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ORIGINAL ARTICLE

Prognostic value of the MELD-XI score in patients undergoing cardiac resynchronization therapy

Yuki Saito*, Toshiko Nakai, Yukitoshi Ikeya, Rikitake Kogawa, Naoto Otsuka, Yuji Wakamatsu, Sayaka Kurokawa, Kimie Ohkubo, Koichi Nagashima and Yasuo Okumura

Division of Cardiology, Department of Medicine, Nihon University School of Medicine, 30-1 Ohyaguchi-kamicho, Itabashi-ku, Tokyo, 173-8610, Japan

Abstract

Aims Multi-organ dysfunction was recently reported to be a common condition in patients with heart failure (HF). The Model for End-stage Liver Disease eXcluding International normalized ratio (MELD-XI) score reflects liver and kidney function. The prognostic relevance of this score has been reported in patients with a variety of cardiovascular diseases who are undergoing interventional therapies. However, the relationship between the severity of hepatorenal dysfunction assessed by the MELD-XI score and the long-term clinical outcomes of HF patients receiving cardiac resynchronization therapy (CRT) has not been evaluated.

Methods and results Clinical records of 283 patients who underwent CRT implantation between March 2003 and October 2020 were retrospectively evaluated (mean age 67 ± 12, 22.6% female). Blood samples were collected before CRT implantation. Patients were divided into three groups based on tertiles of the MELD-XI score: first tertile (MELD-XI = 9.44, n = 95), second tertile (9.44 $<$ MELD-XI $<$ 13.4, n = 94), and third tertile (MELD-XI $\geq$ 13.4, n = 94). The primary endpoint was all-cause mortality. Compared with the other groups, the third tertile group exhibited significantly older age, higher prevalence of diabetes mellitus and hypertension, lower haemoglobin level, and higher N-terminal pro-brain natriuretic peptide level (all $P < 0.05$). The functional CRT response rate was also significantly lower in the third tertile group (P = 0.011). During a median follow-up of 30 months (inter-quartile range, 9–67), 105 patients (37.1%) died. Kaplan–Meier analysis revealed that patients with a higher MELD-XI score had a greater risk of all-cause mortality (log-rank test: $P < 0.001$). Even after adjustment for clinically relevant factors and a conventional risk score, the MELD-XI score was still associated with mortality (adjusted hazard ratio: 1.04, 95% confidence interval: 1.00–1.07, P = 0.014, and adjusted hazard ratio: 1.04, 95% confidence interval: 1.01–1.09, P = 0.005, respectively). A higher MELD-XI score was associated with a greater risk of all-cause mortality than a lower MELD-XI score regardless of whether a pacemaker or defibrillator was implanted (log-rank test: P = 0.010 and $P < 0.001$, respectively).

Conclusions Impaired hepatorenal function assessed by the MELD-XI score was associated with older age, higher prevalence of multiple co-morbidities, severity of HF, lower CRT response rates, and subsequent all-cause mortality in HF patients undergoing CRT implantation. These results suggest that the MELD-XI score can provide additional prognostic information and may be useful for improving risk stratification in this population.

Keywords Heart failure; Arrhythmia; Pacemaker implantation; Multi-organ dysfunction

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**Correspondence to: Yuki Saito, Division of Cardiology, Department of Medicine, Nihon University School of Medicine, 30-1 Ohyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan. Tel: +81-3-3972-8111; Fax: +81-3-3972-1098. Email: saito.yuki@nihon-u.ac.jp*

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients who have advanced-stage heart failure (HF) with a reduced left ventricular ejection fraction (LVEF) and wide QRS complex.[1,2] However, individual outcomes in CRT recipients vary significantly, and long-term death rates remain high.[3] Certain patients, such as those with ischaemic cardiomyopathy, severely dilated ventricles, or right ventricular (RV) dysfunction, have been reported to derive less sur-

vival benefit than expected from CRT.[4,5] Therefore, risk stratification of potential CRT candidates on the basis of pre-implantation assessment remains important.

Low cardiac output and systemic venous congestion due to advanced HF are known to cause multiple organ dysfunction or tissue damage, which leads to disease progression and adverse outcomes.[6,7] Traditionally, organ dysfunction is evaluated in isolation, meanwhile in clinical settings, several organs may be caused, which can be a marker of more severe HF.[8]

The Model for End-stage Liver Disease (MELD) score, which is based on bilirubin, creatinine, and the international normalized ratio, reflects liver and kidney function.[9] This score was originally developed for prognostic assessment in patients with advanced liver disease.[10] The MELD-XI score is one of the several modified MELD scores, and unlike the standard MELD score, it excludes the international normalized ratio value.[11] Recently, several studies reported the prognostic relevance of the MELD-XI score in a variety of patients, including those with advanced HF undergoing left ventricular (LV) assist device implantation, those with severe mitral regurgitation (MR) undergoing percutaneous mitral valve repair, and those with severe aortic valve stenosis undergoing transcatheter aortic valve implantation.[12–14] However, the relationship between the severity of hepatorenal dysfunction assessed by the MELD-XI score and the long-term clinical outcomes of HF patients receiving CRT has not been evaluated.

