Prognostic value of the model for end-stage liver disease excluding INR score (MELD-XI) in patients with adult congenital heart disease

Ryo Konno¹, Shunsuke Tatebe¹, Koichiro Sugimura¹, Kimio Satoh¹, Tatsuo Aoki¹, Masanobu Miura¹, Hideaki Suzuki¹, Saori Yamamoto¹, Haruka Sato¹, Yosuke Terui¹, Satoshi Miyata², Osamu Adachi³, Masato Kimura⁴, Yoshikatsu Saiki³, Hiroaki Shimokawa¹,²*

¹ Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan, 2 Department of Evidence-Based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan, 3 Department of Cardiovascular Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan, 4 Department of Pediatrics, Tohoku University Graduate School of Medicine, Sendai, Japan

* shimo@cardio.med.tohoku.ac.jp

Abstract

Patients with adult congenital heart disease (ACHD) are at increased risk of developing late cardiovascular complication. However, little is known about the predictive factors for long-term outcome. The Model for End-Stage Liver Disease excluding INR (MELD-XI) score was originally developed to assess cirrhotic patients and has the prognostic value for heart failure (HF) patients. In the present study, we examined whether the score also has the prognostic value in this population. We retrospectively examined 637 ACHD patients (mean age 31.0 years) who visited our Tohoku University hospital from 1995 to 2015. MELD-XI score was calculated as follows; 11.76 x ln(serum creatinine) + 5.11 x ln(serum total bilirubin) + 9.44. We compared the long-term outcomes between the high (≥10.4) and the low (<10.4) score groups. The cutoff value of MELD-XI score was determined based on the survival classification and regression tree (CART) analysis. The major adverse cardiac event (MACE) was defined as a composite of cardiac death, HF hospitalization, and lethal ventricular arrhythmias. During a mean follow-up period of 8.6 years (interquartile range 4.4–11.4 years), MACE was noted in 51 patients, including HF hospitalization in 37, cardiac death in 8, and lethal ventricular arrhythmias in 6. In Kaplan-Meier analysis, the high score group had significantly worse MACE-free survival compared with the low score group (log-rank, P<0.001). Multivariable Cox regression analysis showed that the MELD-XI score remained a significant predictor of MACE (hazard ratio 1.36, confidence interval 1.17–1.58, P<0.001) even after adjusting for patient characteristics, such as sex, functional status, estimated glomerular filtration rate, and cardiac function. Furthermore, CART analysis revealed that the MELD-XI score was the most important variable for predicting MACE. These results demonstrate that the MELD-XI score can effectively predict MACE in ACHD patients, indicating that ACHD patients with high MELD-XI score need to be closely followed.
Introduction

Along with the advances in the treatment of congenital heart disease (CHD), more than 90% of CHD patients are expected to reach adulthood [1]. As a result, the number of patients with adult congenital heart disease (ACHD) has been progressively increasing worldwide [2]. Accumulating epidemiological evidence showed that these patients are not cured and at high risk of developing late cardiovascular complications, such as heart failure (HF), lethal arrhythmias, pulmonary hypertension, and even sudden cardiac death [3–6]. We have recently demonstrated that HCV antibody positivity predicts cardiovascular outcomes in selected ACHD patients [7]. However, little evidence is available regarding the risk factors that affect the long-term prognosis in ACHD patients in general.

The Model for End-Stage Liver Disease (MELD) score was originally developed to assess the short-term survival of patients with liver cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures [8]. This score uses 3 objective biochemical values, including serum total bilirubin, creatinine, and international normalized ratio for prothrombin time (INR), and effectively reflects hepatic and renal dysfunction after TIPS procedures [8]. Since congestion due to impaired cardiac function causes multiple end organ dysfunctions including liver and kidneys, the MELD score has been reported to be an excellent predictor for major cardiac adverse events (MACE) in HF patients [9]. Furthermore, the Model for End-Stage Liver Disease eXcluding INR (MELD-XI) score was subsequently developed as an alternative to the original MELD score to assess cirrhotic patients receiving anticoagulation therapy with vitamin K antagonists [10]. The MELD-XI score has also been reported to predict poor outcomes in HF patients [11–13].

In the present study, we thus examined whether the MELD-XI score could also be a useful predictor for long-term outcomes in ACHD patients, by conducting a retrospective cohort study with our ACHD database in the Tohoku University Hospital.

Materials and methods

Study population

A total of 1,031 ACHD patients older than 18 years visited our hospital from 1995 to 2015. Patients with follow-up time of less than one year (n = 317), or limited data unable to calculate the MELD-XI score (n = 76) were excluded. We also excluded a patient with dialysis-dependent renal failure. Finally, 637 ACHD patients (47% male, mean age 31.0±14.5 years) were enrolled in the present study. The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (No. 2016-1-510, UMIN000025734). Informed consent was obtained by the opt-out method.

