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ORIGINAL ARTICLE

MELD3.0 is superior to MELDNa and MELD for prediction of mortality in patients with cirrhosis: An external validation in a multi-ethnic population

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liver cirrhosis, liver failure, liver transplantation, model for end-stage liver disease.

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Abstract

Background and Aim: The model for end-stage liver disease (MELD) was updated to MELDNa and recently to MELD3.0 to predict survival of cirrhotic patients. We validated the prognostic performance of MELD3.0 and compared with MELDNa and MELD amongst cirrhotic inpatients.
Methods: Demographical, clinical, biochemical, and survival data of cirrhotic inpatients in Singapore General Hospital (SGH) from 01 January 2018 to 31 December 2018, were studied retrospectively. Patients were followed up from first admission in 2018 until death or until 01 April 2023. Area under the receiver operating characteristic curves (AUROC) were computed for the discriminative effects of MELD3.0, MELDNa, and MELD to predict 30-, 90-, and 365-day mortalities. AUROC was compared with DeLong's test. The cutoff MELD3.0 score for patients at high risk of 30-day mortality was determined using Youden's Index. Survival curves of patients with MELD3.0 score above and below the cutoff were estimated with Kaplan–Meier method and compared with log-rank analysis.
Results: Totally 862 patients were included (median age 71.0 years [interquartile range, IQR: 64.0–79.0], 65.4% males, 75.8% Chinese). Proportion of patients with Child-Turcotte-Pugh classes A/B/C were 55.5%/35.5%/9.0%. Median MELD3.0/MELDNa/MELD scores were 12.2 (IQR: 8.7–18.3)/11.0 (IQR: 8.0–17.5)/10.3 (IQR: 7.8–15.0). Median time of follow-up was 51.9 months (IQR: 8.5–59.6). The proportion of 30-/90-/365-day mortalities was 5.7%/13.2%/26.9%. AUROC of MELD3.0/MELDNa/MELD in predicting 30-, 90-, and 365-day mortalities, respectively, were 0.823/0.793/0.783, 0.754/0.724/0.707, 0.682/0.654/0.644 ($P < 0.05$). Optimal cutoff to predict 30-day mortality was MELD3.0 > 19 (sensitivity = 67.4%, specificity = 82.4%). Patients with MELD3.0 > 19, compared with patients with MELD3.0 ≤ 19, had shorter median time to death (98.0 days [IQR: 28.8–398.0] *vs* 390.0 days [IQR: 134.3–927.5]), and higher proportion of 30-day mortality (68.8% *vs* 43.0%) ($P < 0.001$).
Conclusion: MELD3.0 performs better than MELDNa and MELD in predicting mortality in cirrhotic inpatients. MELD3.0 > 19 predicts higher 30-day mortality.

Introduction

The original model for end-stage liver disease (MELD)[1] was introduced more than 20 years ago to predict the 3-month mortality rate in patients with cirrhosis treated with transjugular intrahepatic portosystemic shunt (TIPS). It was later widely used worldwide to prioritize liver transplantation in patients with advanced cirrhosis.[2,3] In recent years, limitations[4–7] of the original MELD were recognized. One important concern was that hyponatremia, a common comorbidity in patients with cirrhosis, was identified to be a significant determinant of mortality in patients with cirrhosis.[8,9] Serum sodium as a variable was later incorporated into the MELD (MELDNa) in 2016 by the Organ Procurement and Transplantation Network for the allocation of organ for liver transplantation in the United States.[10] However, MELDNa too had its limitations as it overestimates the renal function of female patients when using serum creatinine as a surrogate marker since women generally have smaller body mass and hence lower baseline serum creatinine levels than men.[11] As

a result, MELDNa was criticized for disadvantaging women, as they were less likely to receive a deceased donor liver transplant compared with men.

The latest update of the MELD performed by Kim *et al*., MELD3.0,[12] addressed the sex disparity by including the patient's sex into the model. Serum albumin, which is associated with the synthetic function of the liver, was also added into the model. Other new features in MELD3.0 included a lowered ceiling for serum creatinine from 4.0 to 3.0 mg/dL, as well as adding interaction terms between creatinine and albumin, and between sodium and bilirubin. The MELD3.0 had improved performance for predicting mortality when compared with the original MELD.