In this real-world, observational study, we examine the potential use of the MELD-XI score as a risk assessment tool for all-cause mortality in HF patients receiving CRT. In addition, we investigated whether the predictive value of the MELD-XI score differed between patients receiving CRT with a pacemaker (CRT-P) or an implantable cardioverter–defibrillator (CRT-D).

Methods

Patients and study protocol

This was a single-centre, retrospective, observational cohort study. We screened 285 consecutive patients who underwent CRT implantation at Nihon University Itabashi Hospital between March 2004 and October 2020. Two patients were excluded because of lack of data for one or both of the components of the MELD-XI score (total bilirubin or creatinine), and the remaining 283 patients were investigated. This study was approved by the ethics committee of Nihon University Itabashi Hospital (RK-210209-8). The investigation conformed to the principles outlined in the Declaration of Helsinki.

Laboratory tests and the MELD-XI score

The MELD-XI score was determined based on total bilirubin and creatinine levels obtained before CRT implantation. The MELD-XI score was calculated as previously reported: 11.76 × ln (creatinine [mg/dL]) + 5.11 × ln (total bilirubin [mg/dL]) + 9.44.[11] If a patient had a creatinine or total bilirubin level lower than 1.0 mg/dL, a value of 1.0 mg/dL was used to prevent negative logarithmic values in the formula.[15] Patients were divided into three groups based on the tertile of the MELD-XI score.

Echocardiographic measurement

Echocardiography was performed by experienced technicians according to the guidelines of the American Society of Echocardiography.[16] End-systolic and end-diastolic LV volumes were measured in the apical four-chamber and two-chamber views. LVEF was measured by the modified Simpson's method. The RV end-diastolic diameter (RVDd) was measured at the basal ventricular level of the RV in end-diastole. The RV fractional area change (RVFAC) was obtained by tracing the RV end-diastolic area (RVEDA) and end-systolic area (RVESA) in the apical four-chamber view using the following formula: (RVEDA − RVESA)/RVEDA × 100. MR and tricuspid regurgitation (TR) were graded on a 4-point scale based on colour-flow Doppler images. The TR pressure gradient (TRPG) was measured using continuous-wave Doppler imaging. From the subcostal view, the diameter of the inferior vena cava (IVC) in its long axis was measured within 3 cm of the IVC–right atrium junction during passive respiration.

Cardiac resynchronization therapy

All patients underwent device implantation under local anaesthesia. As previously described, atrioventricular delay was optimized automatically by each device, but if the QRS duration did not narrow sufficiently, the atrioventricular and interventricular delays were optimized manually based on the QRS duration observed on the electrocardiogram.[17] Thereafter, patients were followed up in dedicated device therapy clinics at regular 3–6 month intervals. We evaluated two definitions of CRT response: functional and echocardiographic.[17] The functional CRT response was defined as the combination of improvement by at least one New York Heart Association (NYHA) functional class and the absence of death or hospitalization due to HF at 6 months after CRT implantation.[17,18] The echocardiographic CRT response was defined as an improvement in the LVEF of at least 5% or a reduction in the LV end-systolic volume (LVESV) of at least 15% at 6 months after CRT implantation.[17]

Follow-up and endpoint

The primary endpoint was all-cause mortality, and the secondary endpoint was the incidence of cardiac death. Patients were followed from the date of device implantation to December 2020 or until the endpoint. Follow-up data were collected in a blinded fashion via review of all available medical records.

Statistical analysis

Continuous variables are presented as medians (inter-quartile range) and categorical variables as numbers (percentage). Statistical differences between continuous variables were compared using one-way analysis of variance followed by the *post hoc* Tukey–Kramer test, or the Kruskal–Wallis test followed by the Steel–Dwass test. Categorical variables were compared by the χ^2 test with Bonferroni correction. Correlations between variables were tested by Pearson's correlation coefficient. The Kaplan–Meier method was used to analyse patient survival, and the log-rank test was used to compare group differences.