Data collection

In order to calculate the first MELD-XI score, we collected the baseline data from medical records regarding age, sex, diagnosis of CHD, New York Heart Association (NYHA) functional class, cardiac function, renal function, liver function, anemia, and other clinical characteristics. Anemia was defined as hemoglobin level <13.0 g/dL for men and <12.0 g/dL for women. Liver cirrhosis was defined based on clinical, laboratory, and imaging findings. Estimated glomerular filtration rate (eGFR) was calculated by using Modification of Diet in Renal Disease formula modified for Japanese [14]. MELD-XI score was calculated as previously reported [10]; MELD-XI = 5.11×ln (serum total bilirubin in mg/dL) + 11.76×ln (serum creatinine in mg/dL) + 9.44, where ln means the natural logarithm. Any values less than 1 were given the...
lower limit value of 1 to prevent a negative score. Thus, minimum possible MELD-XI score was 9.44. Systemic ventricular ejection fraction (SVEF) and subpulmonary ventricular (SPV) function were assessed by echocardiography or cardiac magnetic resonance imaging. SPV dysfunction was defined as SPV ejection fraction \( \leq 45\% \) or SPV fractional area change \( \leq 35\% \). Valvular disease was defined as moderate or severe valvular stenosis or regurgitation on echocardiography. Pulmonary hypertension was defined as mean pulmonary artery pressure \( \geq 25\text{mmHg} \) on right heart catheterization or estimated pulmonary artery systolic pressure \( \geq 40\text{mmHg} \) on echocardiography. The complexity of CHD was assigned according to the Bethesda classification [15].

**Definition of the MACE**

The MACE included cardiac death, HF hospitalization, and lethal ventricular arrhythmias. Lethal ventricular arrhythmias were defined as composite arrhythmic events, including ventricular fibrillation and sustained ventricular tachycardia. Hospitalization for HF was defined as an unplanned hospitalization due to worsening HF signs and symptoms of NYHA class III/IV. We retrospectively observed the patients until the occurrence of MACE or the end of August 2018.

**Statistical analysis**

Continuous variables are expressed as the mean ± standard deviation (SD) and were assessed by the Student t-test or Wilcoxon rank-sum test as appropriate. Categorical variables are expressed as proportions and were analyzed by Fisher exact test. Patients were divided into 2 groups according to their MELD-XI score; the low score (MELD-XI < 10.4, \( n = 532 \)) and the high score (MELD-XI \( \geq 10.4, n = 105 \)) groups. The cutoff value of MELD-XI score was determined based on the survival classification and regression tree (CART) analysis [16]. MACE-free survival curves were estimated by the Kaplan-Meier method and compared between the high and the low score groups by using the log-rank test. Univariable and multivariable Cox proportional hazards regression analyses were performed to evaluate the association of baseline variables with the MACE. In the multivariable models, we selected the variables by using a backward stepwise method with variables entered if P-value was less than 0.1 in univariable analysis. Event rate of the MACE and its each component were compared between the high and the low score groups using the Wald method. Survival CART analysis was performed to develop a prediction model for identifying high-risk patients for MACE using variables with P-value less than 0.1 in univariable Cox regression analysis. Survival CART analysis was used not only to determine the risk factors for MACE but to identify the optimal cut-off points and the relative importance of various risk factors. We performed a logistic regression analysis to determine the association of SVEF \(< 50\% \) with renal and hepatic function. Results were considered to be statistically significant at \( P < 0.05 \). All statistical analyses were performed using JMP® Pro 14.1 (SAS Institute Inc., Cary, NC, USA) and R version 3.5.1 (The R Project for Statistical Computing; https://www.r-project.org/).

**Results**

**Baseline characteristics of the study population**

Of the 637 ACHD patients included in the present study, the most common diagnosis of CHD was ventricular septal defect (23%), followed by tetralogy of Fallot (19%), and atrial septal defect (12%) (Table 1). There were 32 (5.0%) patients with Fontan circulation and 20 (3.1%) with Eisenmenger syndrome. Baseline characteristics of the patients are shown in Table 2.
The mean MELD-XI score for all patients was 9.94±1.14 (interquartile range [IQR] 9.44–9.93). The high score group consisted of 105 patients and the low score group 532 patients (Table 2). The prevalence of eGFR <90 ml/min/1.73m² and total bilirubin >1.0 mg/dl in the entire population was 31% and 25%, respectively. Hepatitis virus infection was detected in 71, including positive hepatitis B virus antigen in 6 and positive HCV antibody in 65. The prevalence of hepatitis virus infection was comparable between the 2 groups (Table 2). Moreover, MELD-XI score was comparable between the patients with and those without hepatitis virus infection (10.07±1.13 vs. 9.97±1.23, P = 0.249). Compared with the low score group, the high score group was characterized by a male predominance, increased γ-glutamyl transpeptidase (GGT) and aspartate aminotransferase (AST), a lower platelet count, higher prevalence of great complexity of CHD, NYHA functional class ≥II, Fontan circulation, renal insufficiency (eGFR <60 ml/min/1.73m²), SVEF<50%, and SPV dysfunction (Table 2).