External validation studies were performed on the MELD3.0 in South Korea in patients with cirrhosis awaiting liver transplantation[13] and in China amongst patients with cirrhosis following TIPS.[14] These studies concur with the original study by Kim *et al*. that MELD3.0 performed better than the previous versions in predicting the mortality of patients with cirrhosis. However, there are no studies to date that validate the MELD3.0 in a diverse multi-ethnic population such as in Singapore. There is an important need to do so given the pressing scarcity of organs available and the increasing need for an efficient liver transplantation allocation protocol. The aims of this study were to externally validate the MELD3.0 in predicting mortality amongst admitted patients with cirrhosis in a multi-ethnic population, and to compare its performance with MELDNa and MELD.

Patients and methods

Study design and patients. A retrospective observational cohort study was performed, which included patients who were admitted to Singapore General Hospital's (SGH) Department of Gastroenterology and Hepatology between 01 January 2018 and 31 December 2018, with a diagnosis of liver cirrhosis based on International Classification of Diseases, Tenth Revision (ICD-10) classification. The exclusion criteria were patients under the age of 18; patients who were not admitted in the year 2018; and patients who did not have an ICD-10 classification of cirrhosis.

Patients with cirrhosis were identified using an ICD-10 codes specific for cirrhosis from the hospital's electronic health records. Cirrhosis was diagnosed by one or a combination of the following modalities: (i) radiological imaging using transabdominal ultrasound, computed tomography, or magnetic resonance imaging to detect the presence of coarse and nodular outlines; (ii) liver stiffness measurement >13 kPa using transient elastography; (iii) liver biopsy showing a histological diagnosis of cirrhosis.

Etiologies of cirrhosis were determined based on clinical assessment using one or a combination of the following: clinical history, laboratory results, and histology. Chronic hepatitis C and hepatitis B infections were determined based on the presence of anti-hepatitis C IgG and hepatitis B surface antigen for ≥6 months, respectively. Alcoholic liver disease was diagnosed if the patient had alcohol use disorder (consumption of >21 units of alcohol per week if male; >14 units per week if female). Nonalcoholic fatty liver disease (NAFLD) was diagnosed based on radiological or histological evidence of hepatic steatosis without significant alcohol use. Primary biliary cirrhosis was diagnosed based on detection of anti-mitochondrial antibodies or histology. Primary sclerosing cholangitis was diagnosed if there was a cholestatic pattern of liver function test, along with classic findings on cholangiography and liver histology. Autoimmune hepatitis was diagnosed based on the detection of auto-antibodies (anti-nuclear, anti-smooth muscle, and/or anti-liver-kidney-microsomal 1 antibodies) with supporting histological features. Patients were assigned the etiology of cryptogenic liver cirrhosis if no identifiable causes could be determined from the clinical, laboratory, radiological, and histological investigations. In patients with multiple etiologies of liver cirrhosis, the predominant etiology was determined by the discretion of the treating physician. Severity of ascites was determined from clinical and radiological findings. Severity of encephalopathy was assessed based on clinical records and graded according to the West Haven Criteria.

All patients were followed up from the first admission in year 2018 to the date of death or to 01 April 2023, if they were still alive. The necessary demographical, clinical, biochemical data of the patients at their first admission in 2018 were collected between 01 October 2022 and 01 April 2023, from the SGH's electronic medical records in a secure electronic form. Further details of the data collected from the electronic medical records can be found in Table S1, Supporting information.

Calculation of prognostic models. The following scores were computed according to the formula from the original authors:

$\text{MELD}^{1} = 9.57 \times \log_e(\text{creatinine}) + 3.78 \times \log_e(\text{bilirubin}) + 11.20 \times \log_e(\text{INR}) + 6.43$. The values of serum creatinine (mg/dL), bilirubin (mg/dL), or INR which were <1, were set to 1.

$\text{MELDNa}^{15} = \text{MELD} + [1.32 \times (137 - \text{Na})] - [0.033 \times \text{MELD} \times (137 - \text{Na})]$. The lower and upper limits of serum sodium (Na) are 125 and 137 mEq/L, respectively.

$\text{MELD3.0}^{12} = 1.33\ (\text{if female}) + [4.56 \times \log_e(\text{bilirubin})] + [0.82 \times (137 - \text{Na})] - [0.24 \times (137 - \text{Na}) \times \log_e(\text{bilirubin})] + [9.09 \times \log_e(\text{INR})] + [11.14 \times \log_e(\text{creatinine})] + [1.85 \times (3.5 - \text{albumin})] - [1.83 \times (3.5 - \text{albumin}) \times \log_e(\text{creatinine})] + 6$. The values of serum creatinine, bilirubin, or INR which were <1, were set to 1. The lower and upper limits of serum Na are 125 and 137 mEq/L, respectively. The lower and upper limits of serum albumin are 1.5 and 3.5 g/dL, respectively. The upper limit of serum creatinine was set to 3.0 mg/dL.

