61–4.94)	<0.01
Concomitant CABG	1.98 (1.11–3.54)	0.02		NS		NS

ALT indicates alanine transaminase; AST, aspartate transaminase; CABG, coronary artery bypass grafting; CI, confidence interval; CRHD, chronic rheumatic heart disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; NS, not statistically significant; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; TA, tricuspid annuloplasty; TR, tricuspid regurgitation.

*Model for End-stage Liver Disease excluding international normalized ratio (MELD-XI) and Model for End-stage Liver Disease with albumin replacing international normalized ratio (MELD-Albumin) scores were not entered into the same multivariable analysis because of collinearity (r=0.78).

relationship between TR and liver stiffness,[9] the present data confirm that the severity of TR is an important attribute of congestive hepatopathy.

The established MELD score that reflects both liver and renal function was developed to risk-stratify patients with hepatic cirrhosis. Recent studies have suggested that the score (based on total bilirubin, creatinine, and INR) has prognostic value in various cardiac conditions including heart failure[14,30] and orthotopic heart transplantation.[15] In patients with valvular heart disease, the prevalence of atrial fibrillation is high and thus a large proportion of patients are prescribed anticoagulation. A study by Ailawadi et al[31] demonstrated that the MELD score was predictive of adverse outcome in patients undergoing tricuspid surgery, although 44% were prescribed warfarin preoperatively. Nonetheless, the accuracy of the MELD score that includes INR assessment in evaluating hepatopathy in patients who require anticoagulation is arguable. The MELD-XI[14,20,32] and MELD-Albumin[15] scores were designed specifically to exclude INR assessment in order to better reflect hepatopathy in patients prescribed anticoagulation. For example, a study that evaluated 343 patients undergoing heart transplantation evaluation demonstrated that MELD-XI, but not MELD score, was associated with adverse events in those prescribed anticoagulation.[14] The present findings first reported that both MELD-XI and MELD-Albumin scores provided meaningful value in predicting adverse outcome in patients undergoing TA.

It is noteworthy that the MELD-Albumin score had a higher area under the curve value for 1-year adverse outcome and higher Harrell C index for long-term adverse outcome and

Table 4. Comparing Liver and Renal Function Before TA and 1 Year Post-TA

	Patients Without Adverse Events (n=342)			Patients With Heart Failure (n=31)		
	Pre-TA	1 Year Post-TA	*P* Value	Pre-TA	1 Year Post-TA	*P* Value
eGFR, mL/min per 1.73 m^2	69.0±19.6	72.2±20.1	<0.01	63.8±30.1	56.5±20.6	0.09
Creatinine, mg/dL	0.94 (0.39)	0.87 (0.37)	0.03	1.06 (0.63)	1.21 (0.49)	0.37
Total bilirubin, mg/dL	0.97 (0.70)	0.82 (0.53)	<0.01	1.05 (0.90)	0.94 (0.58)	0.14
Albumin, g/dL	4.2 (0.6)	4.1 (0.2)	0.24	3.9 (0.8)	3.8 (0.4)	0.54
ALT, U/L	21 (13)	22 (15)	0.46	21 (11)	23 (10)	0.29
AST, U/L	31 (13)	28 (13)	<0.01	30 (14)	26 (11)	0.39
MELD-XI score	10.8 (3.6)	9.5 (2.2)	<0.01	12.1 (6.6)	11.9 (5.6)	0.89
MELD-Albumin score	8.5 (4.2)	8.5 (3.8)	0.03	12.8 (7.3)	11.7 (6.7)	0.92

Values are mean±SD or median (interquartile range). ALT indicates alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; MELD-Albumin, Model for End-stage Liver Disease with albumin replacing international normalized ratio; MELD-XI, Model for End-stage Liver Disease excluding international normalized ratio; TA, tricuspid annuloplasty.

better calibration than the MELD-XI score. This observation supports the incorporation of serum albumin into the modified MELD score to provide additional risk information for patients undergoing TA. Indeed, albumin is an important secretory protein produced by the liver. In addition, recent evidence has suggested that systemic inflammation may be a primary regulator of hepatic protein metabolism.[33] As such, chronic hepatic congestion together with systemic inflammation may contribute to hypoalbuminemia in patients with TR awaiting TA. A previous study has demonstrated that a low albumin level was independently associated with increased risk of mortality in patients with heart failure[34] and became part of a risk score to risk-stratify patients undergoing heart transplantation.[15] The present study supports the addition of albumin to the modified MELD score to better predict outcome in patients undergoing TA. Nonetheless, a larger study is required to determine the optimal cutoff value for accurate risk stratification.