### Incidence rates of MACE

During the mean follow-up period of 8.6±5.3 years (IQR 4.4–11.4 years), MACE was noted in 51 (8.0%) patients, including HF hospitalization in 37, cardiac death in 8, and lethal ventricular arrhythmias in 6. The incidence rate of MACE was 0.93% per person-year in overall patients. The incidence rate of MACE for 3 CHD complexity groups (% per person-year) was 0.5%, 1.1%, and 1.4% for the simple, moderate, and severe groups, respectively (P = 0.037). MACE occurred more frequently in the high score group compared with the low score group (2.6 vs. 0.6% per person-year, P<0.001) (Fig 1). Moreover, the incidence rate of cardiac death and HF hospitalization was significantly higher in the high score group compared with the low score.
Table 2. Baseline characteristics of all patients and by MELD-XI score status.

| Variables                        | All (n = 637) | MELD-XI score | P value |
|----------------------------------|--------------|---------------|---------|
|                                 |              | High (≥10.4)  | Low (<10.4) |
|                                  |              | (n = 105)     | (n = 532)  |
| Age (years), mean               | 31.0 ± 14.5  | 29.1 ± 13.0   | 31.4 ± 14.8 | 0.084 |
| Male sex                         | 298 (47)     | 75 (71)       | 223 (42)   | <0.001 |
| CHD complexity                   |              |               | <0.001   |
| Simple                           | 254 (40)     | 25 (24)       | 229 (43)  |
| Moderate                         | 242 (38)     | 41 (39)       | 201 (38)  |
| Great                            | 141 (22)     | 39 (37)       | 102 (19)  |
| Repaired status                  | 498 (78)     | 88 (84)       | 410 (77)  | 0.155 |
| NYHA functional class ≥II        | 194 (30)     | 51 (49)       | 143 (27)  | <0.001 |
| Systemic right ventricle         | 32 (5.0)     | 6 (5.7)       | 26 (4.9)  | 0.633 |
| Fontan circulation               | 32 (5.0)     | 14 (13)       | 18 (3.4)  | <0.001 |
| Eisenmenger syndrome             | 20 (3.1)     | 4 (3.8)       | 16 (3.0)  | 0.758 |
| Tetralogy of Fallot              | 118 (19)     | 18 (17)       | 100 (19)  | 0.784 |
| PMI in childhood                 | 18 (2.8)     | 1 (1.0)       | 17 (3.2)  | 0.334 |
| Hypertension                     | 39 (6.1)     | 4 (3.8)       | 35 (6.6)  | 0.374 |
| Dyslipidemia                     | 20 (3.1)     | 1 (1.0)       | 5 (3.6)   | 0.225 |
| Diabetes mellitus                | 18 (2.8)     | 3 (2.9)       | 15 (2.8)  | 1.0 |
| Liver cirrhosis                  | 5 (0.8)      | 2 (1.9)       | 3 (0.6)   | 0.192 |
| Hepatitis virus infection        | 71/519 (14)  | 18/93 (19)    | 53/426 (12)| 0.095 |
| HBV antigen positivity           | 6/519 (1.2)  | 1/93 (1.1)    | 5/426 (1.2)|         |
| HCV antibody positivity          | 65/519 (13)  | 17/93 (18)    | 48/426 (11)|         |
| Serum creatinine >1.0 mg/dl      | 9/637 (1.4)  | 8 (7.6)       | 1 (0.2)   | <0.001 |
| eGFR (ml/min/1.73m²)             |              |               | 0.021     |
| ≥90 ml/min/1.73m²                | 439 (69)     | 69 (66)       | 370 (70)  |
| 60 to 89 ml/min/1.73m²           | 175 (27)     | 27 (26)       | 148 (28)  |
| <60 ml/min/1.73m²                | 23 (3.6)     | 9 (8.6)       | 14 (2.6)  |
| mean                            | 105.2 ± 30.6 | 101.6 ± 33.8  | 106.0 ± 29.9 | 0.264 |
| Total bilirubin >1.0 mg/dl       | 161/637 (25) | 98 (93)       | 63 (12)   | <0.001 |
| GGT >50 mg/dl                   | 122/629 (19) | 31/105 (30)   | 91/524 (17)| 0.007 |
| AST >40 IU/dl                   | 38/637 (6.0) | 11/105 (10)   | 27/532 (5.1)| 0.042 |
| ALT >40 IU/dl                   | 60/637 (9.4) | 13/105 (12)   | 47/532 (8.8)| 0.272 |
| Anemia                           | 104/637 (16) | 6/105 (5.7)   | 98/532 (18)| <0.001 |
| Serum albumin <3.5 g/dl         | 29/613 (4.7) | 3/103 (2.9)   | 26/510 (5.1)| 0.451 |
| Platelet count <150,000 /µl     | 98/637 (15)  | 25/105 (24)   | 73/532 (14)| 0.012 |
| MELD-XI score                    | 9.94 ± 1.14  | 12.05 ± 1.49  | 9.53 ± 0.25| <0.001 |
| SVEF (%), mean                   | 66.2 ± 11.7  | 64.9 ± 13.2   | 66.4 ± 11.4| 0.314 |
| <50%                             | 43/602 (7.1) | 13/98 (13)    | 30/504 (6.0)| 0.017 |
| SPV dysfunction                  | 54/542 (10)  | 15/79 (19)    | 39/463 (8.4)| 0.007 |
| Valvular disease                 | 168/597 (28) | 30/96 (31)    | 138/501 (28)| 0.459 |
| Pulmonary hypertension           | 80/595 (13)  | 16/96 (17)    | 64/499 (13)| 0.327 |