Outcomes. The primary outcome was to compare the ability of MELD3.0, MELDNa, and MELD to predict 30-, 90-, and 365-day mortalities. The secondary outcomes were to determine the optimal cutoff for MELD3.0 in predicting 30-day mortality and to compare the survival of the patients above the cutoff and those who fall at or below the cutoff.

Data analysis. The receiver operating characteristic (ROC) curves were plotted and the area under the ROC curves (AUROC) were computed to study the discriminative ability of MELD3.0, MELDNa, and MELD to predict 30-, 90-, and 365-day mortalities. DeLong's test[16] was performed for pairwise comparison of the AUROC of the respective prognostic models against MELD3.0. The optimal cutoff for high-risk patients in

predicting 30-day mortality was determined using Youden's index, and the sensitivity and specificity for each cutoff were calculated.

Overall survival was defined to be the time interval between the first date of admission in the year 2018 and death from any cause. Survival curves were estimated using the Kaplan–Meier method for two groups of patients: (i) above the optimal cutoff, (ii) below or at the optimal cutoff. Time was censored for surviving patients and patients who did not complete the follow-up to 01 April 2023. Log-rank test was performed to compare the survival analysis of these two groups of patients.

The statistical analyses were performed with SPSS (version 26.0; IBM, New York, NY) and the MedCalc Statistical Software (version 20.0.3; MedCalc Software Ltd., Ostend, Belgium). $P < 0.05$ was considered to be statistically significant in all calculations.

Ethics. Approval was obtained from the hospital's centralized institutional review board (IRB number: 2022/2239).

Results

Baseline characteristics. Our study included 862 subjects who fulfilled the inclusion criteria. The baseline characteristics of the study cohort are described in Table 1. The median age at admission was 71.0 years (interquartile range [IQR]: 64.0–79.0), and 65.4% were men. There are 75.8% Chinese, 8.9% Malays, 8.7% Indians, and 6.6% of patients from other ethnicities. The ethnic distribution of our study population is reflective of the national ethnic distribution of Singapore (74.3% Chinese, 13.4% Malays, 9.0% Indians, and 3.2% others),[17] except for a slightly lower proportion of Malays and a greater proportion of patients from other ethnicities in our study cohort. The main etiologies for cirrhosis were chronic hepatitis B (29.0%), NAFLD (25.3%), and alcoholic liver disease (11.7%). There were 24.8% and 3.1% of patients with ascites and encephalopathy, respectively. Notably, 24.9% of the patients had HCC. The proportion of patients with Child-Turcotte-Pugh (CTP) classes A/B/C were 55.5%, 35.5%, and 9.0%, respectively. The median CTP score was 6 (IQR: 5–8). The median MELD3.0, MELDNa, and MELD scores were 12.2 (IQR: 8.7–18.3), 11.0 (IQR: 8.0–17.5), and 10.3 (IQR: 7.8–15.0) respectively.

Table 1 Baseline characteristics of study cohort ($n = 862$)

Median age, years (IQR)	71.0 (64.0–79.0)
Men, *n* (%)	564 (65.4)
Ethnicity, *n* (%)	
Chinese	653 (75.8)
Malay	77 (8.9)
Indian	75 (8.7)
Others	57 (6.6)
Etiologies of cirrhosis, *n* (%)	
Nonalcoholic fatty liver disease	218 (25.3)
Hepatitis B	250 (29.0)
Hepatitis C	61 (7.1)
Alcohol	101 (11.7)
Autoimmune hepatitis	15 (1.7)
Primary biliary cirrhosis	26 (3.0)
Primary sclerosing cholangitis	2 (0.2)
Cryptogenic	152 (17.6)
Others	36 (4.2)
Median time from cirrhosis diagnosis to first admission in 2018, months (IQR)	10.5 (0–59.3)
Modalities to diagnose cirrhosis, *n* (%)	
Ultrasound	504 (58.5)
Computed tomography	420 (48.7)
Magnetic resonance imaging	104 (12.1)
Transient elastography	47 (5.5)
Liver biopsy	129 (15.0)
Ascites, *n* (%)	
Absent	648 (75.2)
Slight	121 (14.0)
Moderate	93 (10.8)
Encephalopathy, *n* (%)	
Absent	835 (96.9)
Grades 1–2	15 (1.7)
Grades 3–4	12 (1.4)
Hepatocellular carcinoma, *n* (%)	215 (24.9)
Median laboratory results	
Serum Na, mmol/L (IQR)	137.0 (134.0–140.0)
Serum creatinine, μmol/L (IQR)	80.0 (62.0–109.0)
Serum albumin, g/L (IQR)	34.0 (29.0–39.0)
Serum total bilirubin, μmol/L (IQR)	20.0 (12.0–38.0)
International normalized ratio, INR (IQR)	1.12 (1.05–1.24)
Patients requiring dialysis at least twice in the past week from first admission in 2018, *n* (%)	39 (4.5)
Model for end-stage liver disease scores	
MELD 3.0 (IQR)	12.2 (8.7–18.3)
MELDNa (IQR)	11.0 (8.0–17.5)
MELD-original (IQR)	10.3 (7.8–15.0)
Median Child-Turcotte-Pugh (CTP) score (IQR)	6 (5–8)
CTP class A, *n* (%)	478 (55.5)
CTP class B, *n* (%)	306 (35.5)
CTP class C, *n* (%)	78 (9.0)

