Incorporation of frailty estimated by gait speed within MELD-Na and the predictive potential for mortality in cirrhosis

You Deng*, Lin Lin*, Xiaofei Fan*, Binxin Cui, Lijun Hou, Tianming Zhao, Junjie Hou, Lihong Mao, Xiaoyu Wang, Wei Zhao, Bangmao Wang, Qingxiang Yu and Chao Sun

Ther Adv Chronic Dis

2020, Vol. 11: 1–11

DOI: 10.1177/2040622320922023

Correspondence to:
Qingxiang Yu
Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Anshan Road 154, Heping District, Tianjin 300052, China

Tianjin Institute of Digestive Disease, Tianjin Medical University General Hospital, Heping District, Tianjin, China
xyu01@tmu.edu.cn

Chao Sun
Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Anshan Road 154, Heping District, Tianjin 300052, China

Tianjin Institute of Digestive Disease, Tianjin Medical University General Hospital, Heping District, Tianjin, China

Department of Gastroenterology, Tianjin Medical University General Hospital Airport Hospital, Tianjin, China
chaosun@tmu.edu.cn

You Deng
Xiaofei Fan
Lijun Hou
Tianming Zhao
Junjie Hou
Lihong Mao
Xiaoyu Wang
Wei Zhao
Bangmao Wang
Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Heping District, Tianjin, China

Tianjin Institute of Digestive Disease, Tianjin Medical University General Hospital, Heping District, Tianjin, China

Lin Lin
Binxin Cui
Department of Gastroenterology, Tianjin Medical University General Hospital Airport Hospital, Tianjin, China

* These authors contributed equally to this work.

Abstract

Background: The 5 m gait speed (5MGS), a simple and reliable performance metric and surrogate indicator of frailty, consistently predicts adverse events in elders. Additionally, MELD-Na (model for end-stage liver disease-sodium) scores fail to capture nutritional and functional decline of cirrhotic patients that may confer excess mortality. We hypothesized that 5MGS might be associated with all-cause mortality, and that inclusion of frailty assessment within MELD-Na could improve the prediction of mortality in cirrhosis.

Methods: 5MGS was measured at baseline in 113 hospitalized cirrhotic patients. Survival status over 2 years and cirrhosis-related complications were recorded. We evaluated the prognostic value of 5MGS (as a continuous variable and as a dichotomous variable). The definition of slow *versus* preserved 5MGS was 0.8 ms^{-1} based on previous publication. Using Cox proportional hazards regression, a novel MELDNa-5MGS score was derived. Receiver operating characteristics (ROC) curves estimated discrimination between the new score model and established prognostic indices.

Results: The continuous 5MGS and slow 5MGS were independent predictors of all-cause mortality [5MGS: hazard ratio (HR) 0.133 (0.047–0.347), $p < 0.001$; slow 5MGS: HR 4.805 (1.536–15.026), $p < 0.007$]. The equation derived from Cox regression analysis was as follows: MELDNa-5MGS: MELD-Na score + 11 × slow 5MGS. The 2-year mortality in patients with high MELDNa-5MGS score was significantly higher ($p < 0.001$). Discriminatory power was significantly better for MELDNa-5MGS than MELD-Na score (AUC: 0.802 *versus* 0.724, $p = 0.014$ for 1 year; 0.773 *versus* 0.709, $p = 0.044$ for 2 years).

Conclusion: In cirrhotic patients, 5GMS is an independent risk factor of mortality. Modification of MELD-Na to include frailty estimated by low 5GMS is related to improved prognostication of mortality.

Keywords: gait speed, frailty, cirrhosis, model for end-stage liver disease

Received: 5 December 2019; revised manuscript accepted: 24 March 2020.

Introduction

Frailty, a biological syndrome of decreased reserve and resistance to stressors, has been well and widely investigated in the realm of geriatrics.[1] It has also been recognized that physical frailty applies in chronic liver disease and contributes to prediction of mortality and morbidity.[2–4] Conventional scores used to prognosticate mortality, such as model for end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) classification, may fail to reflect global status of a cirrhotic patient due to their sole reliance on laboratory parameters, and the inability to quantify physical performance. As frailty serves as a modifiable risk factor to an extent, appropriate identification gives rise to a target for optimization and, in the context of cirrhosis, potentially allows more feasible follow-up trajectory and exercise intervention.[5]

Although frailty is gaining more attention with respect to its pivotal role in cirrhosis, we still lack a unanimous consensus on the most appropriate measurement. The 5-m gait speed (5MGS) test is a surrogate indicator of physical frailty.[6,7] This metric is quick to determine and acceptable to inpatients. Gait speed has been proved to be a consistent risk factor of adverse events and poor outcomes including non-elective hospitalization, disability, and all-cause mortality.[8,9] More recently, Dunn *et al.* found frailty as measured by 5MGS is an independent and potential modifiable predictor for complications requiring hospitalization, in contrast to hand grip.[4] Frailty and sarcopenia, two interrelated concepts, share similarities in their etiological roots. Sarcopenia may be a contributor to the development of physical frailty. Additionally, the European Working Group on Sarcopenia in Older People (EWGSOP) group also advise measures of low physical performance to assess severe sarcopenia by applying gait speed.[10] Notably, gait speed has also been recognized as the best validated functional performance estimation for pharmacological trials in frailty and sarcopenia.[11] Taken together, we hypothesized that 5MGS could more effectively predict all-cause mortality in cirrhosis. We also explored whether the inclusion of frailty assessment within MELD-Na could improve the prediction of mortality in cirrhosis. Our preliminary results may facilitate further clinical trials by balancing cirrhotic individuals at high risk of adverse outcome or treatment arms at baseline.

