Prognostic value of the modified Model for End-Stage Liver Disease score in patients treated with cardiac resynchronization therapy

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BACKGROUND Hepatorenal dysfunction is prevalent among individuals with heart failure (HF).

OBJECTIVE This study investigated prognostic value of the modified Model for End-Stage Liver Disease (Model for End-Stage Liver Disease excluding international normalized ratio [MELD-XI] scores and Model for End-Stage Liver Disease with albumin replacing international normalized ratio [MELD-Albumin]) score in patients undergoing cardiac resynchronization therapy (CRT).

METHODS We retrospectively evaluated 365 patients (mean age 58.7 ± 11.1 years; 64.9% men) undergoing CRT implantation between 2007 and 2019. Patients were divided into 4 groups based on the modified MELD score quartiles before CRT. The primary endpoint was the combination of all-cause mortality and HF hospitalization, whereas the secondary endpoint was CRT response at 6 months.

RESULTS During mean follow-up of 3.3 years (interquartile range 1.9–5.2 years), 168 patients reached the primary endpoint. Logistic regression revealed the MELD-Albumin score was independently associated with CRT response, even after adjusting for covariates (odds ratio 1.10; 95% confidence interval [CI] 1.02–1.19; P = .013). Kaplan-Meier analysis revealed that patients with a higher MELD-XI and MELD-Albumin score had a greater risk of adverse outcomes (log-rank test: $P < .001$). A Cox proportional hazards analysis showed that the modified MELD score remained significantly associated with adverse outcomes after adjusting for clinical and echocardiographic factors (MELD-XI: hazard ratio 1.06, 95% CI 1.02–1.11, P = .006; MELD-Albumin: hazard ratio 1.10, 95% CI 1.05–1.16, $P < .001$). Furthermore, receiver-operating characteristic analysis indicated that the MELD-Albumin score provided a stronger prognostic value for long-term adverse outcomes in patients undergoing CRT than the MELD-XI score (MELD-Albumin: area under the curve 0.692, 95% CI 0.644–0.742; MELD-XI: area under the curve 0.659, 95% CI 0.608–0.715; P = .008).

CONCLUSION The MELD-Albumin score may be useful for stratifying patients at risk for CRT response and adverse outcomes in those undergoing CRT for HF.

KEYWORDS Modified MELD score; MELD-Albumin score; MELE-XI score; Cardiac resynchronization therapy; CRT response; Prognosis

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Introduction

Cardiac resynchronization therapy (CRT) is a well-established interventional treatment for patients with heart failure (HF) characterized by reduced left ventricular (LV) function and prolonged QRS duration, despite optimal medical therapy.[1,2] Previous studies have shown that improved clinical and mechanical response to CRT is associated with reduced rates of HF-related hospitalization and mortality.[3,4] However, more than 30% of CRT recipients do not respond to this therapy.[5] Recently, several studies have explored the use of postoperative electrocardiographic and imaging-based markers to predict response to CRT and patient outcomes.[6–8] Nonetheless, these markers are not suitable for preimplantation assessment in CRT candidates. Therefore, to better identify patients unlikely to benefit clinically or echocardiographically from CRT, risk stratification based on per-implantation evaluation is crucial.

Liver dysfunction is independently associated with an increased risk of adverse outcomes in HF patients.[9] Additionally, cardiorenal syndrome, a common complication of HF, is linked to poor prognosis and higher mortality risk.[9,10] Thus, hepatorenal indices, which reflect multiorgan dysfunction

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KEY FINDINGS

- The Model for End-Stage Liver Disease with albumin replacing international normalized ratio (MELD-Albumin) score was significantly associated with cardiac resynchronization therapy (CRT) nonresponse.
- Both Model for End-Stage Liver Disease excluding international normalized ratio (MELD-XI) and MELD-Albumin scores independently predicted long-term adverse outcomes, including all-cause mortality and heart failure (HF) hospitalizations, in patients undergoing CRT.
- The MELD-Albumin score demonstrates superior prognostic value compared with the MELD-XI score, particularly in patients receiving a CRT defibrillator.
- As a tool derived from readily available laboratory parameters, the MELD-Albumin score holds significant potential for risk stratification and guiding clinical decision making in patients undergoing CRT.

due to hemodynamic impairment, may serve as independent predictors of outcomes in HF patients undergoing CRT.

The Model for End-Stage Liver Disease (MELD) score, calculated using bilirubin, creatinine, and the international normalized ratio (INR), was originally developed to assess long-term mortality in patients with end-stage liver disease.[11] Studies have demonstrated that elevated MELD scores are associated with poor prognosis in various patient populations, including those with advanced HF undergoing LV assist device implantation,[12] orthotopic heart transplantation,[13] outpatient HF management,[14] acute HF,[15] and valvular disease.[16,17] To minimize the instability caused by anticoagulant use, modified versions of the MELD score, such as Model for End-Stage Liver Disease excluding INR (MELD-XI) scores and Model for End-Stage Liver Disease with albumin replacing INR MELD-Albumin), were developed to optimize prognostic accuracy. Recent studies suggest that the MELD-XI score provides enhanced prognostic utility in HF patients undergoing CRT.[18] However, the prognostic significance of the MELD-Albumin score, and how it compares with the MELD-XI score in patients receiving CRT, remains underexplored.

This study aims to (1) evaluate the predictive value of the MELD-Albumin and MELD-XI scores for CRT nonresponse and long-term adverse outcomes in CRT recipients and (2) compare the prognostic strengths of these MELD scoring systems in predicting patient outcomes.

Methods

Study population

We conducted a retrospective evaluation of 686 patients who successfully underwent CRT device implantation at Fuwai Hospital between March 2007 and March 2019. Eligibility for CRT implantation was based on class I and II indications according to national guidelines. Blood tests were performed before implantation to assess clinical status, and all patients underwent comprehensive echocardiographic evaluation at baseline and 6 months post-CRT implantation. The choice between a cardiac resynchronization therapy defibrillator (CRT-D) or CRT pacemaker was guided by the patient's clinical history and arrhythmic risk profile. A total of 276 patients were excluded due to missing data on total bilirubin, creatinine, and albumin, while 44 patients were excluded due to incomplete echocardiographic data, and 1 patient was excluded for missing endpoint data. Ultimately, the study included clinical data from a total of 365 patients (Figure 1). The study was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (No. IRB2012-BG–006), and all participants or their guardians provided written informed consent.