Continuous variables and categorical variables are expressed as mean ± SD and number (percentage), respectively. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, congenital heart disease; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD-XI, model for end-stage liver disease excluding international normalized ratio; NYHA, New York Heart Association; PMI, pacemaker implantation; SD, standard deviation; SPV, subpulmonary ventricle; SVEF, systemic ventricular ejection fraction.

https://doi.org/10.1371/journal.pone.0225403.t002
group (0.8 vs. 0.02% per person-year, P < 0.001, 1.8 vs. 0.5% per person-year, P < 0.001, respectively) (Fig 1). In contrast, there was no significant difference in the incidence rate of lethal ventricular arrhythmias was comparable between the two groups. HF, heart failure; MACE, major adverse cardiac events; MELD-XI, model for end-stage liver disease excluding international normalized ratio; p-y, person-year.

Fig 1. Comparison of event rate between the high and the low MELD-XI score groups. During the mean follow-up of 8.6±5.3 years, MACE was noted in 51 patients. The incidence rate of MACE, cardiac death, and HF hospitalization was significantly higher in the high score group compared with the low score group. In contrast, the incidence rate of lethal ventricular arrhythmias was comparable between the two groups. HF, heart failure; MACE, major adverse cardiac events; MELD-XI, model for end-stage liver disease excluding international normalized ratio; p-y, person-year.

Survival analysis
Kaplan-Meier survival analysis for MACE is shown in Figs 2 and 3. The overall estimated 5-years MACE-free survival rate for all ACHD patients was 96% (95% CI: 94–98%). MACE-free survival was significantly lower in the high score group compared with the low score group (log-rank, P < 0.001). The estimated 5 and 10-years MACE-free survival rates were 89% and 78% for the high score group, and 98% and 95% for the low score group, respectively (Fig 2). In patients with Fontan circulation, there was no significant difference in MACE-free survival between the high and the low score groups (log-rank, P = 0.071) (Fig 3).

Univariable Cox proportional hazard analysis showed that 17 risk factors were significantly associated with MACE, including MELD-XI score, age, male sex, great complexity of CHD, NYHA functional class ≥ II, HCV antibody positivity, serum creatinine, eGFR, total bilirubin, GGT, AST, alanine aminotransferase (ALT), platelet count, SVEF < 50%, SPV dysfunction, valvular disease, and pulmonary hypertension (Table 3). Multivariable Cox analysis revealed that
MELD-XI score remained an independent predictor of MACE (HR 1.36, 95% CI: 1.17–1.58, \(P<0.001\)) even after adjustment of sex, NYHA functional class, eGFR, ALT, SVEF \(<50\%\), and the presence of valvular disease and pulmonary hypertension (Table 4). In survival CART analysis, MELD-XI score was identified as a primary discriminator of MACE (\(P<0.001\)), indicating that the score was the most useful variable in the risk prediction model in terms of explanatory power (Fig 4). The subgroup of 11 patients with the highest MACE rate was characterized by 2 criteria; MELD-XI \(\geq 10.4\) and SVEF \(\leq 48\%\) (Fig 4). This group had a 16-fold increased risk of MACE compared with the entire group (15.1 vs. 0.93% per person-year, \(P<0.001\)). In the logistic regression analysis, SVEF \(<50\%\) was associated with total bilirubin \(>1.0\) mg/dl (\(P = 0.010\)) and GGT \(>50\) mg/dl (\(P = 0.004\)) but not with AST \(>40\) IU/l (\(P = 0.376\)), ALT \(>40\) IU/l (\(P = 0.301\)), or eGFR (\(P = 0.408\)).

**Discussion**

In the present study, we demonstrated that ACHD patients at increased risk of MACE were characterized by advanced NYHA functional class, decreased eGFR, increased ALT, elevated...
MELD-XI score, decreased SVEF, and the presence of valvular disease. Importantly, the MELD-XI score was the most useful variable among these risk factors. To the best of our knowledge, this is the first report that identifies the MELD-XI score as a novel predictor of long-term prognosis of ACHD patients.