The associations between pre-CRT implantation characteristics and all-cause mortality were assessed with a Cox proportional hazards regression analysis. Hazard ratios with 95% confidence intervals were calculated. To satisfy the model assumptions, data of N-terminal pro-brain natriuretic peptide (NT-proBNP) were subjected to natural log transformation (ln). Until January 2010, we measured BNP levels instead of NT-proBNP levels, and all BNP data were converted to NT-proBNP data using the following formula: NT-proBNP = $BNP^{1.341} - 15$.[19]

Multivariate Cox proportional hazards regression analysis was used to evaluate the impact of the MELD-XI score. We constructed multivariate models to adjust for the effect of established confounders such as the following: age, sex, diabetes mellitus (DM), ischaemic myopathy, atrial fibrillation, QRS duration >150 ms, LVESV, and moderate or severe MR (Model 1); the effect of a conventional risk score (the VALID-CRT risk score, Model 2); and the effect of echocardiographic parameters related to the severity of right HF (RVDd, RVFAC, TRPG, moderate or severe TR, and maximal IVC diameter) (Model 3). The VALID-CRT risk score was constructed and validated using the following variables: age, sex, implantable cardioverter defibrillator backup, atrial fibrillation, presence or absence of atrioventricular junction ablation in the case of atrial fibrillation, ischaemic aetiology, DM, NYHA class, and LVEF.[20] Furthermore, to assess whether the accuracy of predicting all-cause mortality would improve after adding the MELD-XI score to a baseline model consisting of the VALID-CRT risk score, the *C*-statistics, net reclassification improvement, and integrated discrimination improvement were calculated.

In the sensitive analysis, we classified patients into three groups based on the lowest 20%, middle 60%, and the highest 20% of the MELD-XI score. We then compared the clinical characteristics and clinical outcomes among three groups.

For all analyses, $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP 13.0 (SAS Institute, Cary, NC, USA) and the R Statistics Version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

The distribution of MELD-XI scores among the study patients is shown in *Figure 1*. The median (inter-quartile range) MELD-XI score was 10.5 (9.4–14.6). The cut-off values used to define the MELD-XI score tertiles were determined to be 9.44 and 13.3, and patients were stratified into three groups accordingly: first tertile (MELD-XI = 9.44, n = 95), second tertile (9.44 < MELD-XI < 13.4, n = 94), and third tertile (MELD-XI ≥ 13.4, n = 94). The baseline clinical characteristics for each group are shown in *Table 1*. Compared with the other two groups, the third tertile group exhibited the following significant differences: older age; higher prevalence of men; higher prevalence of diabetes mellitus and hypertension; lower administration rates of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker; lower haemoglobin level; and higher levels of total bilirubin, blood urea nitrogen, creatinine, and NT-proBNP (all $P < 0.05$). The third tertile group also exhibited a higher prevalence of moderate or severe TR, as well as higher TRPG (all $P < 0.05$). Echocardiographic parameters related to left HF (LV end-diastolic volume, LVESV, LVEF, and MR severity) did not differ significantly between the three groups.

Figure 1 Distribution of MELD-XI scores.

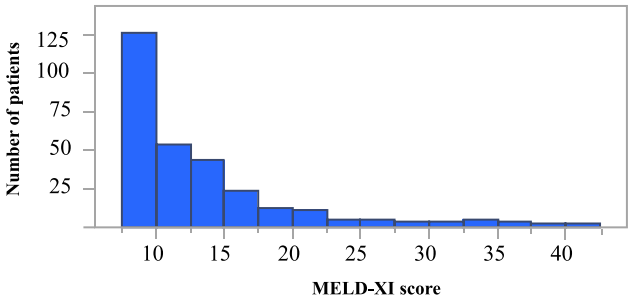


Table 1 Clinical characteristics of patients stratified into three groups according to tertiles of the MELD-XI score