IQR, interquartile range; MELD, model for end-stage liver disease.

Survival status. Median time of follow-up was 51.9 months (IQR: 8.5–59.6). A total of 416 (48.3%) subjects died by the census point of the study in 2023. Median time to death was 270.5 days (IQR: 74.5–757.5). The 30-, 90-, and 365-day mortalities were 5.7%, 13.2%, and 26.9%, respectively (Table 2).

ROC analyses comparing the prognostic models in predicting mortality. The performance of the prognostic models of MELD3.0, MELDNa, and MELD was compared using the ROC analyses (Table 3 and Figs. 1–3). For predicting 30-day mortality, the AUROC of MELD3.0, MELDNa, and MELD, respectively, were 0.823 (95% CI: 0.761–0.886), 0.793 (95% CI: 0.725–0.860), and 0.783 (95% CI: 0.717–0.849) ($P = 0.018$ and $P = 0.029$ when comparing AUROC of MELD3.0 with MELDNa and MELD, respectively). For predicting 90-day mortality, the AUROC of MELD3.0, MELDNa and MELD, respectively, were 0.754 (95% CI: 0.705–0.803), 0.724 (95% CI: 0.673–0.776), and 0.707 (95% CI: 0.655–0.759) ($P = 0.0061$ and $P = 0.0001$ when comparing AUROC of MELD3.0 with MELDNa and MELD, respectively). For predicting 365-day

mortality, the AUROC of MELD3.0, MELDNa and MELD, respectively, were 0.682 (95% CI: 0.642–0.723), 0.654 (95% CI: 0.611–0.696), and 0.644 (95% CI: 0.602–0.686) ($P = 0.0023$ and $P = 0.00002$ when comparing AUROC of MELD3.0 with MELDNa and MELD, respectively).

Optimal MELD3.0 score cutoff for risk stratification of 30-day mortality and survival analysis. Given that the MELD3.0 performed the best with the highest AUROC in predicting 30-day mortality compared with predicting 90- and 365-day mortalities, we aimed to determine the optimal MELD3.0 cutoff score in predicting 30-day mortality. Using Youden's index, the optimal cutoff value for using MELD3.0 score to predict 30-day mortality was 19 (Table S2). The baseline and the survival characteristics of the patients with a MELD3.0 > 19 compared with MELD3.0 ≤ 19 were summarized in Tables S3, 4 and Figure 4. At MELD3.0 score >19, the sensitivity was 67.4% and the specificity was 82.4% in predicting 30-day mortality. Therefore, we determined that patients with MELD3.0 score of 20 and above to be at high risk of 30-day mortality. From the survival analysis (Fig. 4), high-risk patients (MELD3.0 score >19) have significantly poorer survival compared with patients with MELD3.0 score ≤19 ($P < 0.001$ using log-rank test). The median time to death for patients with high risk of 30-day mortality (MELD3.0 > 19) compared with patients with MELD3.0 score ≤19 were 98.0 days (IQR: 28.8–398.0) and 390.0 days (IQR: 134.3–927.5) respectively. High-risk patients (MELD3.0 > 19) also had higher proportion of 30-day mortality (68.8%) compared with patients with MELD3.0 score ≤19 (43.0%). Additionally, the optimal cutoff values for MELD3.0 score to predict 90- and 365-day mortalities are 17 and

Table 2 Survival characteristics of study cohort ($n = 862$)

Median time of follow-up, months (IQR)	51.9 (8.5–59.6)
Number of deaths, *n* (%)	416 (48.3)
Median time to death, days (IQR)	270.5 (74.5–757.5)
30-day mortality, *n* (%)	49 (5.7)
90-day mortality, *n* (%)	114 (13.2)
365-day mortality, *n* (%)	232 (26.9)

IQR, interquartile range.