Liver and renal dysfunctions are common in HF patients and associated with poor prognosis [17]. These interactions are known as cardio-renal and cardio-hepatic syndromes [17]. Both increased serum total bilirubin and decreased eGFR have been reported as risk factors for adverse cardiovascular outcomes not only in HF patients [18, 19] but also in ACHD patients [20, 21]. Consistent with these reports, we noted a high prevalence of increased total bilirubin (25%) and reduced eGFR (31%) in our ACHD patients, both of which were significantly associated with MACE. Although the exact mechanism for this association remains to be elucidated, venous congestion and insufficient organ perfusion are thought to be hemodynamically involved in the development of organ-related co-morbidities in HF patients [17].

The MELD score was initially developed to predict early mortality in patients undergoing TIPS procedures [8]. Since the MELD score is composed of 3 laboratory values reflecting
hepatic and renal dysfunctions, it has emerged as a novel biomarker to assess multi-organ dysfunctions in HF. Increased MELD score has been reported to predict poor cardiovascular outcome in patients with advanced HF referred for ventricular assist device implantation [22], or heart transplantation [23, 24]. However, there could be an overestimation in the risk prediction when MELD score is applied to patients with warfarin therapy. In this situation, INR is artificially elevated by antagonizing vitamin K-dependent pathways, leading to a high MELD score. In fact, anticoagulation with warfarin is commonly used in patients with various cardiovascular conditions, such as HF, atrial fibrillation, venous thromboembolism, mechanical

| Table 3. Univariable Cox regression analysis for prediction of MACE. |
|----------------|------------------|----------------|
| Variables          | HR (95% CI)      | P value |
| Age (years)       | 1.02 (1.00–1.04) | 0.028 |
| Male sex          | 2.64 (1.49–4.90) | <0.001 |
| CHD complexity    |                  |        |
| Simple            | Ref              |        |
| Moderate          | 2.00 (0.98–4.41) | 0.057 |
| Great             | 2.69 (1.25–6.10) | 0.011 |
| Repaired status   | 1.65 (0.76–4.34) | 0.223 |
| NYHA functional class ≥II | 3.31 (1.87–6.10) | <0.001 |
| Systemic right ventricle | 1.01 (0.24–2.76) | 0.986 |
| Fontan circulation | 0.83 (0.13–2.67) | 0.784 |
| Eisenmenger syndrome | 3.02 (0.91–7.48) | 0.068 |
| Tetralogy of Fallot | 1.57 (0.84–2.81) | 0.139 |
| PMI in childhood | 1.14 (0.19–3.70) | 0.856 |
| Hepatitis virus infection | 1.83 (0.93–3.36) | 0.078 |
| HBV antigen positivity | 2.31 (1–6.1)       | 0.215 |
| Hypertension      | 0.85 (0.14–2.74) | 0.811 |
| Dyslipidemia      | 1.20 (0.21–4.22) | 0.726 |
| Diabetes mellitus | 0.70 (0.04–3.19) | 0.706 |
| Liver cirrhosis   | 4.00 (0.65–13.0) | 0.114 |
| Serum creatinine >1.0 mg/dl | 7.13 (1.72–19.7) | 0.011 |
| eGFR (ml/min/1.73m²) | 0.98 (0.97–0.99) | 0.004 |
| Total bilirubin >1.0 mg/dl | 2.90 (1.67–5.05) | <0.001 |
| GGT >50 mg/dl     | 2.76 (1.54–4.81) | <0.001 |
| AST >40 IU/l      | 3.11 (1.51–5.87) | 0.003 |
| ALT >40 IU/l      | 2.35 (1.17–4.36) | 0.018 |
| Anemia            | 1.29 (0.59–2.53) | 0.506 |
| Serum albumin <3.5 g/dl | 1.29 (0.31–3.52) | 0.678 |
| Platelet count <150,000 /µl | 2.75 (1.48–4.89) | 0.002 |
| MELD-XI score     | 1.46 (1.26–1.65) | <0.001 |
| SVEF (%)          | 0.95 (0.93–0.97) | <0.001 |
| SVEF <50%         | 7.83 (3.93–14.7) | <0.001 |
| SPV dysfunction   | 4.92 (2.47–9.26) | <0.001 |
| Valvular disease  | 2.87 (1.63–5.06) | <0.001 |
| Pulmonary hypertension | 2.81 (1.49–5.08) | 0.002 |

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event; Ref, reference. See Table 2 for other abbreviations.