Item	First tertile MELD-XI = 9.44 (n = 95)	Second tertile 9.44 < MELD-XI < 13.4 (n = 94)	Third tertile MELD-XI ≥ 13.4 (n = 94)	P value
Baseline clinical data				
Age (years)	69 (60–74)	67 (57–76)	72 (64–79)*,†	0.019
Male, n (%)	64 (67.3)	79 (84.0)*	76 (80.8)*	0.016
Body mass index (kg/m^2)	21.4 (18.8–24.3)	22.4 (20.4–25.3)	22.3 (19.9–24.8)	0.096
NYHA IV, n (%)	9 (9.4)	11 (11.7)	20 (21.8)	0.052
Diabetes mellitus, n (%)	25 (26.3)	36 (38.3)	44 (46.8)*	0.012
Hypertension, n (%)	38 (40.0)	49 (52.1)	56 (59.5)*	0.024
Ischaemic cardiomyopathy, n (%)	25 (26.3)	36 (38.3)	35 (37.2)	0.15
Atrial fibrillation, n (%)	17 (17.8)	23 (24.4)	27 (28.7)	0.21
QRS duration (ms)	152 (128–172)	150 (123–174)	150 (130–168)	0.89
VALID-CRT risk score	0.80 (−0.08–1.23)	0.76 (0.19–1.35)	0.89 (0.27–1.51)	0.066
Medications				
ACE-I or ARB, n (%)	65 (68.4)	70 (75.2)	52 (55.3)†	0.013
Beta-blocker, n (%)	85 (89.4)	89 (95.7)	83 (88.3)	0.16
Diuretic, n (%)	86 (90.5)	87 (93.5)	78 (82.9)	0.058
Laboratory data				
Haemoglobin (g/dL)	12.7 (11.7–13.8)	13.4 (11.2–14.3)	11.7 (10.4–13.0)*,†	<0.001
Platelet count (× 10^3/μL)	201 (169–253)	188 (157–221)	190 (146–220)	0.033
Total bilirubin (mg/dL)	0.6 (0.4–0.8)	0.8 (0.5–1.1)*	0.6 (0.3–1.3)	0.002
AST (U/L)	22 (19–31)	25 (19–34)	23 (17–31)	0.37
ALT (U/L)	18 (13–30)	19 (15–28)	17 (12–28)	0.42
GGT (U/L)	41 (22–84)	49 (27–97)	43 (24–72)	0.58
Sodium (mEq/L)	140 (138–142)	139 (137–141)	139 (136–141)	0.15
BUN (mg/dL)	18 (13–22)	21 (16–26)*	33 (25–47)*,†	<0.001
Cr (mg/dL)	0.8 (0.7–0.9)	1.0 (1.0–1.1)*	1.7 (1.4–2.5)*,†	<0.001
NT-proBNP (pg/mL)	2310 (1018–5689)	2743 (1417–8029)	7119 (2319–15,461)*,†	<0.001
Echocardiographic data				
LVEDV (mL)	199 (162–259)	215 (163–263)	197 (144–255)	0.46
LVESV (mL)	147 (105–191)	153 (101–201)	134 (90–189)	0.36
LVEF (%)	30 (21–38)	27 (21–36)	30 (23–38)	0.35
Moderate or severe MR, n (%)	17 (17.8)	10 (10.6)	19 (20.2)	0.17
RVDd (mm)	31 (25–35)	34 (30–38)	32 (29–38)	0.13
RVFAC (%)	45 (34–52)	44 (32–50)	42 (35–52)	0.41
Moderate or severe TR, n (%)	11 (14.3)	22 (29.7)	26 (34.2)*	0.009
TRPG (mmHg)	18 (5–30)	22 (5–31)	27 (15–39)*,†	0.019
Maximal IVC diameter (mm)	14 (11–17)	16 (11–19)	15 (13–19)	0.17

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; CRT, cardiac resynchronization therapy; GGT, γ-glutamyl transferase; IVC, inferior vena cava; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MELD-XI, Model for End-stage Liver Disease excluding the International normalized ratio; MR, mitral regurgitation; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RVDd, right ventricular end-diastolic diameter; RVFAC, right ventricular fractional area change; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient.
Values are shown as the median (inter-quartile range) or number (%). For multiple comparisons, the ANOVA test was used for symmetrical continuous variables, the Kruskal–Wallis test was used for non-symmetrical continuous variables, and the χ^2 test was used for categorical variables. All pair comparisons were performed based on the Tukey–Kramer test for symmetrical continuous variables, the Steel–Dwass test for non-symmetrical continuous variables, and the χ^2 test with Bonferroni correction for categorical variables.
*$P < 0.05$ vs. first tertile.
†$P < 0.05$ vs. second tertile.

Hepatorenal function and cardiac resynchronization therapy response

In this study population, 277 patients underwent 6 months of follow-up. Of these patients, 210 (75.8%) were categorized as functional CRT responders. The functional CRT response rates were 79.3% in the first tertile group, 82.9% in the second tertile group, and 64.8% in the third tertile group. The functional CRT response rate was significantly lower in the third tertile group than in the other two groups (P = 0.011). Of 263 patients who underwent follow-up echocardiography 6 months after CRT implantation, 190 (72.2%) were categorized as echocardiographic CRT responders. The echocardiographic CRT response rates were 78.6% in the first tertile group, 73.3% in the second tertile group, and 64.2% in the third tertile group (P = 0.10). The MELD-XI score before CRT implantation was not significantly correlated with the rate of LVEF change from before to after CRT implantation (r = −0.08, P = 0.18).