Assessment of modified MELD score before CRT

In this study, the modified MELD scores were calculated using preprocedure measurements of total bilirubin, creatinine, and albumin. The MELD-XI score and MELD-Albumin score were calculated using the following formulas:

- MELD-XI score = $5.11 \times \ln(\text{Total Bilirubin}) + 11.76 \times \ln(\text{Creatinine}) + 9.44$.[19]
- For the MELD-Albumin score,

when albumin is $\geq$4.1 g/dL, the formula is $11.2 \times \ln(1) + 3.78 \times \ln(\text{Total Bilirubin}) + 9.57 \times \ln(\text{Creatinine}) + 6.43$ and

When albumin is <4.1 g/dL, the formula is $11.2 \times \ln[1 + (4.1 - \text{Albumin})] + 3.78 \times \ln(\text{Total\_Bilirubin}) + 9.57 \times \ln(\text{Creatinine}) + 6.43$.[13]

Patients were categorized into 4 groups based on quartiles of the modified MELD score before CRT implantation.

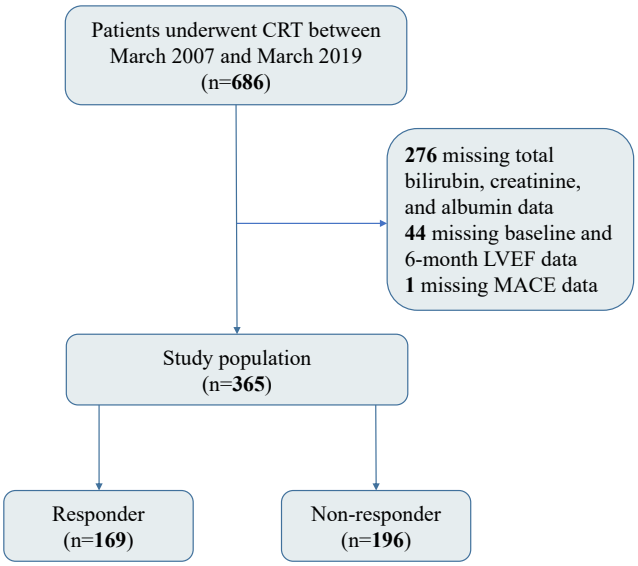

Figure 1 Flowchart of the study. CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events.

Comparative analyses were conducted on laboratory results, echocardiographic data, and clinical outcomes among these groups. Total bilirubin and albumin were measured in the Fuwai Hospital laboratory using a LABOSPECT 008 AS automatic biochemistry analyzer (Hitachi High-Tech). All patients underwent transthoracic 2-dimensional M-mode echocardiography (EPIC7, iE33; Philips Medical Systems) before CRT implantation. LV end-diastolic diameter (LVEDD) was measured using the internal diameter of the LV in the parasternal long-axis view, and LV ejection fraction (LVEF) was calculated using the Simpson method from LV end-diastolic volume and LV end-systolic volumes. LVEF was defined as LVEF = (LV end-diastolic volume – end-systolic volume) / LV end-diastolic volume × 100%.

Endpoint and follow-up

The primary endpoint was the composite of all-cause mortality and HF hospitalization, while the secondary endpoint was CRT nonresponse 6 months after implantation. CRT responders were defined as those with a >10% improvement in LVEF at 6 months compared with baseline. In cases of death during the 6-month follow-up, the last available echocardiogram was used for evaluation. Follow-up of adverse outcomes, including total mortality and HF hospitalization, continued until March 2019 or until an endpoint was reached. Data were collected from medical records, device interrogations, clinical visits, or telephone interviews.

Statistical analysis

Continuous variables were expressed as mean ± SD for normally distributed data and as median (interquartile range) for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Baseline differences between CRT responders and nonresponders were analyzed using independent-sample *t* tests or Mann-Whitney *U* tests, as appropriate. Comparisons among the 4 groups with different modified MELD scores were made using 1-way analysis of variance, followed by post hoc Tukey-Kramer tests or Kruskal-Wallis tests with Steel-Dwass post hoc tests. Chi-square or Fisher's exact tests were used to analyze categorical variables. Restricted cubic spline analysis was used to assess the shape of the association between MELD scores and endpoints. Logistic regression was applied to assess the independent predictive value of modified MELD scores on CRT response. Pearson's correlation coefficient was used to test correlations between continuous variables. The cumulative incidence of adverse events was assessed using the Kaplan-Meier method, with differences between groups compared using the log-rank test. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to evaluate the association between modified MELD scores and adverse events. Model 1 was adjusted for age and sex. Model 2 included additional adjustments for body mass index (BMI), New York Heart Association (NYHA) functional class, LVEF, LVEDD, hemoglobin, and creatinine. Model 3 was further adjusted for atrial fibrillation (AF), left bundle branch block (LBBB), hypertension, ventricular tachycardia/ventricular fibrillation, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. To evaluate the prognostic strength of the MELD-Albumin and MELD-XI scores, receiver-operating characteristic (ROC) analysis was used to calculate the area under the curve (AUC) for poor response and adverse events. ROC curves were compared using the DeLong test. A sensitivity analysis was conducted by excluding patients with severe tricuspid regurgitation to assess the potential impact of severe tricuspid regurgitation (TR) on the associations between modified MELD scores and clinical outcomes. Statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing), and statistical significance was set at $P < .05$ for all analyses.