https://doi.org/10.1371/journal.pone.0225403.t003

hepatic and renal dysfunctions, it has emerged as a novel biomarker to assess multi-organ dysfunctions in HF. Increased MELD score has been reported to predict poor cardiovascular outcome in patients with advanced HF referred for ventricular assist device implantation [22], or heart transplantation [23, 24]. However, there could be an overestimation in the risk prediction when MELD score is applied to patients with warfarin therapy. In this situation, INR is artificially elevated by antagonizing vitamin K-dependent pathways, leading to a high MELD score. In fact, anticoagulation with warfarin is commonly used in patients with various cardiovascular conditions, such as HF, atrial fibrillation, venous thromboembolism, mechanical
heart valve, and ACHD including Fontan circulation [25, 26]. Thus, the MELD-XI score, a modification of the MELD score, was subsequently developed for better risk prediction in cirrhotic patients with warfarin therapy [10]. The MELD-XI score omits INR from the equation and has been validated to predict the prognosis in HF patients effectively [11–13]. Three groups have previously reported the usefulness of the MELD-XI score in the field of ACHD. Assenza et al. reported that a higher MELD-XI score was associated with worse survival for the composite endpoint of death or cardiac transplantation in Fontan patients [27]. Lewis et al. and Adams et al. independently reported that the MELD-XI score predicted mortality and morbidity in ACHD patients undergoing heart transplantation [28, 29]. In the present study, we were able to demonstrate that high MELD score has an important prognostic value for MACE in the entire ACHD patients. Thus, the MELD-XI score could be useful as a novel and useful predictor of future cardiovascular events in patients with a wide spectrum of both acquired and congenital heart disease, regardless of warfarin use.

In the present study, contrary to the previous report [27], MACE-free survival was comparable between the high and low MELD-XI score groups in Fontan patients. This discordance may be attributable to the smaller number of Fontan patients and the lower incidence of MACE event in our study compared with the previous report (32 vs. 96 patients, 0.76 vs. 3.0% per person-year, respectively) [27]. However, the MACE rate in the present study was comparable with other reports [30, 31].

Survival CART analysis revealed that the MELD-XI score was the primary discriminator of MACE. Assenza et al. reported that MELD-XI score was a better predictor of adverse events than serum creatinine in patients with Fontan circulation [27]. We consider that high MELD-XI score comprehensively represents the severity of multi-organ dysfunctions in HF associated with ACHD, as the elevation results from hemodynamic effects of venous congestion and low cardiac output, thus predicting future cardiovascular events better than a single measurement of total bilirubin or creatinine. Indeed, in the present study, SVEF was also associated with MACE and was identified as a primary discriminator in the subgroup of high MELD-XI group. In the logistic regression analysis, SVEF <50% was associated with increased total bilirubin and GGT but not with eGFR. Contrary to our study, it was previously reported that renal dysfunction was associated with systemic ventricular dysfunction [21]. This discordance may be attributable to younger age and relatively lower prevalence of reduced eGFR in our study compared with the previous report (31.0 ± 14.5 vs. 36.0 ± 14.2 years, 31% vs. 50%, respectively) [21].

Table 4. Multivariable Cox regression analysis for prediction of MACE.

| Variables               | HR (95% CI)   | P value |
|-------------------------|---------------|---------|
| Male sex                | 1.66 (0.85–3.26) | 0.140   |
| NYHA functional class ≥II | 2.05 (1.07–3.92) | 0.030   |
| eGFR (ml/min/1.73m²)    | 0.99 (0.98–1.00) | 0.007   |
| ALT >40 IU/l            | 2.31 (1.14–4.67) | 0.020   |
| MELD-XI score           | 1.36 (1.17–1.58) | <0.001  |
| SVEF <50%               | 3.78 (1.84–7.79) | <0.001  |
| Valvular disease        | 1.91 (1.03–3.56) | 0.042   |
| Pulmonary hypertension  | 1.84 (0.90–3.76) | 0.095   |

Association of MELD-XI score with the composite endpoint, adjusted for sex, CHD severity, New York Heart Association functional class, increased AST, reduced SVEF, valvular disease, and pulmonary hypertension (model P<0.001). CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event; Ref, reference. See Tables 2 and 3 for other abbreviations.

https://doi.org/10.1371/journal.pone.0225403.t004
Limitations

Several limitations should be mentioned for the present study. First, the present study was a single-center retrospective study and included selected ACHD patients who visited our institute from 1995 to 2015. In addition, the cohort consisted of patients with a wide variety of CHD, including Fontan circulation, systemic right ventricle, and Eisenmenger syndrome. Thus, the present results remain to be confirmed in future multi-center studies. Second, there were missing data due to the retrospective nature of the present study. The variable with the highest percentage of missing data was HCV antibody status (19%), followed by SPV dysfunction (15%). These two variables were excluded from the multivariable analysis. Third, we could not obtain either detailed patient history, such as previous hospital admission, or pathophysiology, such as extracardiac shunt and hemodynamic data from cardiac catheterization. Further studies are needed to clarify whether these factors could be independent predictors of MACE in ACHD patients. Forth, the two MELD-XI groups had different characteristics, in terms of CHD complexity and the prevalence of SPV dysfunction, SVEF <50%, and Fontan circulation. This may affect the outcome of the present study. Finally, we were unable to assess the association between the MELD-XI score and central venous pressure or cardiac output.
because of the lack of hemodynamic data. Further studies are needed to evaluate whether early intervention for decreasing the MELD-XI score could improve the clinical outcome of ACHD patients.