Table 3 AUROC of each prognostic model at various survival timepoints.

	30-day mortality (95% CI)	*P*-value	90-day mortality (95% CI)	*P*-value	365-day mortality (95% CI)	*P*-value
MELD3.0	0.823 (0.761–0.886)	NA	0.754 (0.705–0.803)	NA	0.682 (0.642–0.723)	NA
MELDNa	0.793 (0.725–0.860)	0.018*	0.724 (0.673–0.776)	0.0061*	0.654 (0.611–0.696)	0.0023*
MELD	0.783 (0.717–0.849)	0.0029*	0.707 (0.655–0.759)	0.0001*	0.644 (0.602–0.686)	0.00002*

*Statistical significance at $P < 0.05$.

Comparison of the AUROC of the prognostic model against MELD3.0 was performed using DeLong's test.

AUROC, area under the receiver operating characteristic curves; CI, confidence interval; MELD, model for end-stage liver disease; NA, not applicable; *P*-value, *P*-value against MELD3.0 score.

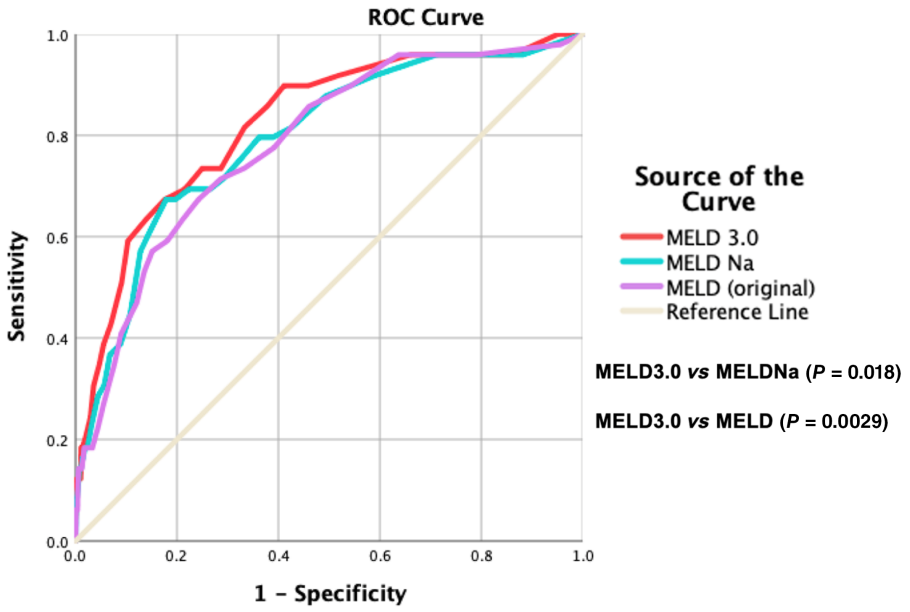

Figure 1 Receiver operating characteristic curves of the MELD3.0, MELDNa, and MELD in predicting 30-day mortality. MELD, model for end-stage liver disease.