Results

Baseline characteristics

Baseline clinical characteristics of all 365 patients evaluated for CRT eligibility are summarized in Table 1. Among the participants, there were 237 (64.9%) men and 128 (35.1%) women, with a mean age of 58.7 ± 11.1 years. The mean QRS duration was 165.3 ± 19.8 ms, and 80% of patients (n = 292) had LBBB QRS configuration. Approximately two-thirds of patients were classified as being in NYHA functional class III, with the majority receiving optimal medical therapy prior to CRT. Of the study population, 168 patients underwent CRT pacemaker implantation, while 197 patients received a CRT-D. The mean LVEF at baseline was 29.1 ± 6.9%. Of the 365 patients who underwent follow-up echocardiography 6 months after CRT implantation, 169 (46.3%) patients were categorized as CRT responders (Table 1). Nonresponders exhibited a higher prevalence of AF, ventricular tachycardia/ventricular fibrillation, and severe TR compared with responders. Nonresponders also had significantly lower albumin levels. In contrast, total bilirubin and N-terminal pro–B-type natriuretic peptide, as well as MELD-XI (8.4 ± 3.3 vs 9.7 ± 4.5, $P = .003$) and MELD-Albumin (6.1 ± 2.8 vs 7.4 ± 4.1, $P < .001$) scores, were significantly higher, indicating deteriorated hepatorenal function (Supplemental Figure 1). Compared with responders, nonresponders demonstrated greater left atrial diameter and LVEDD. However, LVEF and QRS duration were similar between the 2 groups.

The distribution of MELD-XI and MELD-Albumin scores in the overall population approximately followed a normal distribution (Supplemental Figure 2). In the study cohort, the mean MELD-XI score was 9.1 ± 4.0 and the mean MELD-Albumin score was 6.8 ± 3.6. Supplemental Tables 1 and 2 present the baseline characteristics of the study samples, stratified by MELD-XI score, and MELD-Albumin quartiles. Regardless of the MELD-XI or MELD-Albumin scores, patients in the fourth quartile were more likely to have coronary heart disease; a lower prevalence of LBBB; higher levels of total bilirubin, hemoglobin,

Table 1 Baseline characteristics of patients.

Characteristics	Total (N = 365)	Responder (>10%) (n = 169)	Nonresponder (<10%) (n = 196)	*P* value
Age, y	58.7 ± 11.1	58.9 ± 10.6	58.6 ± 11.7	.799
Sex				.032
Male	237 (64.9)	100 (59.2)	137 (69.9)	
Female	128 (35.1)	69 (40.8)	59 (30.1)	
BMI, kg/m^2	24.4 ± 4.4	24.5 ± 3.7	24.3 ± 4.9	.706
NYHA functional class				.188
I–II	80 (21.9)	39 (23.1)	41 (20.9)	
III	233 (63.8)	112 (66.3)	121 (61.7)	
IV	52 (14.2)	18 (10.7)	34 (17.3)	
Comorbidities				
AF	73 (20.0)	23 (13.6)	50 (25.5)	.005
CAD	100 (27.4)	47 (27.8)	53 (27.0)	.869
Hypertension	120 (32.9)	60 (35.5)	60 (30.6)	.321
Diabetes	89 (24.4)	37 (21.9)	52 (26.5)	.304
VT/VF	71 (19.5)	22 (13.0)	49 (25.0)	.004
LBBB	292 (80.0)	152 (89.9)	140 (71.4)	<.001
Severe TR	21 (5.8)	5 (3.0)	16 (8.2)	.029
Medication				
ACE inhibitor/ARB	334 (91.5)	157 (92.9)	177 (90.3)	.376
Beta-blocker	342 (93.7)	158 (93.5)	184 (93.9)	.88
Diuretics	351 (96.2)	161 (95.3)	190 (96.9)	.407
CRT type				.499
CRT-P	168 (46.0)	81 (47.9)	87 (44.4)	
CRT-D	197 (54.0)	88 (52.1)	109 (55.6)	
Hemoglobin, g/L	139.8 ± 16.4	139.7 ± 17.3	139.8 ± 15.5	.944
ALT, U/L	23.0 (17.0–34.0)	23.0 (16.0–33.0)	24.0 (17.0–35.0)	.528
AST, U/L	20.0 (16.0–26.0)	20.0 (16.0–26.0)	21.0 (16.0–28.0)	.14
TB, μmol/L	17.3 (13.2–24.4)	15.9 (13.1–21.0)	18.9 (13.4–26.8)	<.001
Albumin, g/L	42.0 ± 4.0	42.8 ± 3.8	41.3 ± 3.9	<.001
NT-proBNP, pg/mL	1533.0 (810.0–2718.3)	1115.0 (576.0–2154.4)	1995.0 (1017.0–3404.7)	<.001
Cr, mg/dL	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	.098
LVEF, %	29.1 ± 6.9	28.8 ± 6.2	29.5 ± 7.5	.349
LVEF at 6 mo, %	38.9 ± 11.2	47.2 ± 8.3	31.7 ± 8.1	<.001
QRS duration, ms	165.3 ± 19.8	165.8 ± 20.4	164.9 ± 19.3	.661
LAD, mm	43.6 ± 7.5	41.8 ± 7.7	45.1 ± 7.0	<.001
LVEDD, mm	69.9 ± 9.5	67.5 ± 8.2	71.9 ± 10.0	<.001
MELD-XI score	9.1 ± 4.0	8.4 ± 3.3	9.7 ± 4.5	.003
MELD-Albumin score	6.8 ± 3.6	6.1 ± 2.8	7.4 ± 4.1	<.001

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ALT = alanine aminotransferase; ARB, angiotensin receptor blocker; AST = aspartate aminotransferase; BMI = body mass index; CAD = coronary artery disease; Cr = creatinine; CRT = cardiac resynchronization therapy; LAD = left atrial diameter; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; 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; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; TB = total bilirubin; TR = tricuspid regurgitation; VF = ventricular fibrillation; VT = ventricular tachycardia.

creatinine, and N-terminal pro–B-type natriuretic peptide; and larger LV volumes at baseline. Notably, there were no significant differences among the 4 groups regarding QRS duration, LVEF, CRT type, or medication therapy.