Methods

Study population

Adult cirrhotic patients were enrolled prospectively at the Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital between 2016 and 2017. This study was conducted in accordance with the Declaration of Helsinki and was approved by Ethics Committee of Tianjin Medical University General Hospital (2015-024). Written informed consent was obtained from all participants. We identified subjects with cirrhosis by collecting medical history, laboratory examinations, imaging results, endoscopy data, and/or liver biopsy. Meanwhile, the presence of cirrhosis-associated complications, such as gastroesophageal varices, hepatic encephalopathy (HE), ascites, hypersplenism, and hypoalbuminemia, were reviewed. The exclusion criteria were as follows: (1) presence of acute-on-chronic liver failure (ACLF) on admission; (2) presence of severe HE (as recognized by the time to complete a numbers connection test of > 120 s)[12]; (3) primary liver cancer or extrahepatic malignancies; (4) liver transplantation; (5) refusal to follow-up trajectory. A total of 137 patients with cirrhosis were recruited prospectively at initial assessment, 4, 2, 9, 2, and 7 cases were excluded owing to admission ACLF, severe HE, malignancies, liver transplantation, and refusal to follow-up trajectory. Finally, a total of 113 participants were left for final analysis (Figure S1). Liver failure for definition of ACLF include jaundice (serum total bilirubin ≥ 5 mg/dl) and coagulation dysfunction [international normalized ratio (INR) > 1.5] complicated within 4 weeks by clinical ascites and/or HE in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis [Asian Pacific Association for the Study of the Liver (APASL) definition].

Clinical and laboratory measurement

Demographic information, clinical characteristics, and laboratory parameters, including age, gender, etiology of cirrhosis, presence of complications, complete blood count, liver function tests, prothrombin-international normalized ratio (PT-INR), CTP classification and MELD-Na (MELD-sodium) score were retrieved within 24 h after hospitalization. The primary outcome of interest was patient death over 2 years. Patients who underwent liver transplantation or were diagnosed with malignancies during follow-up period were censored.

Physical frailty measurement

We detected self-selected (usual pace) gait speed (5MGS) over a 5-m marked distance from a fixed start in our wards for patients with cirrhosis who could ambulate (more information in Supplementary File). The average of three consecutive trials were calculated and illustrated in ms^{-1} for final analysis.[4] We selected gait speed on account of its ease and validity across a variety of studies in multiple populations as being indicative of health situations and physical performance decline.[9,13] This parameter was measured by well-trained nurses. Prior to study initiation, two nurses simultaneously tested gait speed in a sample of 10

subjects in order to identify intra-observer agreement for the metrics as described by Bland and Altman.[14] Patients unable to walk at all were assigned a gait speed of 0.01 ms^{-1} according to previous publication.[15]

Statistical analysis

Data were presented as mean ± standard deviation (SD), median [interquartile range (IQR)], simple frequencies, or percentages (%) as appropriate. Continuous data were compared using an independent Student *t* test or the Mann–Whitney test for groups with non-normal distribution. Categorical variables were compared by chi-square test or Fisher's exact test. Correlations between continuous variables were assessed using Pearson correlation coefficients. Multivariable analysis performed by Cox proportional hazard analysis was used to identify the independent predictors of 2-year mortality. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. The survival rate was calculated using the Kaplan–Meier method and compared in order to detect statistically significant differences using the log-rank test. The receiver operating characteristics (ROC) curve was used to evaluate sensitivity and specificity of all predictive indices.

5MGS was evaluated as a continuous measure but also a binary variable [slow 5MGS ($<0.8\,ms^{-1}$) *versus* preserved 5MGS ($\geqslant 0.8\,ms^{-1}$)]. We have selected this threshold since international consensus statements have implied that it is a consistent indicator of adverse outcomes,[9,16] and is advised by EWGSOP2 on account of simplicity.[10]

Using Cox proportional hazard regression, we developed a novel MELDNa-5MGS score based on the prediction of all-cause mortality according to the formula: MELDNa-5MGS = MELD-Na score + [β(slow 5MGS)/β(MELD-Na score)] × slow 5MGS. Discriminative ability (referring to the potential of a model to correctly distinguish between distinct outcomes), was determined using the area under ROC curve (AUC). The *p*-value for comparison of AUCs was calculated using the DeLong method. Clinical usefulness and net benefit of MELDNa-5MGS score were estimated with decision-curve analysis.[17] The trends of mortality with respect to 5MGS and MELDNa-5MGS score increment were determined using the Cochran-Armitage test as previously described.[18] We considered $p<0.05$ as statistically significant. All statistical analyses were carried out using Stata 14.0 (Stata Corporation, College Station, TX, USA), MedCalc 15.2.2 (MedCalc, Mariakerke, Belgium), or R 3.3.2 (http://www.r-project.org/).