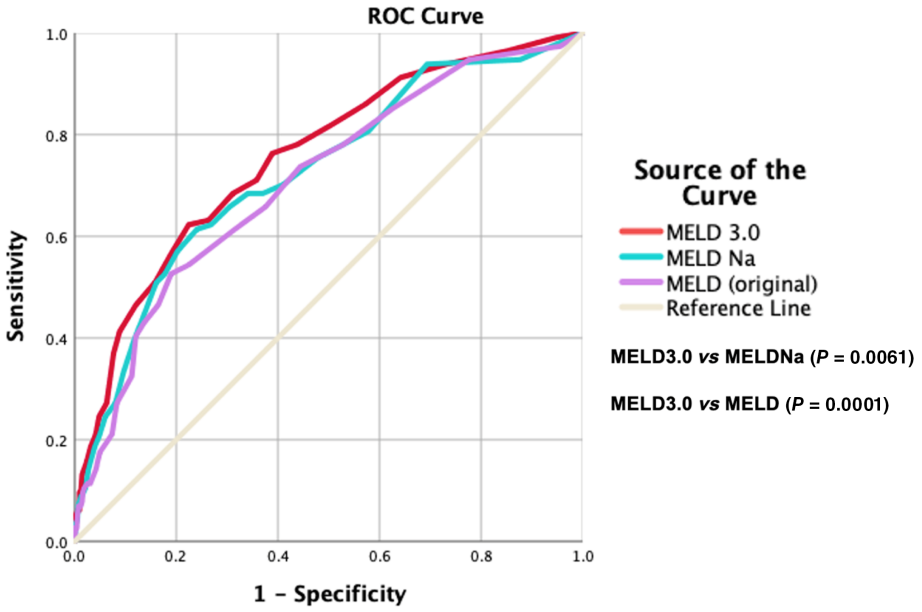

Figure 2 Receiver operating characteristic curves of the MELD3.0, MELDNa, and MELD in predicting 90-day mortality. MELD, model for end-stage liver disease.

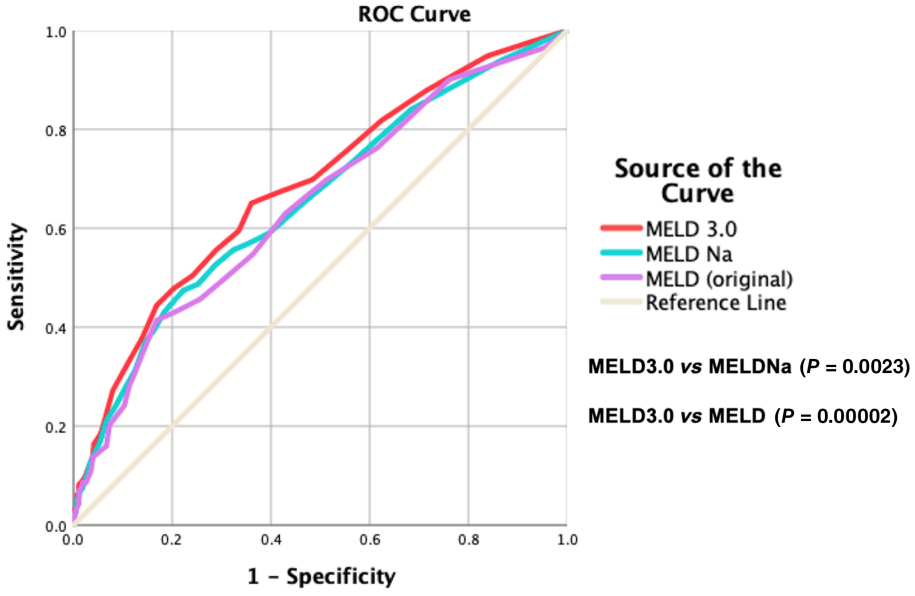

Figure 3 Receiver operating characteristic curves of the MELD3.0, MELDNa, and MELD in predicting 365-day mortality. MELD, model for end-stage liver disease.

13, respectively. Further information can be found in Tables S4 and S5.

Discussion

In this study, we confirmed that MELD3.0 performs better than MELDNa and MELD to predict mortality in hospitalized patients with cirrhosis. Importantly, this is the first study to validate the performance of MELD3.0 in a multi-ethnic Asian population of patients with cirrhosis. While other studies have evaluated the prognostic performance of the MELD3.0 in predicting 90- and 365-day mortalities,[12–14] we are the first study to evaluate the prognostic performance of the MELD3.0 in predicting 30-day mortality. Furthermore, we found that the AUROC of MELD3.0 was significantly higher than MELDNa and MELD in predicting 30-, 90-, and 365-day mortalities in patients with cirrhosis,

Table 4 Survival characteristics of patients with cirrhosis following risk stratification ($n = 862$)

	MELD3.0 ≤ 19	MELD3.0 > 19
Number of deaths, *n* (%)	295 (43.0)	121 (68.8)
Median time to death, days (IQR)	390.0 (134.3–927.5)	98.0 (28.8–398.0)

IQR, interquartile range; MELD, model for end-stage liver disease.