Hepatorenal function and clinical outcomes

The median (inter-quartile range) follow-up period was 30 (9–67) months, and 105 patients died (58 cardiac deaths and 47 non-cardiac deaths). Kaplan–Meier curves revealed that patients with a higher MELD-XI score had a greater risk of all-cause mortality than those with lower MELD-XI scores (log-rank test: $P < 0.001$, *Figure 2*). Furthermore, the rate of cardiac deaths was significantly higher in patients with a higher MELD-XI score (log-rank test: $P = 0.002$, *Figure 3*). Univariate Cox proportional hazards regression analysis revealed that a higher MELD-XI score was significantly associated with all-cause mortality, along with lower body mass index, higher NYHA functional class, atrial fibrillation, QRS duration, higher VALID-CRT risk score, lower haemoglobin and sodium levels, and higher blood urea nitrogen and NT-proBNP levels (all $P < 0.05$, *Table 2*). Regarding echocardiographic parameters, lower RVFAC, moderate or severe TR, and higher TRPG were significantly associated with all-cause mortality in univariate Cox proportional hazards regression analysis (all $P < 0.05$, *Table 2*). Total bilirubin and creatine levels did not separately show a significant association with all-cause mortality. A higher MELD-XI score was significantly associated with all-cause mortality after adjusting for the VALID-CRT risk score, other previously reported clinically relevant factors (age, sex, DM, ischaemic myopathy, atrial fibrillation, QRS duration >150 ms, LVESV, and moderate or severe MR), and echocardiographic parameters related to right HF (RVDd, RVFAC, moderate or severe TR, TRPG, and maximal IVC diameter) (*Table 3*). Furthermore, adding the MELD-XI score to a baseline model consisting of the VALID-CRT risk score significantly increased the net reclassification improvement and integrated discrimination improvement for predicting all-cause mortality (*Table 4*).

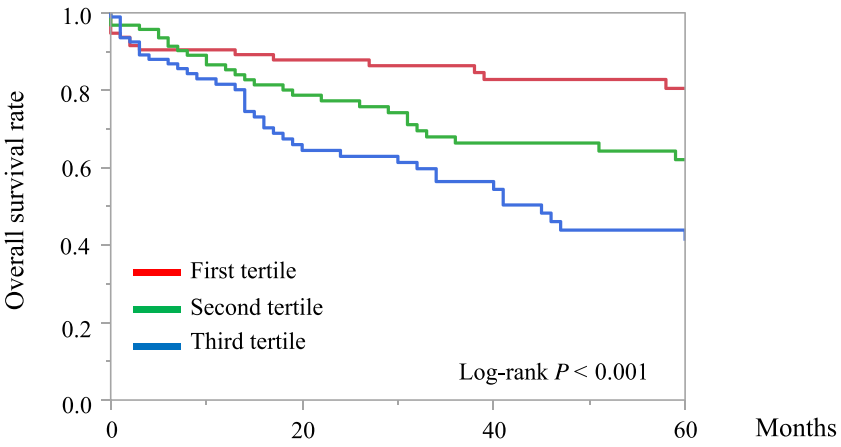
Prognostic value of MELD-XI score in patients receiving cardiac resynchronization therapy with a pacemaker or implantable cardioverter–defibrillator

In our study population, 109 patients received CRT-P and 174 patients received CRT-D. In both groups, a higher MELD-XI score was associated with a greater risk of all-cause mortality than a lower MELD-XI score [log-rank test: $P = 0.010$ (CRT-P) and $P < 0.001$ (CRT-D), *Figure 4*].

Sensitive analysis

In the sensitive analysis, patients were stratified into three groups accordingly: lowest group (MELD-XI = 9.44, $n = 95$), middle group ($9.49 \leq$ MELD-XI < 15.4, $n = 132$), and highest group (MELD-XI ≥ 15.4, $n = 56$). Trend in the baseline clinical characteristics for each group did not change in a sensitive analysis (Supporting Information, *Table S1*). The lowest group had significantly lower risk of all-cause mortality (log-rank test: $P < 0.001$) and cardiac deaths (log-rank test: $P = 0.024$) compared with the other two groups (Supporting Information, *Figures S1* and *S2*).

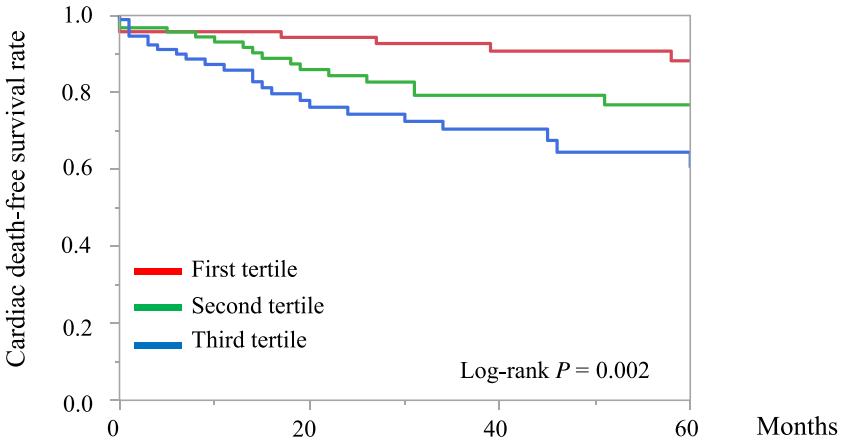
Figure 2 Kaplan–Meier curves of overall survival for patient groups defined according to the first, second, and third tertiles of the MELD-XI score.