Results

Characteristics of patients

The baseline characteristics and laboratory data are shown in Table 1. A total of 113 cirrhotic patients (males: $n=60$, 53%) with an average age of 64 ± 11 years were recruited to the study. The etiology of liver cirrhosis (LC) was attributed to chronic viral hepatitis in 43 (38%), alcoholism/nonalcoholic steatohepatitis (NASH) in 14 (12%), autoimmune liver disease in 16 (14%), and cryptogenic in 40 participants (35%). The cirrhosis-associated complications consisted of gastroesophageal varices in 45, HE in 21, ascites in 36, hypersplenism in 35, and hypoalbuminemia in 48 patients, respectively. Of these patients, 42 were classified as CTP-A, 51 as CTP-B, and 20 as CTP-C. The mean MELD-Na at admission was 11.4 ± 4.7 points; 25% ($n=28$) of the cohort died during the 2-year follow-up period. When stratified by 5MGS (slow: $n=80$; preserved: $n=33$), there was a trend toward worse survival in patients with slow 5MGS compared with patients with preserved 5MGS, but without statistical significance (slow: 30% *versus* preserved: 12%; $p=0.056$).

MELDNa-5MGS score

We first determined the correlation between 5MGS and conventional scoring system as well as age. Figure 1 shows that MELD-Na score and 5MGS was not significantly related. The univariable analysis for risk of all-cause mortality is shown in Table 2. The crude HR for mortality decreased for each 1 ms^{-1} increase in 5MGS (0.100, 95% CI: 0.034–0.299, $p<0.001$). Similarly, when estimated as a binary measure, those with slow 5MGS had an increased crude HR compared with participants with preserved 5MGS (2.881, 95% CI: 0.999–8.309, $p=0.005$). Further multivariable analysis confirmed that 5MGS (binary and continuous) remained an independent predictor for 2-year mortality (Table 2). Moreover, the Kaplan–Meier analysis demonstrated a shorter survival time in those with slow compared with preserved 5MGS (log-rank: $p=0.04$, Figure S2). Cox

Table 1. Baseline characteristics of cirrhotic patients.

Characteristic	Total (*n* = 113)	Surviving (*n* = 85)	Deceased (*n* = 28)	*p* value
Age, years	64 ± 11	63 ± 11	67 ± 11	0.65
Sex, *n* (%)				0.196
Female	53 (47)	43 (51)	10 (36)	
Male	60 (53)	42 (49)	18 (64)	
Etiology, *n* (%)				0.215
Chronic viral hepatitis	43 (38)	31 (26)	12 (21)	
Alcohol	14 (12)	8 (9)	6 (21)	
Autoimmune	16 (14)	14 (16)	2 (7)	
Cryptogenic	40 (35)	32 (48)	8 (50)	
CTP, *n* (%)				0.009
CTP-A	42 (37)	36 (42)	6 (21)	
CTP-B	51 (45)	39 (46)	12 (43)	
CTP-C	20 (18)	10 (12)	10 (36)	
MELD-Na	11.4 ± 4.7	11.5 ± 4.3	13.9 ± 4.9	0.001
Albumin, g/l	30.6 ± 5.9	31.5 ± 5.5	27.5 ± 5.8	0.001
PT-INR	1.4 ± 0.6	1.4 ± 0.7	1.4 ± 0.4	0.674
TBIL, mg/dl	2.0 ± 2.4	1.8 ± 2.1	2.8 ± 3.1	0.111
Creatinine, µmol/l	70.2 ± 33.9	63.2 ± 26.7	91.4 ± 42.7	0.003
Sodium, mmol/l	139.7 ± 5.0	140.1 ± 4.7	138.4 ± 5.3	0.106
5MGS, ms^{-1}	0.56 ± 0.35	0.64 ± 0.31	0.34 ± 0.36	<0.0001
Complications, *n* (%)				
Hepatic encephalopathy	21 (19)	9 (11)	12 (43)	0.0004
Gastroesophageal varices	45 (40)	34 (40)	11 (39)	0.999
Hypersplenism	35 (31)	27 (32)	8 (29)	0.818
Hypoalbuminemia	48 (42)	29 (34)	19 (68)	0.002
Ascites	36 (32)	26 (31)	10 (36)	0.645
Hematological indices				
NLR	5.3 ± 6.9	5.0 ± 7.3	6.0 ± 5.1	0.472
PLR	136.3 ± 124.9	138.4 ± 106.3	130.0 ± 167.5	0.808
LMR	2.3 ± 2.1	2.5 ± 2.3	1.7 ± 1.0	0.011
ALT, U/l	19 (14,32)	19 (14,36)	18 (14,28)	0.485
AST, U/l	30 (22,44)	30 (21,48)	29 (25,40)	0.869
GGT, U/l	39 (25,79)	39 (24,81)	40 (28,56)	0.861

5MGS, 5-m gait speed; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh classification; GGT, gamma glutamyl transferase; IQR, interquartile range; LMR, lymphocyte-to-monocyte ratio; MELD-Na, model for end-stage liver disease-sodium; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PT-INR, prothrombin-international normalized ratio; SD, standard deviation; TBIL, total bilirubin.
Percentages might not add up to 100% because of rounding.
Values are presented as the mean ± SD, median (IQR), or number of patients (%).