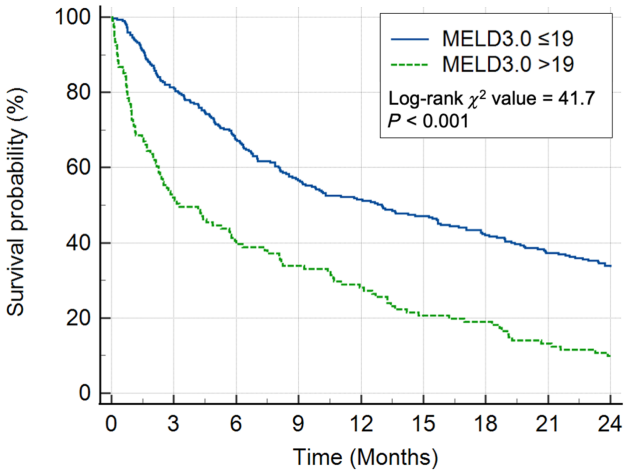

Figure 4 Survival curves of patients with cirrhosis stratified into high-risk (MELD3.0 > 19) and MELD3.0 ≤ 19. $P < 0.001$ using log-rank comparison. MELD, model for end-stage liver disease.

confirming the superior performance of MELD3.0 compared with MELDNa and MELD in predicting mortality at these timepoints. Our findings concur with the original study that developed the MELD3.0 in the United States, which also reported that MELD3.0 is superior to MELDNa in predicting 90-day mortality.[12] We determined that MELD3.0 score of 19 was the optimal cutoff to stratify patients with high risk of 30-day mortality. Patients with MELD3.0 score >19 demonstrated significantly poorer survival and higher 30-day mortality compared with patients with MELD3.0 score ≤19.

MELD3.0 performs better than MELDNa and MELD to predict the mortality patients with cirrhosis for the following reasons. Firstly, the ceiling of serum creatinine was lowered from 4.0 mg/dL in MELDNa and MELD, to 3.0 mg/dL in MELD3.0. This reduces the weight of serum creatinine in calculating the MELD3.0. Serum creatinine was initially implemented in the model as a marker of renal function. Serum creatinine is often elevated in acute kidney injuries, which commonly occurs in patients with cirrhosis and is a poor prognostic feature.[18] However, serum creatinine may also be elevated from many other causes. With more end-stage liver disease patients today having NAFLD, the elevated serum creatinine may instead arise from chronic kidney disease secondary to diabetes mellitus or hypertension.[19] In such situations, using the MELDNa or MELD may overstate the severity of the patient's condition. Secondly, MELD3.0 accounted for the female sex in the model. It was reported that a systematic bias that disadvantaged females existed in the MELD score and its derivative, MELDNa.[20] Females with similar renal function as males were found to have lower MELD scores, indicating a more favorable prognosis despite similar severity of liver dysfunction. Females with the same serum creatinine as males were also found to have poorer renal function than males, suggesting that serum creatinine could have overestimated the renal function in females.[20] Females generally have a lower level of serum creatinine in relation to their renal function as compared with males as a result of a smaller muscle mass, which could account for their lower serum creatinine levels.[21] In summary, the optimized MELD3.0 accounted for the significant confounding factors for elevated serum creatinine levels, particularly the increasingly prevalent NAFLD, which contributes to chronic kidney disease. Furthermore, gender differences were also adjusted for more accurate prognoses of females with cirrhosis. Our study has validated that MELD3.0 performed better than the MELDNa and MELD. MELD3.0 could be a valuable tool to facilitate the allocation of the scarce supply of liver for transplantation by more accurately risk stratifying patients with liver cirrhosis.

MELD3.0 demonstrated the best performance in predicting 30-day mortality. From our study, we found that the AUROC of MELD3.0 in predicting 30-, 90-, and 365-day mortalities were 0.823 (95% CI: 0.761–0.886), 0.754 (95% CI: 0.705–0.803), and 0.682 (95% CI: 0.642–0.723), respectively (Table 3). Additionally, we found that MELD3.0 score >19 predicts high risk of 30-day mortality (Table S2). Therefore, the MELD3.0 may be a useful clinical tool in this context for early identification of patients with liver cirrhosis who are at high risk of short-term mortality who will not survive with purely medical support. The MELD3.0 facilitates the risk stratification of these patients to determine if an urgent life-saving liver transplant is warranted. In settings where donor liver availability is scarce, MELD3.0 can help to identify patients who may benefit from early referral to an end-of-life care program.