Associations between modified MELD scores and CRT response

The CRT response rates were 57% in the first quartile of the MELD-Albumin score, 54.3% in the second quartile, 45.1% in the third quartile, and 28.6% in the fourth quartile ($P <$ .001). A similar trend of decreasing CRT response rates with increasing MELD-XI scores was observed (P = .007). Additionally, restricted cubic spline analysis showed a monotonic increase between the MELD-Albumin score and CRT response after surpassing the median (Figure 2). In univariate analysis, both MELD-XI scores and MELD-Albumin scores were associated with CRT nonresponse (odds ratio [OR] 1.10 per 1-unit increase, 95% CI 1.04–1.17, P = .001; and OR 1.14 per 1-unit increase, 95% CI 1.07–1.22, $P <$ .001, respectively) (Table 2). After multivariable adjustment, the MELD-XI score showed poor predictive value for CRT response (OR 1.51, 95% CI 0.75–3.02), whereas the highest MELD-Albumin score group remained associated with increased CRT nonresponse compared with the lowest MELD-Albumin score group (OR 2.42, 95% CI 1.19–4.89). Furthermore, the correlation between changes in LVEF and LVEDD before and after CRT implantation

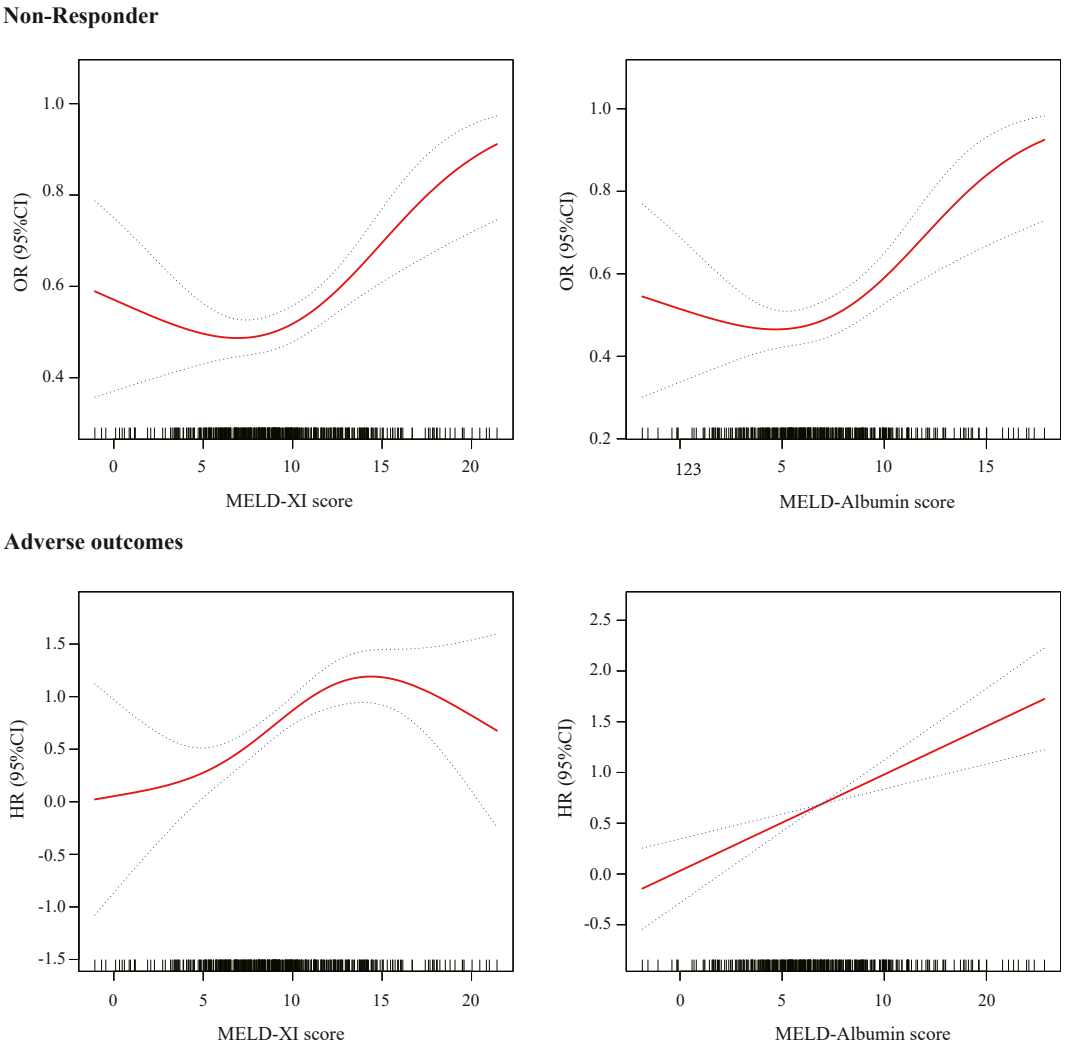

Figure 2 Restricted cubic spline analysis for the relationship between modified Model for End-Stage Liver Disease score and outcomes. Adjusted for age, sex, body mass index, New York Heart Association functional class, left ventricular ejection fraction, left ventricular end-diastolic diameter, hemoglobin, creatinine, atrial fibrillation, left bundle branch block, hypertension, ventricular tachycardia/ventricular fibrillation, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. CI = confidence interval; MELD-Albumin = Model for End-Stage Liver Disease with albumin; MELD-XI = Model for End-Stage Liver Disease excluding international normalized ratio; OR = odds ratio.

in relation to the modified MELD scores was present in Supplemental Table 3 and Supplemental Figure 3. Both the MELD-XI and the MELD-Albumin scores were negatively correlated with changes in LVEF (MELD-XI score: r = –0.20, $P < .001$; MELD-Albumin score: r = –0.26, $P < .001$) and positively correlated with changes in LVEDD (MELD-XI score: r = 0.15, $P = .004$; MELD-Albumin score: r = 0.21, $P < .001$). Notably, the MELD-Albumin score exhibited a stronger relationship with CRT response compared with the MELD-XI score, indicating its potential predictive value.