Conclusions
In the present study, we were able to demonstrate that a higher MEDL-XI score was significantly associated with MACE in ACHD patients. Thus, the MELD-XI score is useful in identifying ACHD patients at high risk for developing late cardiovascular events. ACHD patients with high MELD-XI score need to be closely followed.

Supporting information
S1 Dataset. The data collected from medical records.
(XLSX)

Acknowledgments
The authors would like to thank the staff of the Departments of Cardiovascular Medicine, Cardiovascular Surgery, and Pediatrics at the Tohoku University Hospital for their valuable contributions.

Author Contributions
Conceptualization: Ryo Konno, Shunsuke Tatebe, Koichiro Sugimura, Haruka Sato.
Formal analysis: Ryo Konno, Satoshi Miyata.
Funding acquisition: Shunsuke Tatebe.
Investigation: Ryo Konno.
Methodology: Ryo Konno, Koichiro Sugimura, Masanobu Miura, Saori Yamamoto.
Resources: Yosuke Terui.
Supervision: Shunsuke Tatebe, Hideaki Suzuki, Haruka Sato, Osamu Adachi, Masato Kimura, Yoshikatsu Saiki, Hiroaki Shimokawa.
Writing – original draft: Ryo Konno.
Writing – review & editing: Shunsuke Tatebe, Koichiro Sugimura, Kimio Satoh, Tatsuo Aoki, Masanobu Miura, Hiroaki Shimokawa.

References
1. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. Circulation. 2010; 122 (22):2264–2272. https://doi.org/10.1161/CIRCULATIONAHA.110.946343 PMID: 21096444
2. Mulder BJM. Epidemiology of adult congenital heart disease: demographic variations worldwide. Neth Heart J. 2012; 20(12):505–508. https://doi.org/10.1007/s12471-012-0335-1 PMID: 23225563
3. Verheugt CL, Uiterwaal CS, van der Velden ET, Meijboom FJ, Pieper PG, van Dijk AP, et al. Mortality in adult congenital heart disease. Eur Heart J. 2010; 31(10):1220–1229. https://doi.org/10.1093/eurheartj/ehq032 PMID: 20207625
4. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebling A, Li W, et al. Survival Prospects and Circumstances of Death in Contemporary Adult Congenital Heart Disease Patients Under Follow-Up at a Large Tertiary Centre. Circulation. 2015; 132(22):2118–2125. https://doi.org/10.1161/CIRCULATIONAHA.115.017202 PMID: 26369353
5. Engelings CC, Helm PC, Abdul-Khalig H, Asfour B, Bauer UM, Baumgartner H, et al. Cause of death in adults with congenital heart disease—An analysis of the German National Register for Congenital Heart Defects. Int J Cardiol. 2016; 211:31–36. https://doi.org/10.1016/j.ijcard.2016.02.133 PMID: 26970963

6. Naidu P, Grigg L, Zentner D. Mortality in adults with congenital heart disease. Int J Cardiol. 2017; 245:125–130. https://doi.org/10.1016/j.ijcard.2017.05.132 PMID: 28874283

7. Konno R, Tatebe S, Sugimura K, Satoh K, Aoki T, Miura M, et al. Effects of Hepatitis C Virus Antibody-Positivity on Cardiac Function and Long-Term Prognosis in Patients With Adult Congenital Heart Disease. Am J Cardiol. 2018; 122(11):1965–1971. https://doi.org/10.1016/j.amjcard.2018.08.045 PMID: 30442226

8. 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(4):864–871. https://doi.org/10.1001/he.2000.5852 PMID: 10733541

9. Szygula-Jurkiewicz B, Zakliczynski M, Andrzejczuk M, Moscinski M, Zembala M. The Model for End-Stage Liver Disease (MELD) can predict outcomes in ambulatory patients with advanced heart failure who have been referred for cardiac transplantation evaluation. Kardiochirurgia i torakochirurgia polska = Polish journal of cardio-thoracic surgery. 2014; 11(2):178–181. https://doi.org/10.5114/ktp.2014.43847 PMID: 25336418

10. Heuman DM, Mihas AA, Habib A, Gilles HS, Stravitz RT, Sanyal AJ, et al. MELD-XI: a rational approach to “sickest first” liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl. 2007; 13(1):30–37. https://doi.org/10.1002/lt.20906 PMID: 17154000

11. Abe S, Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, et al. Liver dysfunction assessed by model for end-stage liver disease excluding INR (MELD-XI) scoring system predicts adverse prognosis in heart failure. PLoS One. 2014; 9(6):e100618. https://doi.org/10.1371/journal.pone.0100618 PMID: 24955578

12. Inohara T, Kohsaka S, Shiraishi Y, Goda A, Sawano M, Yagawa M, et al. Prognostic impact of renal and hepatic dysfunction based on the MELD-XI score in patients with acute heart failure. Int J Cardiol. 2014; 176(3):571–573. https://doi.org/10.1016/j.ijcard.2014.08.052 PMID: 25305701