Liver and renal function are dynamic and reflect the hemodynamic state of various cardiac diseases. In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, which reviewed longitudinal liver function in patients with acute decompensated heart failure, liver function was significantly improved upon treatment at 6-month follow-up.[28] In another study that evaluated patients with acute heart failure, an increase in the MELD-XI score during hospital stay was related to increased risk of mortality at 1-year follow-up.[32] Building on these results, we have demonstrated that bilirubin, aspartate transaminase, estimated glomerular filtration rate, MELD-XI score, and MELD-Albumin score were all improved in patients who were free of adverse events 1 year post-TA. On the contrary, no such improvement was observed in patients who experienced adverse events 1 year following TA. The variable course of liver and renal function may reflect different hemodynamic consequences following TA. Patients who do not have an improved modified MELD score may represent those with a less favorable postoperative response. This finding may suggest that comparing presurgical and postsurgical MELD scores is worthwhile to reflect the reversibility of hepatic and renal dysfunction and further improve risk stratification and monitoring of patients. Future prospective studies to evaluate longitudinal changes to MELD score and its role in predicting adverse outcome will be required to support our hypothesis.

Clinical Implications

The timing of tricuspid valve surgery remains controversial as a result of limited data available and their heterogeneous nature. According to the current guideline, the optimal timing of tricuspid surgery is determined: (1) by symptoms or progressive right ventricular dysfunction caused by severe primary TR; or (2) at the time of left-side heart valve surgery.[3,4] The present study demonstrated that patients with a high MELD-XI score (≥12.0) and MELD-Albumin score (≥10.7) were at increased risk of an adverse event. These findings suggest that early TA, preferably before the development of liver and renal dysfunction, can improve clinical outcome. Further, modified MELD scores can be evaluated continuously before and following TA to identify patients who remain at high risk for adverse events. It is thus clinically relevant to consider the modified MELD score when determining optimal surgical timing and risk stratification following TA.

Limitations

There are several limitations in the present study. First, we did not include all possible residual variables that were not strong

in the univariate model because of the limited sample size in the multivariable model. Furthermore, novel liver and renal biomarkers such as gamma-glutamyltransferase, cystatin C, and kidney injury molecule-1 were not measured. Finally, a larger sample size is required to validate the cutoff value suggested in the present study in association with adverse events at 1-year follow-up.

Conclusions

Our study demonstrates that both MELD-XI score and MELD-Albumin score can provide useful information to predict adverse outcome in patients undergoing TA, beyond standard clinical and demographic parameters. The use of a modified MELD score might complement and enhance the current management of patients undergoing TA.

Acknowledgments

We thank the medical and nursing staff of the Division of Cardiology, Queen Mary Hospital, for their help and support with this study.

Sources of Funding

This study was supported by the Health and Medical Research Fund (03143996) from the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region.

Disclosures

None.