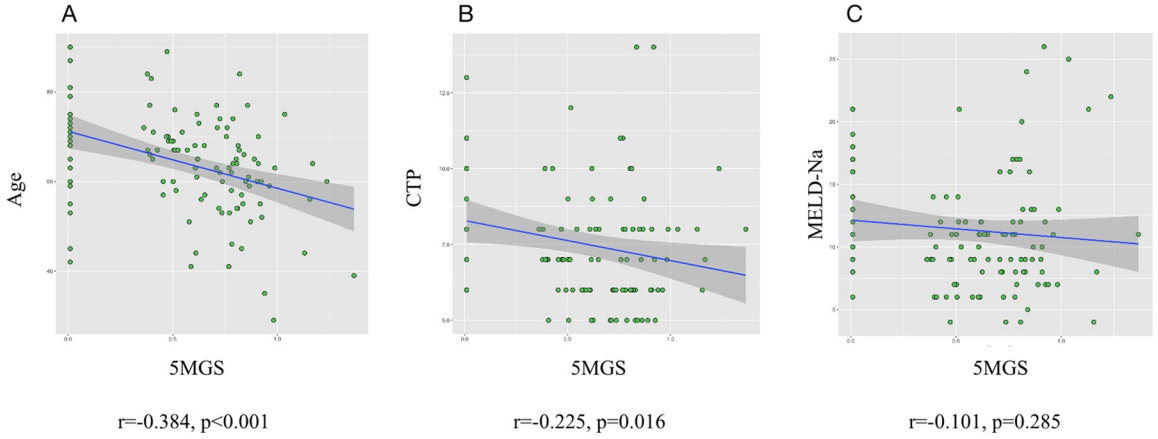

Figure 1. Correlations among 5MGS and age (A) as well as conventional scores (B, C). No significant correlation was identified between MELD-Na and 5MGS.
CTP, Child-Turcotte-Pugh classification; 5MGS, 5-m gait speed; MELD-Na, model for end-stage liver disease-sodium.

Table 2. Univariable and multivariable analyses for 2-year all-cause mortality.

	Univariable analysis		Multivariable Analysis-model 1*		Multivariable Analysis-model 2*	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
5MGS (ms^{-1})	0.100 (0.034–0.299)	<0.001	0.133 (0.047–0.347)	<0.001		
Slow 5MGS (reference: preserved 5MGS)	2.881 (0.999–8.309)	0.005			4.805 (1.536–15.026)	0.007
Age	1.034 (0.999–1.071)	0.056				
Sex	0.593 (0.274–1.284)	0.185				
CTP	0.229 (0.083–0.631)	0.012				
MELD-Na	1.103 (1.036–1.174)	0.002	1.104 (1.027–1.187)	0.008	1.153 (1.070–1.243)	0.001

Multivariable model 1: 5MGS (continuous format); age; sex; CTP; MELD-Na. *Final model presented.
Multivariable model 2: Slow 5MGS (binary format); age; sex; CTP; MELD-Na. *Final model presented.
5MGS, 5-m gait speed; CI, confidence interval; CTP, Child-Turcotte-Pugh classification; HR, hazard ratio; MELD-Na, model for end-stage liver disease-sodium.

regression analysis generated the following equation for MELDNa-5MGS:

$$\text{MELD-Na score} + 11\times \text{ slow 5MGS}.$$

The median MELDNa-5MGS score was 20 points and the AUC revealed a cut-off MELDNa-5MGS score of 23 (AUC = 0.773, $p < 0.001$, sensitivity 0.64, specificity 0.84), resulting in 32 patients having high MELDNa-5MGS scores. Table 3 shows the parameters of patients stratified according to MELDNa-5MGS scores. Apart from the components of MELDNa-5MGS, CTP classification ($p < 0.0001$), HE ($p < 0.0001$), hypoalbuminemia ($p < 0.0001$), neutrophil-to-lymphocyte ratio ($p = 0.032$), and lymphocyte-to-monocyte ratio

Table 3. Baseline characteristics of cirrhotic patients stratified according to MELDNa-5MGS score.

Characteristics	High MELDNa-5MGS (*n* = 32)	Low MELDNa-5MGS (*n* = 81)	*p* value
Age, years	65 ± 10	63 ± 12	0.404
Sex, n (%)			0.531
Female	13 (41)	40 (49)	
Male	19 (59)	41 (51)	
Etiology, *n* (%)			0.195
Chronic viral hepatitis	9 (28)	34 (42)	
Alcohol	6 (19)	8 (10)	
Autoimmune	7 (22)	9 (11)	
Cryptogenic	10 (31)	30 (37)	
CTP, *n* (%)			<0.0001
CTP-A	1 (3)	41 (51)	
CTP-B	15 (47)	36 (44)	
CTP-C	16 (50)	4 (5)	
MELD-Na	16.3 ± 4.0	9.5 ± 3.3	<0.0001
Albumin, g/l	26.1 ± 5.0	32.3 ± 5.2	0.005
PT-INR	1.7 ± 1.1	1.2 ± 0.2	0.012
TBIL, mg/dl	3.1 ± 3.0	1.6 ± 2.1	0.018
Creatinine, μmol/l	91.1 ± 50.0	61.9 ± 19.8	0.003
Sodium, mmol/l	138.1 ± 4.5	140.4 ± 5.0	0.026
5MGS, ms^{-1}	0.35 ± 0.36	0.65 ± 0.31	<0.0001
Complications, *n* (%)			
Hepatic encephalopathy	15 (47)	6 (7)	<0.0001
Gastroesophageal varices	13 (41)	32 (40)	0.999
Hypersplenism	7 (22)	28 (35)	0.259
Hypoalbuminemia	25 (78)	23 (28)	<0.0001
Ascites	13 (41)	23 (32)	0.263
Hematological indices			
NLR	8.6 ± 11.5	4.0 ± 3.0	0.032
PLR	175.1 ± 195.2	120.9 ± 79.0	0.137
LMR	1.5 ± 0.9	2.6 ± 2.4	<0.0001
ALT, U/l	14 (23,36)	18 (14,29)	0.390
AST, U/l	36 (25,64)	30 (21,41)	0.118
GGT, U/l	35 (28,49)	43 (24,83)	0.610