However, the MELD3.0 score, which was initially developed and validated in the United States, performed poorer in predicting the mortality of the patients from the Asian population as compared with the Western population. The original US study which developed and validated the MELD3.0, reported AUROCs of the MELD3.0 and MELDNa in predicting three-month mortality that were superior to the corresponding AUROCs in our study (AUROC of the MELD3.0 and MELDNa in predicting three-month mortality = 0.869 and 0.862, respectively in the US study, *vs* 0.754 *vs* 0.724, respectively, in our study).[12] The MELD score was previously reported to be biased to disadvantage the Asians in liver transplantation allocation when compared with the Whites and African-Americans.[22] There are several factors postulated for the racial differences in the discriminative capabilities of the MELD models. Firstly, Asians are significantly underrepresented in the development of the MELD models. For example, only 4.0% of Asians made up the development set of the US-developed MELD3.0 model.[12] Secondly, the etiologies of chronic liver disease differ in the Western and the Asian population, which may contribute to different clinical trajectories.[23] HCV and alcohol use are the dominant etiologies of cirrhosis in North America and Western Europe, whereas in East Asia, HBV remains the dominant etiology and the prevalence of NAFLD is

on the rise.[24] In our cohort, HBV and NAFLD are also the top two causes of cirrhosis. NAFLD tend to occur on a background of various cardiometabolic diseases, such as diabetes mellitus, chronic kidney disease, hypertension, and coronary artery disease.[25] These may increase the likelihood of transplant waitlist deaths and reduce the eligibility of liver transplant. Liver-related variables used in the MELD models may not accurately predict the prognosis of NAFLD-cirrhosis patients due to the multisystemic nature of the disease. In addition, it was reported that while patients with alcoholic liver disease have a higher MELD score at presentation, they were less likely to die in the next 90 days as compared with patients with NAFLD.[26] As the MELD models were mainly developed and validated in the West where alcoholic liver disease predominates, the MELD models may not be fully generalizable in the Asian context.

In addition, the prognostic performance of the MELD models appears to be generally consistent amongst the different Asian populations with liver cirrhosis. For instance, Yoo *et al.* validated the MELD models in South Korean cirrhotic patients who were pending for liver transplantation. They reported that the AUROC of the MELD3.0, MELDNa, and MELD scores in predicting patients with 3-month mortality were 0.738, 0.730, and 0.718, respectively.[13] Additionally, Song *et al.* studied the performance of the MELD models in cirrhotic patients who were mainly from Western China and had undergone TIPS. They reported that the AUROC of the MELD3.0, MELDNa, and MELD scores in predicting patients with 3-month mortality were 0.732, 0.678, and 0.671, respectively. Furthermore, they also reported that the AUROC of the MELD3.0, MELDNa, and MELD scores in predicting patients with 1-year mortality were 0.715, 0.706, and 0.672, respectively.[14] These findings were largely consistent with our results (Table 3). Additionally, we observe that the prognostic performance of MELD3.0 was superior to MELDNa, which was followed by the MELD, across the Asian studies.

Limitations

We acknowledge several limitations in this study design. Firstly, this study was conducted in a single hospital in Singapore. Nonetheless, SGH is the largest tertiary hospital in central Singapore with a diverse patient population, providing a decent sample size of 862 subjects in this study. Secondly, the data were collected retrospectively for this study. However, the patients were followed up in a prospective manner from their first admission in 2018, there was minimal loss of data as the variables were collected from the hospital records during the admission and the end point of death was a well-defined, hard end point.

Additionally, we recognize that the median age of our study cohort is 70.0 years, which is at the cutoff age to be eligible for the allocation of deceased donor liver transplant in some centers. While the original MELD was developed and used for prioritization for organ allocation, it is also widely used in clinical practice beyond transplantation to prognosticate patients with liver cirrhosis.[2,27,28] The focus of our study is situated within the latter context, which is to investigate the performance and clinical utility of MELD3.0 *versus* MELDNa and MELD to prognosticate survival in cirrhotics in a population with a low liver transplant rate for appropriate clinical management. Moreover, as the population ages and the prevalence of liver disease increase in the elderly,[29] we believe that it is appropriate to validate the MELD3.0 in our study cohort, and using mortality as the primary endpoint.

Finally, we acknowledge that the cutoff MELD3.0 score of >19 to identify patients with excessively high mortality will require further validation from larger multi-center studies before it can be implemented in clinical use. The external validation is helpful as it provides confirmation that MELD3.0 is a clinically dependable score which is able to maintain its performance in different populations, including a multi-ethnic population.

Conclusion

MELD3.0 performs significantly better than MELDNa and MELD in predicting 30-, 90-, and 365-day mortalities in hospitalized patients with cirrhosis. Patients with cirrhosis with MELD3.0 scores >19 were at higher risk of 30-day mortality and have poorer survival compared with patients with MELD3.0 scores ≤19.

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Ethics approval statement

Approval was obtained from the Singapore General Hospital's centralized institutional review board (IRB number: 2022/2239).

Data availability statement. The data that support the findings of this study are available from the corresponding author, Hong-Yi Lin, upon reasonable request.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Data S1. Supporting information.