Associations between modified MELD scores and adverse outcomes

During a median follow-up of 3.3 years (interquartile range 1.9–5.2 years), adverse outcomes of all-cause death and HF hospitalization occurred in 168 (46.03%) patients. The dose-response analysis indicated that the positive linear trend observed in MELD-Albumin scores was more pronounced than that in MELD-XI scores (Figure 2). The cumulative survival rates at 2, 4, and 6 years for patients in the highest MELD-Albumin quartile were 65.4%, 42.40%, and 22.6%, respectively, significantly lower than the other 3 groups (Figure 3). Furthermore, Kaplan-Meier analysis revealed that high MELD-Albumin scores were associated with high risk of adverse outcomes (log-rank test: $P < .001$). In univariate analysis, patients in the highest MELD-XI or MELD-Albumin scores group had over a 3-fold increased risk of reaching the clinical endpoint at long-term follow-up compared with those in the lowest scores group (MELD-XI score: HR 3.15, 95% CI 1.99–5.00, $P < .001$; MELD-Albumin score: HR 3.22, 95% CI 2.05–5.06, $P < .001$) (Table 3). After adjusting for previously identified clinically

Table 2 Association between modified MELD scores and nonresponders.

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
MELD-XI (per 1-unit increase)	1.10 (1.04 to 1.17)	.001	1.09 (1.03 to 1.16)	.004	1.06 (0.99 to 1.13)	.081
MELD-XI score quartiles						
Q1 (−1.06 to 6.75)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (6.75 to 8.91)	0.84 (0.47 to 1.50)	.552	0.76 (0.42 to 1.40)	.380	0.74 (0.40 to 1.38)	.348
Q3 (8.91 to 11.33)	1.25 (0.70 to 2.23)	.459	1.11 (0.60 to 2.07)	.745	1.03 (0.54 to 1.97)	.921
Q4 (11.33 to 21.43)	2.28 (1.25 to 4.17)	.007	1.99 (1.04 to 3.83)	.039	1.51 (0.75 to 3.02)	.250
P for trend	.003		.013		.145	
MELD-Albumin (per 1-unit increase)	1.14 (1.07 to 1.22)	<.001	1.14 (1.06 to 1.22)	<.001	1.10 (1.02 to 1.19)	.013
MELD-Albumin score quartiles						
Q1 (−1.85 to 4.61)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (4.61 to 6.41)	1.36 (0.76 to 2.45)	.298	1.31 (0.71 to 2.41)	.3908	1.33 (0.71 to 2.51)	.374
Q3 (6.41 to 8.89)	1.56 (0.87 to 2.80)	.138	1.46 (0.79 to 2.70)	.224	1.33 (0.71 to 2.51)	.377
Q4 (8.89 to 17.84)	3.31 (1.79 to 6.10)	<.001	3.10 (1.60 to 5.98)	<.001	2.42 (1.19 to 4.89)	.014
P for trend	.003		.013		.145	

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, BMI, NYHA functional class, LVEF, LVEDD, hemoglobin, and Cr. Model 3 was adjusted for age, sex, BMI, NYHA functional class, LVEF, LVEDD, hemoglobin, Cr, AF, LBBB, hypertension, VT/VF, and ACE inhibitor/ARB.

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CI = confidence interval; Cr = creatinine; HR = hazard ratio; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; 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; OR = odd ratio; Q = quartile; VF = ventricular fibrillation; VT = ventricular tachycardia.

relevant factors, echocardiographic parameters related to HF, and the laboratory parameters of hepatorenal function, both MELD-XI scores and MELD-Albumin scores still were independently associated with adverse outcomes (MELD-XI score: HR 1.06, 95% CI 1.02–1.11, $P = .006$; MELD-Albumin score: HR 1.10, 95% CI 1.05–1.16, $P < .001$). When analyzing each outcome separately, we found that patients in the highest quartile of modified MELD scores had significantly higher rates of all-cause mortality compared with those in the lowest quartile (Supplemental Table 4). This association was evident for both the MELD-XI and MELD-Albumin scores (all-cause mortality: MELD-XI score, HR 4.26, 95% CI 1.92–9.46; MELD-Albumin score, HR 4.59, 95% CI 2.25–9.38). However, after adjusting for multiple variables, only the MELD-Albumin score remained significantly associated with HF rehospitalization (Supplemental Table 5). Specifically, each unit increase in the MELD-Albumin score was associated with an 8% higher risk of HF rehospitalization (HR 1.08, 95% CI 1.01–1.15). In contrast, the MELD-XI score did not show a significant association with HF rehospitalization after multivariable adjustment.

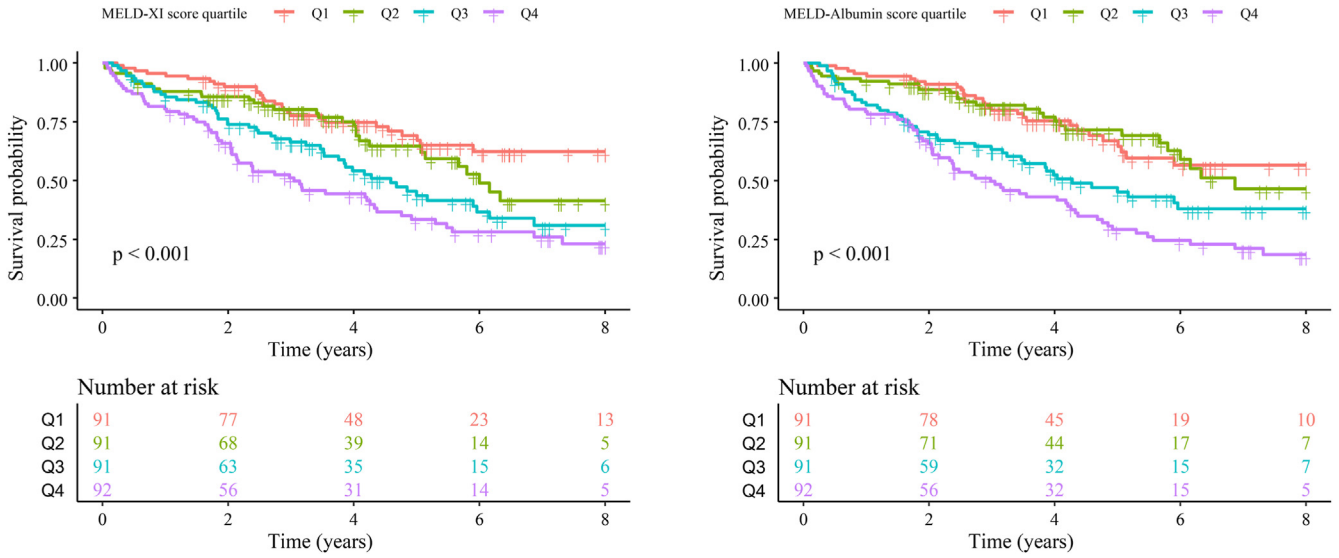

Figure 3 Kaplan-Meier survival curves for adverse outcomes by Model for End-Stage Liver Disease excluding international normalized ratio (MELD-XI) scores and Model for End-Stage Liver Disease with albumin (MELD-Albumin) scores. Q = quartile.