5MGS, 5-m gait speed; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh classification; GGT, gamma glutamyl transferase; IQR, interquartile range; LMR, lymphocyte-to-monocyte ratio; MELD-Na, model for end-stage liver disease-sodium; MELDNa-5MGS, MELDNa-5 meter gait speed; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PT-INR, prothrombin-international normalized ratio; SD, standard deviation; TBIL, total bilirubin.
Percentages might not add up to 100% because of rounding.
Values are presented as the mean ±SD, median (IQR), or number of patients (%).

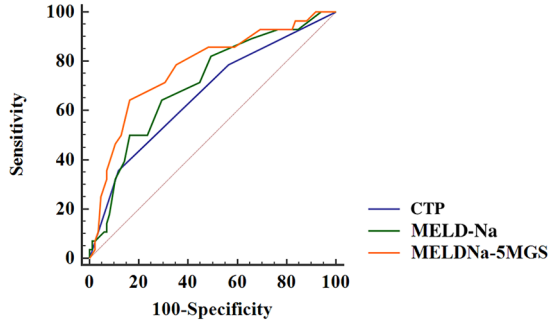

Figure 2. Cut-off values for MELDNa-5MGS determined by ROC analysis.
CTP, Child-Turcotte-Pugh classification; MELD-Na, model for end-stage liver disease-sodium; MELDNa-5MGS, MELDNa-5-m gait speed; ROC, receiver operating characteristics curve.

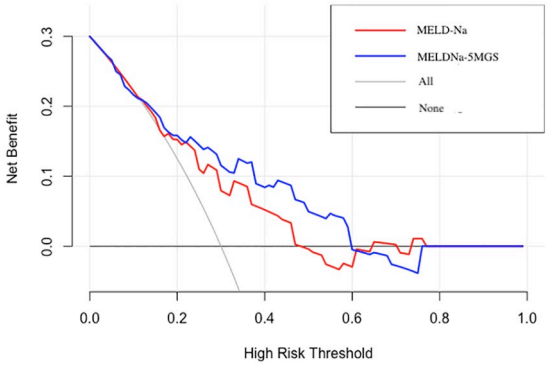

Figure 3. Decision-curve analysis of MELDNa-5MGS *versus* MELD-Na for the prediction of 2-year mortality in cirrhosis.
MELD-Na, model for end-stage liver disease-sodium; MELDNa-5MGS, MELDNa-5-m gait speed.

($p < 0.0001$) differed significantly between patients with low and high MELDNa-5MGS scores.

Discriminatory power and clinical utility of MELDNa-5MGS score

Supplementary Table and Figure 2 depict the AUC of MELDNa-5MGS, the conventional MELD-Na, and CTP classification for predicting 3-momth, 6-month, 1-year, and 2-year all-cause mortality. MELDNa-5MGS scores predicted mortality more accurately than MELD-Na ($p = 0.014$ for 1-year, $p = 0.044$ for 2-years). In addition, our decision curve analysis implicated the net benefit achieved from the MELDNa-5MGS than MELD-Na were higher, with threshold probabilities of 0.16–0.6 (Figure 3).

Prediction of mortality on account of MELDNa-5MGS score

All-cause mortality was significantly higher in patients with high (⩾15) ($n = 23$) than low (<15) ($n = 90$) MELD-Na scores ($p = 0.0028$, Figure S3).[19] Additionally, all-cause mortality was significantly higher among patients with high ($n = 32$) than low ($n = 81$) MELDNa-5MGS scores ($p < 0.0001$, Figure 4A). The 6-month, 1- and 2-year mortality rates with high and low MELDNa-5MGS scores were 31%, 47% and 56% *versus* 5%, 7% and 12%, respectively. Furthermore, even among patients with low MELD-Na scores ($n = 90$), mortality rates were significantly higher in 14 patients with high MELDNa-5MGS scores compared with 76 patients with low MELDNa-5MGS scores ($p = 0.0003$, Figure 4B).

Distribution of 5MGS and MELDNa-5MGS scores

The distribution of 5MGS and MELDNa-5MGS in our patients is shown in Figure 5. The mortality rate decreased significantly ($p = 0.003$ for trend) from 58% (14/24) in patients in the 0–0.2 5MGS range to 0% (0/2) in the 1.2–1.4 5MGS range. Moreover, the mortality rate increased significantly ($p < 0.001$ for trend) from 0% (0/2) in patients in the 0–5 MELDNa-5MGS score range to 50% (2/4) in the 30–35 MELDNa-5MGS score range.