References

1. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol*. 2004;43:405–409.
2. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, Pislaru S, Park S, Mahoney DW, Biner S, Enriquez-Sarano M. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging*. 2014;7:1185–1194.
3. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–e643.
5. Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg S. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg*. 2012;143:1043–1049.
6. Navia JL, Nowicki ER, Blackstone EH, Brozzi NA, Nento DE, Atik FA, Rajeswaran J, Gillinov AM, Svensson LG, Lytle BW. Surgical management of secondary tricuspid valve regurgitation: annulus, commissure, or leaflet procedure? *J Thorac Cardiovasc Surg*. 2010;139:1473–1482.e5
7. Pfannmuller B, Doenst T, Eberhardt K, Seeburger J, Borger MA, Mohr FW. Increased risk of dehiscence after tricuspid valve repair with rigid annuloplasty rings. *J Thorac Cardiovasc Surg*. 2012;143:1050–1055.
8. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol*. 2002;90:1405–1409.
9. Chen Y, Seto WK, Ho LM, Fung J, Jim MH, Yip G, Fan K, Zhen Z, Liu JH, Yuen MF, Lau CP, Tse HF, Yiu KH. Relation of tricuspid regurgitation to liver stiffness measured by transient elastography in patients with left-sided cardiac valve disease. *Am J Cardiol*. 2016;117:640–646.
10. Yajima S, Yoshioka D, Toda K, Fukushima S, Miyagawa S, Yoshikawa Y, Saito S, Domae K, Ueno T, Kuratani T, Sawa Y. Definitive determinant of late significant tricuspid regurgitation after aortic valve replacement. *Circ J*. 2018;82:886–894.
11. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31:864–871.
12. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464–470.
13. Habib S, Berk B, Chang CC, Demetris AJ, Fontes P, Dvorchik I, Eghtesad B, Marcos A, Shakil AO. Meld and prediction of post-liver transplantation survival. *Liver Transpl*. 2006;12:440–447.
14. Kim MS, Kato TS, Farr M, Wu C, Givens RC, Collado E, Mancini DM, Schulze PC. Hepatic dysfunction in ambulatory patients with heart failure: application of the meld scoring system for outcome prediction. *J Am Coll Cardiol*. 2013;61:2253–2261.
15. Chokshi A, Cheema FH, Schaefle KJ, Jiang J, Collado E, Shahzad K, Khawaja T, Farr M, Takayama H, Naka Y, Mancini DM, Schulze PC. Hepatic dysfunction and survival after orthotopic heart transplantation: application of the meld scoring system for outcome prediction. *J Heart Lung Transplant*. 2012;31:591–600.
16. Heuman DM, Mihas AA, Habib A, Gilles HS, Stravitz RT, Sanyal AJ, Fisher RA. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. *Liver Transpl*. 2007;13:30–37.
17. Grimm JC, Shah AS, Magruder JT, Kilic A, Valero V III, Dungan SP, Tedford RJ, Russell SD, Whitman GJ, Sciortino CM. MELD-XI score predicts early mortality in patients after heart transplantation. *Ann Thorac Surg*. 2015;100:1737–1743.
18. Deo SV, Al-Kindi SG, Altarabsheh SE, Hang D, Kumar S, Ginwalla MB, ElAmm CA, Sareyyupoglu B, Medalion B, Oliveira GH, Park SJ. Model for end-stage liver disease excluding international normalized ratio (MELD-XI) score predicts heart transplant outcomes: evidence from the registry of the United Network for Organ Sharing. *J Heart Lung Transplant*. 2016;35:222–227.
19. Assenza GE, Graham DA, Landzberg MJ, Valente AM, Singh MN, Bashir A, Fernandes S, Mortele KJ, Ukomadu C, Volpe M, Wu F. MELD-XI score and cardiac mortality or transplantation in patients after Fontan Surgery. *Heart*. 2013;99:491–496.
20. Arai T, Yashima F, Yanagisawa R, Tanaka M, Shimizu H, Fukuda K, Watanabe Y, Naganuma T, Araki M, Tada N, Yamanaka F, Shirai S, Yamamoto M, Hayashida K. Prognostic value of liver dysfunction assessed by MELD-XI scoring system in patients undergoing transcatheter aortic valve implantation. *Int J Cardiol*. 2017;228:648–653.
21. Yiu KH, Wong A, Pu L, Chiang MF, Sit KY, Chan D, Lee HY, Lam YM, Chen Y, Siu CW, Lau CP, Au WK, Tse HF. Prognostic value of preoperative right ventricular geometry and tricuspid valve tethering area in patients undergoing tricuspid annuloplasty. *Circulation*. 2014;129:87–92.
22. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247–254.
23. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, Wilson DJ, Zuckerman A, Wenger NK. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008;51:1448–1454.
24. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
25. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713; quiz 786–688.

26. Demler OV, Paynter NP, Cook NR. Tests of calibration and goodness-of-fit in the survival setting. *Stat Med*. 2015;34:1659–1680.
27. Samsky MD, Patel CB, DeWald TA, Smith AD, Felker GM, Rogers JG, Hernandez AF. Cardiohepatic interactions in heart failure: an overview and clinical implications. *J Am Coll Cardiol*. 2013;61:2397–2405.
28. Scholfield M, Schabath MB, Guglin M. Longitudinal trends, hemodynamic profiles, and prognostic value of abnormal liver function tests in patients with acute decompensated heart failure: an analysis of the escape trial. *J Cardiac Fail*. 2014;20:476–484.
29. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. *Eur J Clin Invest*. 2012;42:153–163.
30. Matthews JC, Pagani FD, Haft JW, Koelling TM, Naftel DC, Aaronson KD. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. *Circulation*. 2010;121:214–220.
31. Ailawadi G, Lapar DJ, Swenson BR, Siefert SA, Lau C, Kern JA, Peeler BB, Littlewood KE, Kron IL. Model for end-stage liver disease predicts mortality for tricuspid valve surgery. *Ann Thorac Surg*. 2009;87:1460–1467; discussion 1467–1468.
32. Biegus J, Zymlinski R, Sokolski M, Siwolowski P, Gajewski P, Nawrocka-Millward S, Poniewierka E, Jankowska EA, Banasiak W, Ponikowski P. Impaired hepato-renal function defined by the MELD XI score as prognosticator in acute heart failure. *Eur J Heart Fail*. 2016;18:1518–1521.
33. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial*. 2004;17:432–437.
34. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J*. 2008;155:883–889.