Table 3 Association between modified MELD scores and adverse outcomes.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
MELD-XI (per 1-unit increase)	1.11 (1.07 to 1.15)	<.001	1.11 (1.06 to 1.15)	<.001	1.06 (1.02 to 1.11)	.006
MELD-XI score quartiles						
Q1 (−1.06 to 6.75)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (6.75 to 8.91)	1.46 (0.87 to 2.45)	.152	1.48 (0.87 to 2.52)	.149	1.36 (0.79 to 2.32)	.264
Q3 (8.91 to 11.33)	2.35 (1.46 to 3.79)	<.001	2.37 (1.42 to 3.95)	.001	2.07 (1.24 to 3.45)	.005
Q4 (11.33 to 21.43)	3.15 (1.99 to 5.00)	<.001	3.12 (1.88 to 5.18)	<.001	2.27 (1.34 to 3.84)	.002
P for trend	<.001		<.001		.001	
MELD-Albumin (per 1-unit increase)	1.15 (1.10 to 1.20)	<.001	1.15 (1.10 to 1.20)	<.001	1.10 (1.05 to 1.16)	<.001
MELD-Albumin score quartiles						
Q1 (−1.85 to 4.61)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (4.61 to 6.41)	1.16 (0.69 to 1.96)	.577	1.19 (0.69 to 2.06)	.531	1.17 (0.68 to 2.03)	.568
Q3 (6.41 to 8.89)	2.10 (1.31 to 3.37)	.002	2.04 (1.24 to 3.35)	.005	1.69 (1.02 to 2.80)	.041
Q4 (8.89 to 17.84)	3.22 (2.05 to 5.06)	<.001	3.20 (1.96 to 5.24)	<.001	2.27 (1.36 to 3.78)	.002
P for trend	<.001		<.001		<.001	

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, BMI, NYHA functional class, LVEF, LVEDD, hemoglobin, and Cr. Model 3 was adjusted for age, sex, BMI, NYHA functional class, LVEF, LVEDD, hemoglobin, Cr, AF, LBBB, hypertension, VT/VF, and ACE inhibitor/ARB.

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CI = confidence interval; Cr = creatinine; HR = hazard ratio; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; 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; Q = quartile; VF = ventricular fibrillation; VT = ventricular tachycardia.

Prognostic value of modified MELD scores in patients receiving CRT

To evaluate the prognostic strength of various MELD scoring systems, we compared their AUC values (Figure 4). The ROC curve analysis demonstrated that the MELD-Albumin score had superior predictive accuracy for adverse outcomes compared with the MELD-XI score (MELD-Albumin AUC: 0.692, 95% CI 0.644–0.742 vs MELD-XI AUC: 0.659, 95% CI 0.608–0.715; $P = .008$) (Table 4). In the CRT-D subgroup, the MELD-Albumin score also showed a higher AUC (0.731, 95% CI 0.654–0.797) compared with the MELD-XI score (0.693, 95% CI 0.628–0.765) ($P = .014$) for predicting adverse outcomes. Although no statistically significant AUC differences were observed in other subgroups, the MELD-Albumin score consistently demonstrated a trend toward a larger AUC than the MELD-XI score.

For predicting CRT nonresponse, the MELD-Albumin score again showed better predictive performance (AUC 0.620, 95% CI 0.564–0.673) compared with the MELD-XI score (AUC 0.601, 95% CI 0.551–0.659); however, this difference did not reach statistical significance ($P = .129$).

Sensitivity analysis

After excluding patients with severe TR, the associations between the modified MELD scores and CRT nonresponse and adverse outcomes remained significant and consistent with the main analysis (Supplemental Table 6).

Discussion

In this long-term follow-up study, we investigated the prognostic utility of modified MELD scores, a measure of hepatorenal function, to predict CRT response and adverse outcomes in patients with CRT implantation. Our results show that the MELD-Albumin score was significantly associated with CRT response, even after adjusting for confounding variables. Furthermore, both the MELD-XI and MELD-Albumin scores independently predicted long-term adverse outcomes, including all-cause mortality and HF hospitalizations, in patients undergoing CRT. Specifically, patients with a higher MELD-XI (>11.3) or MELD-Albumin (>8.89) score exhibited an increased risk of these adverse outcomes. Notably, the MELD-Albumin score demonstrated superior predictive accuracy compared with the MELD-XI score, particularly in patients who received a CRT-D device. Thus, in this real-world cohort of HF patients with CRT devices, the MELD-Albumin score was found to better predict both long-term prognosis and echocardiographic response to CRT.