Discussion

As far as we can determine, MELDNa-5MGS is the first scoring system to include frailty estimated by gait speed, and it was more useful in predicting all-cause mortality than the conventional MELD-Na score. The MELD is derived from three objective parameters, including serum bilirubin, creatinine, and PT-INR. It is reliable for predicting short- and mid-term mortality in cirrhosis,[20,21] and modification of MELD to include sodium has been implemented in standard practice to increase the prognostic value.[22] However, one flaw of scoring systems based on MELD is that they fail to completely capture elements contributing to functional status or physical reserve of patients with cirrhosis. Frailty has been increasingly recognized to apply in advanced liver disease, and is useful in heralding prognosis and predicting outcomes.[2,4,15,23] Among various measurement tools, gait speed has been implemented individually or within an amalgamation of methods for grading frailty.[5,24]

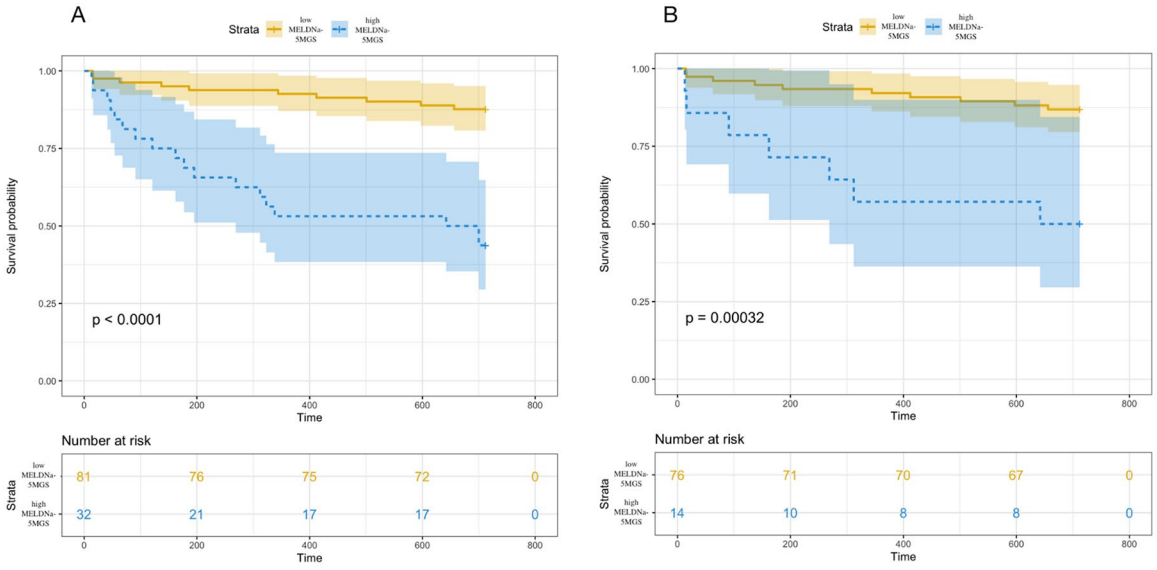

Figure 4. Survival rates among cirrhotic patients classified according to MELDNa-5MGS. (A) Survival rates were significantly higher in patients with low ($n = 81$), than high ($n = 32$) MELDNa-5MGS scores ($p < 0.0001$). (B) Among 90 patients with low MELD-Na scores, mortality rates were significantly higher among those who also had high MELDNa-5MGS scores, than among patients with low MELD-Na and low MELD-Na scores ($p = 0.0003$).
MELD-Na, model for end-stage liver disease-sodium; MELDNa-5MGS, MELDNa-5-m gait speed.

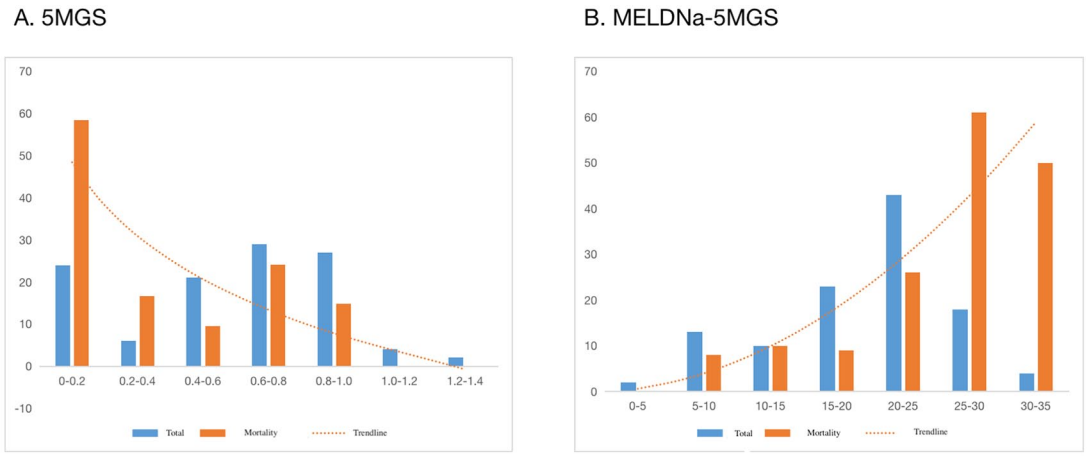

Figure 5. Two-year all-cause mortality related to 5MGS and MELDNa-5MGS. The vertical bars show the percentages of patients (blue: all patients; orange: deceased patients), scaled on the *y*-axis, and corresponded to the indicated intervals of 5MGS (A) and MELDNa-5MGS (B) on the *x*-axis. The trend was statistically significant for 5MGS ($p = 0.003$) and MELDNa-5MGS ($p < 0.001$) using the Cochran-Armitage test.
MELD-Na, model for end-stage liver disease-sodium; MELDNa-5MGS, MELDNa-5-m gait speed.