Number at risk

Months	0	20	40	60
First tertile	95	63	47	36
Second tertile	94	58	39	29
Third tertile	94	44	28	16

Figure 3 Kaplan–Meier curves of event (cardiac death)-free survival for patient groups defined according to the first, second, and third tertiles of the MELD-XI score.



Number at risk

Months	0	20	40	60
First tertile	95	63	47	36
Second tertile	94	58	39	29
Third tertile	94	44	28	16

Table 2 Univariate Cox proportional hazards analysis for risk of all-cause mortality

Item	Hazard ratio	95% CI	*P*
Age (per 1 year increase)	1.00	0.98–1.01	0.69
Male	1.16	0.73–1.94	0.53
Body mass index (per 1 kg/m^2 increase)	0.9	0.87–0.936	<0.001
NYHA IV (vs. NYHA II or III)	9.31	5.73–14.9	<0.001
Diabetes mellitus	1.22	0.81–1.80	0.32
Ischaemic cardiomyopathy	1.22	0.81–1.81	0.33
Atrial fibrillation	1.74	1.14–2.61	0.011
QRS duration >150 ms	0.55	0.37–0.82	0.003
VALID-CRT risk score (per 1 increase)	1.40	1.12–1.76	0.002
Haemoglobin (per 1 g/dL increase)	0.80	0.73–0.88	<0.001
Platelet count (per 1 × 10^3/μL increase)	0.99	0.99–1.00	0.24
Total bilirubin (per 0.1 mg/dL increase)	1.00	0.66–1.45	0.98
AST (per 10 U/L increase)	0.95	0.81–1.00	0.37
ALT (per 10 U/L increase)	0.96	0.85–1.00	0.37
GGT (per 10 U/L increase)	1.00	0.98–1.02	0.40
Sodium (per 1 mmol/L increase)	0.91	0.86–0.96	<0.001
BUN (per 1 mg/dL increase)	1.02	1.00–1.02	<0.001
Cr (per 0.1 mg/dL increase)	1.01	0.99–1.01	0.052
ln [NT-proBNP] (per 1 increase)	1.61	1.38–1.89	<0.001
MELD-XI score (per 1 increase)	1.04	1.01–1.07	0.002
LVEDV (per 10 mL increase)	1.00	0.97–1.02	0.96
LVESV (per 10 mL increase)	1.00	0.97–1.03	0.67
LVEF (per 1% increase)	0.98	0.96–1.00	0.066
Moderate or severe MR	1.26	0.78–1.96	0.32
RVDd (per 1 mm increase)	0.99	0.97–1.02	0.99
RVFAC (per 1% increase)	0.98	0.96–0.99	0.046
Moderate or severe TR	1.74	1.04–2.84	0.032
TRPG (per 1 mmHg increase)	1.02	1.01–1.04	<0.001
Maximal IVC diameter (per 1 mm increase)	1.02	0.98–1.06	0.19

CI, confidence interval. Other abbreviations as in *Table 1*.

Table 3 Multivariate Cox proportional hazards analysis for risk of all-cause mortality

	MELD-XI (per 1 increase)		
Model	Hazard ratio	95% CI	*P*
Model 1	1.04	1.00–1.07	0.014
Model 2	1.04	1.01–1.09	0.005
Model 3	1.04	1.01–1.08	0.020

CI, confidence interval; MELD-XI, Model for End-stage Liver Disease excluding the International normalized ratio.
Model 1 = adjusted for age, sex, and clinically relevant factors (diabetes mellitus, ischaemic cardiomyopathy, atrial fibrillation, QRS duration >150 ms, left ventricular end-systolic volume, and moderate or severe mitral regurgitation). Model 2 = adjusted for VALID–cardiac resynchronization therapy risk score. Model 3 = adjusted for age, sex, and factors related to right heart failure (right ventricular end-diastolic diameter, right ventricular fractional area change, tricuspid regurgitation pressure gradient, moderate or severe tricuspid regurgitation, and maximal inferior vena cava diameter).