13. Biegus J, Zymlinski R, Sokolski M, Siwolowski P, Gajewska P, Nawrocka-Millward S, et al. Impaired hepato-renal function defined by the MELD XI score as prognosticator in acute heart failure. Eur J Heart Fail. 2016; 18(12):1518–1521. https://doi.org/10.1002/ejhf.332 PMID: 27709804

14. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009; 53(6):982–992. https://doi.org/10.1016/j.ajkd.2009.08.034 PMID: 19390088

15. Warnes CA, Libethen R, Danielson GK, Dore A, Harris L, Hoffman JL, et al. Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol. 2001; 37(S):1170–1175. https://doi.org/10.1016/s0735-1097(01)01272-4 PMID: 11300418

16. Lemon SC, Roy J, Clark MA, Friedmann PD, Rakowski W. Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. Ann Behav Med. 2003; 26(3):172–181. https://doi.org/10.1207/S15324796ABM2603_02 PMID: 14644693

17. van Deursen VM, Daamman K, van der Meer P, Wijkstra PJ, Lulijcoek GJ, van Beek A, et al. Co-morbidities in heart failure. Heart Fail Rev. 2014; 19(2):163–172. https://doi.org/10.1007/s10741-012-9370-7 PMID: 23266884

18. Allen LA, Felker GM, Pecock S, McMurray JJ, Pfeffer MA, Swedberg K, et al. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Eur J Heart Fail. 2009; 11 (2):170–177. https://doi.org/10.1038/ejhf301 PMID: 19168515

19. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000; 102 (2):203–210. https://doi.org/10.1161/01.cir.102.2.203 PMID: 10889132

20. Price S, Jaggar SL, Jordan S, Trenfield S, Khan M, Sethia B, et al. Adult congenital heart disease: intensive care management and outcome prediction. Intensive Care Med. 2007; 33(4):652–659. https://doi.org/10.1007/s00134-007-0544-z PMID: 17333117

21. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, et al. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation. 2008; 117(18):2320–2328. https://doi.org/10.1161/CIRCULATIONAHA.107.734921 PMID: 18443238

22. Matthews JC, Pagani FD, Haft JW, Koelling TM, Nafte1 DC, Aaronson KD. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. Circulation. 2010; 121(2):214–220. https://doi.org/10.1161/CIRCULATIONAHA.108.838656 PMID: 20048215
23. Chokshi A, Cheema FH, Schaefle KJ, Jiang J, Collado E, Shahzad K, et al. Hepatic dysfunction and survival after orthotopic heart transplantation: application of the MELD scoring system for outcome prediction. J Heart Lung Transplant. 2012; 31(6):591–600. https://doi.org/10.1016/j.healun.2012.02.008 PMID: 22458996

24. Kim MS, Kato TS, Farr M, Wu C, Givens RC, Collado E, et al. Hepatic dysfunction in ambulatory patients with heart failure: application of the MELD scoring system for outcome prediction. J Am Coll Cardiol. 2013; 61(22):2253–2261. https://doi.org/10.1016/j.jacc.2012.12.056 PMID: 23563127

25. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013; 110(6):1087–1107. https://doi.org/10.1160/TH13-06-0443 PMID: 24226379

26. Wan D, Tsui C, Kiess M, Grewal J, Krahn AD, Chakrabarti S. Anticoagulation for Thromboembolic Risk Reduction in Adults With Congenital Heart Disease. Can J Cardiol. 2017; 33(12):1597–1603. https://doi.org/10.1016/j.cjca.2017.08.009 PMID: 29066332

27. Assenza GE, Graham DA, Landzberg MJ, Valente AM, Singh MN, Bashir A, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. Heart. 2013; 99(7):491–496. https://doi.org/10.1136/heartjnl-2012-303347 PMID: 23406689

28. Lewis M, Ginns J, Schulze C, Lippel M, Chai P, Bacha E, et al. Outcomes of Adult Patients With Congenital Heart Disease After Heart Transplantation: Impact of Disease Type, Previous Thoracic Surgeries, and Bystander Organ Dysfunction. J Card Fail. 2016; 22(7):578–582. https://doi.org/10.1016/j.cardfail.2015.09.002 PMID: 26432646

29. Adams ED, Jackson NJ, Young T, DePasquale EC, Reardon LC. Prognostic utility of MELD-XI in adult congenital heart disease patients undergoing cardiac transplantation. Clin Transplant. 2018; 32(6): e13257. https://doi.org/10.1111/ctr.13257 PMID: 29966074

30. Giannico S, Hammad F, Amodeo A, Michielon G, Drago F, Turchetta A, et al. Clinical outcome of 193 extracardiac Fontan patients: the first 15 years. J Am Coll Cardiol. 2006; 47(10):2065–2073. https://doi.org/10.1016/j.jacc.2005.12.065 PMID: 16697327

31. Khairy P, Fernandes SM, Mayer JE Jr., Triedman JK, Walsh EP, Lock JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008; 117(1):85–92. https://doi.org/10.1161/CIRCULATIONAHA.107.738559 PMID: 18071068