Studies assessing the prognostic ability of gait speed in patients with cirrhosis is limited. Dunn and colleagues measures 5MGS in 373 cirrhotic patients evaluated for, or awaiting, liver transplantation, and uncovered that gait speed was a risk factor for complications requiring hospitalization.[4] Moreover, each 0.1 ms^{-1} gait speed decrease was related to 22% greater hospital days.[4] Ribeiro *et al.* determined gait speed based on a 6-min walk test in 73 participants.[25] They found that slow gait speed was an independent predictor of death, and showed the highest predictive power of decease concomitantly linked to other malnourished indices. Lai *et al.* set out to

develop a novel frailty index and implied that cirrhotics with poor frailty scores exhibited more impaired gait speed.[15] Their final model embodies three performance-based tests (grip strength, chair stands, and balance) and enhances mortality prediction in combination with MELD-Na score over MELD-Na alone. Notwithstanding, substituting walk speed for grip strength would impair the balance between statistical accuracy and ease of use in clinical practice. Intriguingly, another study from Japan found grip strength might be a suitable proxy for gait speed in hospitalized patients with chronic liver disease for hepatocellular carcinoma treatment.[26] Our results implicated that both continuous and slow 5MGS were independently associated with all-cause mortality after adjustment for potential confounders. Taken together, we hypothesized the above-mentioned difference is attributed to a study population with distinct clinical features (clinic *versus* hospitalization) and outcomes of interest (1-year waitlist mortality *versus* 2-year all-cause mortality). Notably, our scoring system might be more feasible among acutely ill inpatients with cirrhosis.

Our results indicated that 5MGS may represent a stratification tool of all-cause mortality in cirrhosis. According to purpose, 5MGS could have the potential to delete or enrich a clinical trial with those at high risk of adverse outcome, or to balance therapy arms at baseline. For instance, an outstanding study by Kitajima *et al.* implied that dietary supplementation with branched-chain amino acids (BCAA) was associated with amelioration of hypoalbuminemia, decreased fat deposits in skeletal muscle, maintenance of skeletal muscle mass, and improved glucose sensitivity.[27] Thus BCAA supplementation may represent a less invasive and a more consistent treatment to inhibit or prevent the pathogenesis of cirrhosis and result in a favorable outcome.[27] However, the authors addressed that the amount of physical activity was not investigated, where we propose that 5MGS may be a valid and feasible endpoint in their study. Indeed, it should be emphasized that gait speed has been implemented as a trial endpoint in other chronic entities and gave rise to the regulatory approval of medications for multiple sclerosis.[28]

Frailty and sarcopenia in cirrhosis are closely related, and sarcopenia likely serves a significant contributor. It is believed by some practitioners that frailty is the result of prolonged sarcopenia.[29] Thus, measuring sarcopenia, by means of radiographic image analysis [computed tomography (CT) or magnetic resonance imaging (MRI)], may encapsulate physical frailty to some extent. However, there are potential limitations associated with using imaging-based results as surrogate parameter for assessment. Specifically, missing values are not avoided because a proportion of patients are unable to perform serial measurements due to expense or concerns about radiation. As frailty occurs on a continuum, gait speed has advantage of being simple, reliable, and reproducible in serial tests. Furthermore, frailty is not a single phenotype but rather varying clusters of multiple traits of vulnerabilities, weaknesses, instabilities, and limitations[30]; these manifestations are not captured by laboratory/radiographic data. Of note, although MELD-Sarcopenia score was shown to be an independent predictor of mortality by Montano-Loza *et al.*, the inclusion of 5MGS in our novel scoring system dramatically improved predictive capacity.[31]

The other disadvantage is that patients with lower MELD-Na scores might not be at low risk for mortality. Our proposed MELDNa-5MGS score extracted patients with high all-cause mortality among those considered to be at low risk according to MELD-Na scores. These results suggested that the MELDNa-5MGS score could serve as a favorable prognostication system that could precisely predict mid-term mortality.

Our study has some limitations. First, we examined baseline 5MGS only at index hospitalization of cirrhotic inpatients, whereas change in gait speed may be more reflective of frailty circumstance, which warrants exploration in future study. Second, patients unable to finish 5MGS were assigned a gait speed of $0.01\,ms^{-1}$, which may result in selection bias. Third, we did not externally validate our results. However, given the consistent demonstration of the predictive capacity of MELD-Na and gait speed in cirrhosis as well as other populations, the need for external validation is less pronounced.[9,16] Finally, the vast majority of published articles have concentrated on frailty assessment in outpatients. Taking account of frailty as a universal condition among subjects with various chronic diseases, we aimed to explore the utility and effectiveness of gait speed for predicting long-term mortality in

cirrhosis. It is inevitable to address the inherent limitation of this frailty metric itself, given the instability of testing gait speed in hospitalized critical patients. Moreover, our group has conducted a series of baseline and longitudinal studies to investigate the impact of frailty screening/assessment upon long-term mortality, such as self-reported frailty index. Further study is warranted to confirm our findings.

In conclusion, we refined the conventional MELD-Na score by incorporating assessment of frailty by gait speed. Moreover, the novel MELDNa-5MGS score is more accurately predictive of mid-term mortality than MELD-Na scores. It is thus plausible to include 5MGS as a surrogate indicator of frailty for cirrhosis in clinic settings.

Acknowledgements
We thank all the nurses who took part in the current study.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Chao Sun https://orcid.org/0000-0002-0380-7999

Supplemental material
Supplemental material for this article is available online.