Previous studies have highlighted the strong association between HF and multiorgan dysfunction, including cardiohepatic and cardiorenal syndromes, both of which are linked to poor prognosis.[20] Cardiogenic liver injury in HF patients can result from 2 primary mechanisms. First, sudden hepatic hypoperfusion due to acute circulatory failure can lead to elevated lactate dehydrogenase and hepatic aminotransferases.[21] Second, hepatic venous congestion due to increased central venous pressure and TR severity can significantly contribute to liver injury.[20] Congestive liver injury often presents asymptomatically, with abnormal cholestasis-related biochemistry, such as elevated bilirubin and gamma-glutamyltransferase.[22] In our study, we observed a higher proportion of severe TR in patients with worse liver-kidney function score (Supplemental Tables 1 and 2). Additionally, prior research has utilized cholestatic liver enzymes to predict clinical outcomes in chronic HF patients.[23,24] The interaction

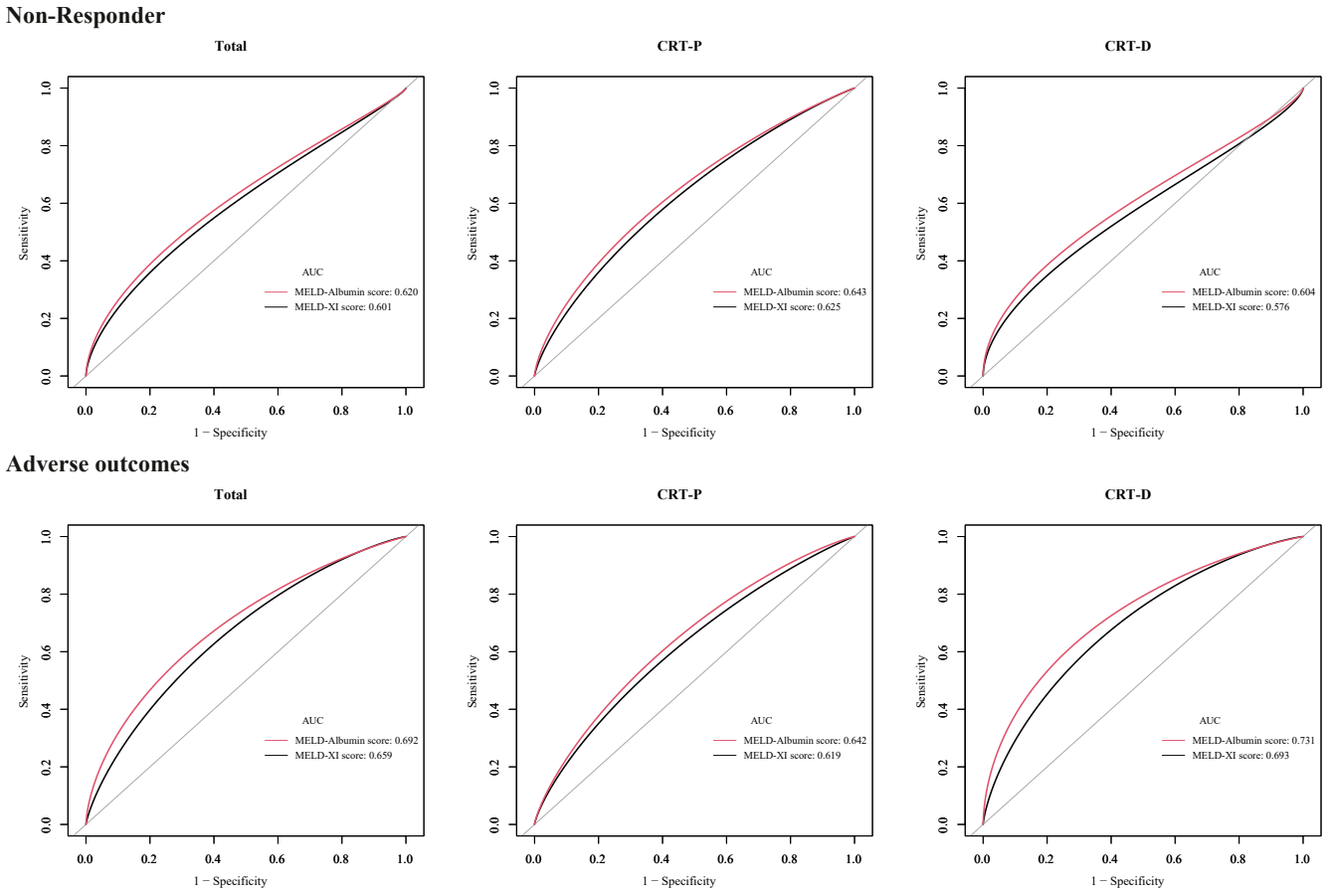

Figure 4 The receiver-operating characteristic curves of modified Model for End-Stage Liver Disease scores to determine the accuracy to predict cardiac resynchronization therapy nonresponder and adverse outcomes. AUC = area under the curve; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker.

between heart and kidney dysfunction in HF is also well established, as both hemodynamic and nonhemodynamic pathways exacerbate HF symptoms and disease progression.[25] Roy and colleagues[26] found that the severity of kidney dysfunction was strongly correlated with higher HF mortality, and a large cohort study confirmed that cardiorenal syndromes were associated with worse prognoses compared with isolated HF or chronic kidney disease.[27] Given these findings, it is logical to explore the prognostic value of hepatorenal indices in patients undergoing CRT.

The MELD score was initially developed to prioritize liver transplant candidates and included bilirubin, creatinine, and INR to assess liver and kidney functions.[28] Over time, the prognostic significance of the MELD score has been demonstrated in patients with HF and valvular disorders.[14,18,29] The modified versions of the MELD score, which exclude or replace INR due to anticoagulation therapy, have shown improved accuracy in assessing outcomes in HF or TR patients.[15,17] Despite these advances, the relationship between modified MELD scores and clinical outcomes in HF patients with CRT implantation remains unclear. One study showed that the MELD-XI score predicted all-cause mortality following CRT implantation.[18] However, whether the MELD-Albumin score offers better predictive performance in CRT-treated requires further investigation.

Our analysis found that modified MELD scores were significantly associated with changes in LVEF and LVEDD from pre- to post-CRT (Supplemental Table 3). Notably, even after adjusting for multiple variables, the highest MELD-Albumin score group still had a 142% increased risk of CRT nonresponse compared with the lowest group. However, there was no statistically significant difference between MELD-XI and CRT responsiveness. These results were consistent with a study by Saito and colleagues,[18] which found no correlation between the MELD-XI score and changes in LVEF at 6 months post-CRT. In our study, we adopted stricter criteria for defining CRT response, considering a >10% improvement in LVEF at 6 months postimplantation, which highlighted an excellent predictive performance of the MELD-Albumin score in CRT response (OR 1.10, 95% CI 1.02–1.19, $P = .013$). These findings suggest that while the MELD-XI score has limited predictive value for CRT nonresponse, the MELD-Albumin score may be a useful marker for LV reverse remodeling.