Discussion

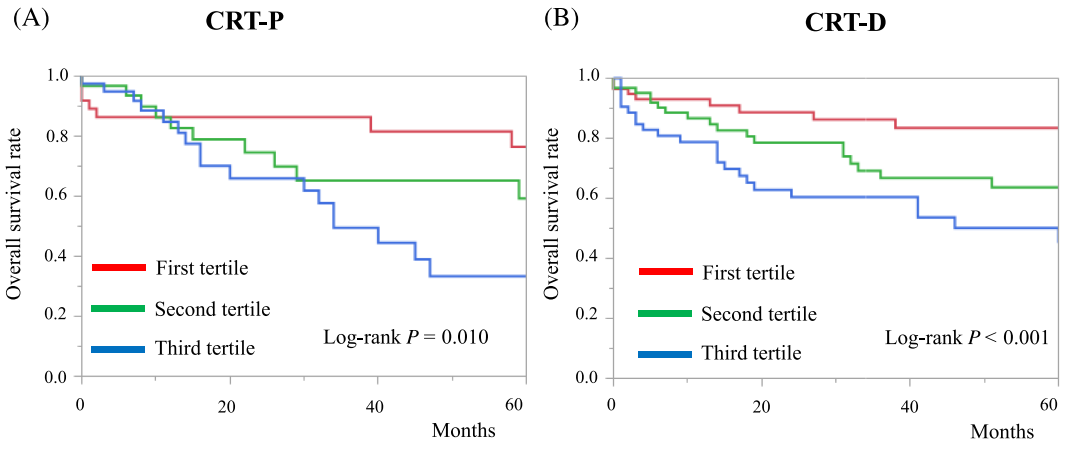
This study was the first to investigate the correlation between hepatorenal dysfunction assessed by the MELD-XI score and survival following CRT implantation. There were three key findings. First, a higher MELD-XI score was associated with older age, a higher prevalence of men, anaemia, renal dysfunction, a higher prevalence of co-morbidities (hypertension and DM), more severe HF, more severe pulmonary hypertension, a higher prevalence of severe TR, and a lower functional CRT response rate. Second, the MELD-XI score was independently associated with all-cause mortality following CRT implantation, even after adjusting for the conventional VALID-CRT risk score. In addition, the use of both the MELD-XI score and the conventional VALID-CRT risk score resulted in an increased prognostic value relative to the

Table 4 Use of the MELD-XI score together with the VALID-CRT risk score improves the prediction of all-cause mortality

Risk score	*C*-statistics (95% CI)	*P*	NRI (95% CI)	*P*	IDI (95% CI)	*P*
VALID-CRT risk score	0.61 (0.54–0.67)	Ref.				
VALID-CRT risk score + MELD-XI score	0.63 (0.57–0.70)	0.16	0.31 (0.08–0.54)	0.007	0.015 (<0.001–0.03)	0.044

CI, confidence interval; IDI, integrated discrimination improvement; MELD-XI, Model for End-stage Liver Disease excluding the International normalized ratio; NRI, net reclassification improvement.

Figure 4 Kaplan–Meier curves of overall survival for patient groups defined according to the first, second, and third tertiles of the MELD-XI score, divided according to cardiac resynchronization therapy device: (A) cardiac resynchronization therapy with a pacemaker (CRT-P) and (B) cardiac resynchronization therapy with implantable cardioverter–defibrillator (CRT-D).



Number at risk				
Months	0	20	40	60
First tertile	37	25	18	16
Second tertile	31	20	15	11
Third tertile	41	17	10	7

Number at risk				
Months	0	20	40	60
First tertile	58	40	31	21
Second tertile	63	38	25	20
Third tertile	53	27	19	10

VALID-CRT risk score alone. Third, the MELD-XI score was significantly associated with all-cause mortality regardless of the type of CRT implant (CRT-P or CRT-D).

Cardiorenal interaction in HF is well known, and pre-implantation renal dysfunction has been reported to be associated with poor outcomes after CRT implantation.[21,22] Recently, cardiohepatic interaction in HF has attracted research interest. Severe HF is often accompanied by liver congestion as a result of elevated central venous pressure. Liver dysfunction caused by liver congestion is known as congestive hepatopathy, and it is associated with a poor prognosis.[23] Furthermore, biliary obstruction caused by elevated hepatic venous pressure leads to increased serum total bilirubin levels,[24] which were reported to correlate with elevated central venous pressure, severity of TR, and pulmonary artery wedge pressure.[25,26] These end-organ dysfunctions often coexist, possibly because their underlying mechanisms have common pathways.[8] Hepatorenal dysfunction is a common co-morbidity and is related to the severity of HF.[8]

The MELD and MELD-XI scores were developed to evaluate liver and kidney function and were originally used as prognostic markers in patients with advanced liver disease.[10,11] Several recent studies demonstrated that the MELD-XI score had prognostic value in HF patients,[8,24] and it was also shown to be a prognostic marker in patients who had undergone LV assist device implantation, transcatheter aortic valve implantation, or cardiac surgery.[12,14,27] However, the relationship between hepatorenal dysfunction assessed by the MELD-XI score and the prognosis of HF patients after CRT implantation has not been fully investigated.