References
1. Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146–M156.
2. Tandon P, Tangri N, Thomas L, *et al*. A rapid bedside screen to predict unplanned hospitalization and death in outpatients with cirrhosis: a prospective evaluation of the clinical frailty scale. *Am J Gastroenterol* 2016; 111: 1759–1767.
3. Sinclair M, Poltavskiy E, Dodge JL, *et al*. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. *World J Gastroenterol* 2017; 23: 899–905.
4. Dunn MA, Josbeno DA, Tevar AD, *et al*. Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospitalization. *Am J Gastroenterol* 2016; 111: 1768–1775.
5. Laube R, Wang H, Park L, *et al*. Frailty in advanced liver disease. *Liver Int* 2018; 38: 2117–2128.
6. Bergquist CS, Jackson EA, Thompson MP, *et al*. Understanding the association between frailty and cardiac surgical outcomes. *Ann Thorac Surg* 2018; 106: 1326–1332.
7. Afilalo J, Kim S, O'Brien S, *et al*. Gait speed and operative mortality in older adults following cardiac surgery. *JAMA Cardiol* 2016; 1: 314–321.
8. Steffen TM, Hacker TA and Mollinger L. Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. *Phys Ther* 2002; 82: 128–137.
9. Studenski S, Perera S, Patel K, *et al*. Gait speed and survival in older adults. *JAMA* 2011; 305: 50–58.
10. Cruz-Jentoft AJ, Bahat G, Bauer J, *et al*. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; 48: 16–31.
11. Working Group on Functional Outcome Measures for Clinical Trials. Functional outcomes for clinical trials in frail older persons: time to be moving. *J Gerontol A Biol Sci Med Sci* 2008; 63: 160–164.
12. Weissenborn K, Ruckert N, Hecker H, *et al*. The number connection tests A and B: interindividual variability and use for the assessment of early hepatic encephalopathy. *J Hepatol* 1998; 28: 646–653.
13. Pamoukdjian F, Paillaud E, Zelek L, *et al*. Measurement of gait speed in older adults to identify complications associated with frailty: a systematic review. *J Geriatr Oncol* 2015; 6: 484–496.
14. Bland JM and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307–310.

15. Lai JC, Covinsky KE, Dodge JL, *et al*. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017; 66: 564–574.

16. Abellan van Kan G, Rolland Y, Andrieu S, *et al*. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) task force. *J Nutr Health Aging* 2009; 13: 881–889.

17. Deng Y, Fan X, Ran Y, *et al*. Prognostic impact of neutrophil-to-lymphocyte ratio in cirrhosis: a propensity score matching analysis with a prespecified cut-point. *Liver Int* 2019; 39: 2153–2163.

18. Yang F, Lin L, Jiang X, *et al*. Increasing diverticulosis in an aging population: a colonoscopy-based study of 5-year trends in 26 463 patients in northern China. *Med Sci Monit* 2018; 24: 2825–2831.

19. Mazumder NR, Atiemo K, Daud A, *et al*. Patients with persistently low MELD-Na scores continue to be at risk of liver related death. *Transplantation*. Epub ahead of print. 21 October 2019. DOI: 10.1097/TP.0000000000002997.

20. Kamath PS, Kim WR and Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology* 2007; 45: 797–805.

21. Biggins SW, Kim WR, Terrault NA, *et al*. Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology* 2006; 130: 1652–1660.

22. Huo TI, Wang YW, Yang YY, *et al*. Model for end-stage liver disease score to serum sodium ratio index as a prognostic predictor and its correlation with portal pressure in patients with liver cirrhosis. *Liver Int* 2007; 27: 498–506.

23. Lai JC, Feng S, Terrault NA, *et al*. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant* 2014; 14: 1870–1879.

24. Kok B and Tandon P. Frailty in patients with cirrhosis. *Curr Treat Options Gastroenterol*. 2018; 16: 215–225.

25. Ribeiro HS, Mauricio SF, Antonio da Silva T, *et al*. Combined nutritional assessment methods to predict clinical outcomes in patients on the waiting list for liver transplantation. *Nutrition* 2018; 47: 21–26.

26. Nagamatsu A, Kawaguchi T, Hirota K, *et al*. Slow walking speed overlapped with low handgrip strength in chronic liver disease patients with hepatocellular carcinoma. *Hepatol Res* 2019; 49: 1427–1440.

27. Kitajima Y, Takahashi H, Akiyama T, *et al*. Supplementation with branched-chain amino acids ameliorates hypoalbuminemia, prevents sarcopenia, and reduces fat accumulation in the skeletal muscles of patients with liver cirrhosis. *J Gastroenterol* 2018; 53: 427–437.

28. Goodman AD, Brown TR, Edwards KR, *et al*. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol* 2010; 68: 494–502.

29. Landi F, Calvani R, Cesari M, *et al*. Sarcopenia as the biological substrate of physical frailty. *Clin Geriatr Med*. 2015; 31: 367–374.

30. Fried LP, Hadley EC, Walston JD, *et al*. From bedside to bench: research agenda for frailty. *Sci Aging Knowledge Environ* 2005; 2005: pe24.

31. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, *et al*. Inclusion of sarcopenia within MELD (MELD-sarcopenia) and the prediction of mortality in patients with cirrhosis. *Clin Transl Gastroenterol* 2015; 6: e102.