Table 4 Comparison of the MELD-XI score and MELD-Albumin scores for detection of adverse outcomes and nonresponders.

Test	AUC (95% CI)	Specificity	Sensitivity	Accuracy	*P* value
Adverse outcomes					
Total					.008
MELD-XI score	0.659 (0.608–0.715)	0.574	0.725	0.643	
MELD-Albumin score	0.692 (0.644–0.742)	0.767	0.569	0.676	
CRT-P					.280
MELD-XI score	0.619 (0.534–0.701)	0.557	0.704	0.619	
MELD-Albumin score	0.642 (0.549–0.723)	0.546	0.732	0.625	
CRT-D					.014
MELD-XI score	0.693 (0.628–0.765)	0.770	0.594	0.684	
MELD-Albumin score	0.731 (0.654–0.797)	0.740	0.708	0.725	
Nonresponder					
Total					.129
MELD-XI score	0.601 (0.551–0.659)	0.741	0.436	0.578	
MELD-Albumin score	0.620 (0.568–0.673)	0.682	0.513	0.592	
CRT-P					.348
MELD-XI score	0.625 (0.539–0.698)	0.659	0.575	0.615	
MELD-Albumin score	0.643 (0.564–0.724)	0.610	0.667	0.639	
CRT-D					.102
MELD-XI score	0.576 (0.491–0.650)	0.852	0.296	0.546	
MELD-Albumin score	0.604 (0.524–0.678)	0.852	0.352	0.577	

AUC = area under the curve; CI = confidence interval; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; 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.

These results are clinically significant as LV reverse remodeling is associated with prolonged survival.[3] Our study's findings are consistent with previous research on the prognostic implications of modified MELD scores. In a cohort of 285 CRT recipients, each 1-unit increase in the MELD-XI score was associated with a 4% increased risk of all-cause mortality (HR 1.04, 95% CI 1.01–1.08, $P = .020$).[18] However, our study expands on previous findings by showing that both the MELD-XI and MELD-Albumin scores independently predicted all-cause mortality and HF hospitalization. In ROC curve analysis, the MELD-Albumin score outperformed the MELD-XI score for predicting adverse outcomes (MELD-Albumin score: AUC 0.692, 95% CI 0.644–0.742; MELD-XI score: AUC 0.659, 95% CI 0.608–0.715; $P = .008$), especially in CRT-D recipients (MELD-Albumin score: AUC 0.731, 95% CI 0.654–0.797; MELD-XI score: AUC 0.693, 95% CI 0.628–0.765; $P = .014$). CRT-D patients are at higher risk of sudden cardiac death, and the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) study demonstrated that increased bilirubin levels and reduced albumin levels were associated with a higher risk of sudden cardiac death (HR 1.35, 95% CI 1.18–1.54, $P < .001$; and HR 1.42, 95% CI 1.14–1.78, $P = .002$).[30] This may explain why the MELD-Albumin score showed better predictive value in CRT-D patients. Although there were no statistically significant differences between MELD-Albumin and MELD-XI in other subgroups (Table 4), higher AUCs for adverse outcomes or CRT response were consistently noted with the MELD-Albumin score. This underscores the score's superior prognostic utility for adverse outcomes in CRT recipients.

Serum albumin, a stable protein, reflects frailty, cachexia, and systemic inflammation.[31] Lima and colleagues[32] found that elevated inflammation levels were closely associated with higher risk of HF hospitalization. Interestingly, we found no significant differences in BMI across different MELD score groups, which suggests that albumin may enhance predictive performance through inflammatory pathways, rather than by reflecting nutritional status alone. Systemic inflammation is known to exacerbate cardiac remodeling and impair myocardial function, which can negatively affect the efficacy of CRT.[33] Inflammatory cytokines such as tumor necrosis factor α and interleukins can promote myocardial fibrosis and apoptosis, leading to reduced contractility and responsiveness to resynchronization therapy.[34] Additionally, chronic inflammation can contribute to endothelial dysfunction and atherosclerosis, further complicating heart failure management.[35] Due to insufficient physiological reserves and increased vulnerability to stressors, frail patients may have diminished ability to recover from invasive procedures and adapt to the hemodynamic changes induced by CRT, leading to suboptimal responses and poorer prognoses.[36]

Despite the valuable insights gained, this study has several limitations. First, it is a retrospective, observational study using a small sample size from a single institution, necessitating further large-scale validation. Second, the study does not account for postoperative alterations in modified MELD scores. Prior research suggests that mechanical therapy can improve hepatorenal function in HF patients,[37] and improvement in liver function following CRT has been linked to better clinical outcomes.[38] Third, the study spanned a 12-year period, and the confounding effects caused by significant

advancements in device technology and HF medical therapy were not considered. For example, improvements in CRT devices, such as enhanced programming capabilities and quadripolar leads, and the introduction of novel pharmacotherapies—including angiotensin receptor-neprilysin inhibitors and sodium-glucose cotransporter 2 inhibitors—may lead to better prognosis. Therefore, our results may not fully reflect the effects of contemporary HF management strategies. Fourth, over 40% of patients were excluded due to missing data on key variables, including bilirubin, creatinine, and albumin. This exclusion may introduce selection bias, as the excluded patients may differ systematically from those included in the analysis, potentially affecting the generalizability of our findings. Larger studies are required to confirm these findings.

Conclusion

Our study provides compelling evidence that the MELD-Albumin score can effectively predict CRT nonresponse and adverse outcomes in patients undergoing CRT implantation. Patients with high MELD-Albumin scores may benefit from closer echocardiographic monitoring, optimized medical therapy, and timely consideration of advanced heart failure therapies such as ventricular assist devices or evaluation for heart transplantation. Additionally, more frequent follow-up appointments and comprehensive management of comorbid conditions like hepatorenal dysfunction and systemic inflammation may improve outcomes in this high-risk population. The MELD-Albumin score shows significant potential as a tool for risk stratification and guiding clinical decision making in patients undergoing CRT.

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Ethics Statement: The research reported in this article adhered to the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (No. IRB2012-BG–006).

Appendix

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2024.12.014.

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