In this study, a higher MELD-XI score was associated with older age, multiple co-morbidities, more severe HF, and a lower functional CRT response rate. Therefore, CRT recipients with high MELD-XI scores may have more severe end-organ impairment due to HF. Univariate Cox regression analysis demonstrated that neither total bilirubin nor creatine was individually associated with mortality in our population, while a higher MELD-XI score was strongly associated with all-cause mortality and cardiac death after CRT implantation. These results suggest that compared with markers of damage to individual organs, the MELD-XI score more sensitively reflects multiple end-organ dysfunction due to severe HF.

Risk stratification of patients using pre-implantation assessments is clinically essential in the field of CRT. While several risk scores have been proposed,[28,29] the VALID-CRT score is the most reliable.[30] Even in an unselected, real-world population, the VALID-CRT score was reported to reliably predict clinical outcome and CRT response after CRT implantation.[30] However, this conventional risk score does not consider the effects of co-morbidities and end-organ dysfunction that accompany HF. Our data demonstrated that the assessment of hepatorenal function using the MELD-XI score identified a high-risk population in patients undergoing CRT. Notably, the MELD-XI score had good prognostic value regardless of whether patients received CRT-P or CRT-D.

In this study, we defined two types of CRT response: functional and echocardiographic. Several recent clinical studies investigated the relationship between renal dysfunction and LV remodelling after CRT. One study reported that CRT resulted in LV reverse remodelling across all stages of chronic kidney disease, but the degree of LVEF improvement was lower in patients with severe renal dysfunction.[31] Another study found that several electrocardiographic and echocardiographic parameters could predict LV reverse remodelling, while blood biomarkers such as creatine had no prognostic value.[32] Our results showed that the MELD-XI score before CRT implantation was not significantly correlated with the rate of LVEF change from before to after CRT implantation, and the echocardiographic CRT response rates did not differ significantly between the three groups. However, the functional CRT response rate was significantly lower in the third tertile MELD-XI score group than in the other two groups. Recent reports revealed that co-morbidities of HF such as frailty or undernutrition were strongly associated with adverse clinical outcomes in CRT recipients.[33,34] Our data suggest that multiple end-organ dysfunction, which is a severe co-morbidity that may occur with HF, is strongly associated with all-cause mortality and cardiac death after CRT, regardless of the degree of echocardiographic LV reverse remodelling.

Calculation of the MELD-XI score is simple, rapid, objective, and repeatable and is based on parameters obtained by standard laboratory examination (total bilirubin and creatine). Furthermore, the speed with which the MELD-XI score can be obtained enables it to be used in time-sensitive emergency situations. Compared with ultrasound examination, this score provides objective information and does not depend on individual experience or skill. In terms of clinical application, the MELD-XI score can be used for risk stratification following CRT implantation. Patients with high MELD-XI scores may be at increased risk of an adverse clinical course and may require more intensive management or more aggressive therapy than those with low MELD-XI scores.

This study has several limitations. First, it was a single-centre, retrospective, observational study with a small sample size. Second, no comprehensive, ultrasonographic assessment of liver dysfunction was performed. Third, we converted BNP to NT-proBNP in 65 patients who underwent CRT implantation before January 2010. Fourth, the MELD-XI score was only determined before implantation; thus, the relationship between score changes and clinical outcomes was unclear. Further large-scale, multicentre, prospective studies are needed to confirm our results.

Conclusion

In HF patients undergoing CRT implantation, a higher MELD-XI score was associated with older age, a higher prevalence of multiple co-morbidities, more severe HF, lower functional CRT response rates, and higher all-cause mortality. These results suggest that the MELD-XI score can provide additional prognostic information and may improve risk stratification in this population.

Conflict of interest

T.N. belongs to a department established by contributions from Abbot Medical, Biotronik Japan, Medtronic Japan, Japan Lifeline, and Boston Scientific. T.N. received lecture fees from Abbott Medical and Medtronic Japan. All other authors have no conflicts of interest to report.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier curves of overall survival for patient groups defined according to the lowest 20%, middle 60% and the highest 20% of the MELD-XI score.
Figure S2. Kaplan–Meier curves of event (cardiac death)–free survival for patient groups defined according to the lowest 20%, middle 60% and the highest 20% of the MELD-XI score.
Table S1. Clinical characteristics of patients stratified into three groups based on the lowest 20%, middle 60% and the highest 20% of the MELD-XI score.

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