Annals of Gastroenterology (2025) **38,** 93-99

Validation of gender-equity model for liver allocation (GEMA) and its sodium variant (GEMA-Na) in candidates for liver transplantation

Magdalini Adamantou[a], Theodora Oikonomou[b], Nedia Georgia Petridou[a], Panagiotis Kalligiannakis[a], Christos Cholokitas[a], Michail Kalpoutzakis[a], Maria Christina Kavalaki[a], Dimitrios Glaros[a], Evangelinos Michelis[a], Apostolos Papageorgiou[a], George V. Papatheodoridis[c], Ioannis Goulis[b], Evangelos Cholongitas[a,c]

Medical School, National and Kapodistrian University, Athens; "Hippocration" General Hospital of Thessaloniki, Aristotelion University of Thessaloniki; "Laiko" General Hospital of Athens, National and Kapodistrian University of Athens, Greece

Abstract

Background The current allocation system for liver transplantation (LT) is based on the sickest-first policy, using objective variables to ensure equal priority. However, under-prioritization of female patients for LT, compared to males, is well demonstrated and new scores have been proposed to overcome this systematic bias. This study evaluated the ability of these new scores to predict the long-term outcomes of patients with cirrhosis.

Methods The clinical and laboratory characteristics of 694 consecutive candidates for liver transplantation from 2 liver transplant centers were recorded. The model for end-stage liver disease (MELD)-based scores (MELD, MELD-Sodium and MELD 3.0), as well as the Gender-Equity Model for liver Allocation (GEMA) and GEMA-Sodium, were used to assess the severity of liver disease. Patients were followed-up prospectively and their outcomes assessed.

Results During a follow-up period of median length 12 months (range: 4-52), 28.5% of patients died, 21% of patients underwent LT, while 50.5% remained alive. Female patients had significantly lower MELD and MELD-Sodium scores compared to males, attributable to their significantly lower creatinine, while MELD 3.0, GEMA and GEMA-Sodium did not differ between the 2 sexes. In multivariate Cox regression analysis, GEMA-Sodium was the only factor independently associated with death/LT, and showed very good discriminative ability (hazard ratio 1.10, 95% confidence interval 1.073-1.128; P<0.001). These findings were confirmed in several subgroup analyses.

Conclusions Our findings show for the first time the predictive ability of GEMA-Sodium for the long-term outcomes of LT candidates. However, further studies are needed to confirm these findings.

Keywords GEMA, GEMA-Na, MELD, liver transplantation, prognosis

Ann Gastroenterol 2025; 38 (1): 93-99

Conflict of Interest: None

Correspondence to: Evangelos Cholongitas, MD, PhD, Professor in Medicine-Hepatology, First Department of Internal Medicine, Medical School, National & Kapodistrian University of Athens, 17 Agiou Thoma St, 11527 Athens, Greece, e-mail: cholongitas@yahoo.gr
Received 20 August 2024; accepted 13 November 2024; published online 12 December 2024

DOI: https://doi.org/10.20524/aog.2024.0933

Introduction

Cirrhosis is associated with significant morbidity and mortality [1] and may progress to decompensated cirrhosis (DeCi) as portal hypertension worsens with the appearance of complications, such as ascites, variceal bleeding and/or encephalopathy [2]. The increased mortality of patients with DeCi, as well as the lack of curative treatments, have placed DeCi at the top of the indications for liver transplantation (LT) worldwide [3]. Most LT centers use the Child-Pugh (CTP) score [4] and model for end-stage liver disease (MELD) score [5] for the evaluation of cirrhotic patients' prognosis, while the latter is also used to prioritize patients for LT, since

it is based only on objective variables: i.e., serum creatinine, serum bilirubin and international normalized ratio (INR) [5]. More recently, the MELD-Sodium (MELD-Na) score, with the addition of serum sodium (Na), has replaced the original MELD score in predicting mortality among candidates on the waiting list for LT [6].

However, MELD and MELD-Na scores have some limitations, including the fact that serum albumin is not considered in their calculation, whereas it is a component in the calculation of the CTP score [4]. In addition, several studies have demonstrated the presence of a sex-disparity effect, with females being under-prioritized for LT compared to males with the same severity of liver disease [7,8]. This discrepancy has been attributed to several factors, including the fact that females have lower serum creatinine values for the same renal function (i.e., glomerular filtration rate) compared to males, as a consequence of a having lower average muscle mass [7,8].

Considering these drawbacks, MELD 3.0 has been proposed, in which female sex and albumin were added to MELD-Na formula to improve the accuracy of stratification among candidates on the waiting list for LT [9]. The development of the MELD 3.0 score was based on the UNOS database; it has been shown to be fairer, ensuring equal priority for LT, particularly in females with lower creatinine values. Along similar lines, a new prognostic score, the Gender-Equity Model for liver Allocation (GEMA), and its variant with the addition of Na (GEMA-Na), were proposed, showing an improvement in the discrimination and a significant reclassification benefit compared with existing scores [10]. GEMA and GEMA-Na are scores designed to predict the 3-month risk of mortality or delisting due to progression of liver disease in patients waiting for LT [10]. Only 2 studies in the literature have externally validated the performance of GEMA/GEMA-Na scores [11,12]. However, both studies were focused only on the 3-month prediction of dropout from the list for LT (i.e., death or severe clinical worsening), while no multivariate analysis that included all prognostic scores was performed. In addition, the lower number of events occurring at 90 days of follow up, and the absence of subgroup analyses, such as those involving candidates for non-hepatocellular carcinoma (HCC), are considered significant limitations of these studies [11,12]. Thus, the aim of our study was to validate the performance of GEMA and GEMA-Na in predicting the long-term outcomes (survival, death, or LT) of patients with stable DeCi, both overall and for various subgroups related to the etiology and severity of the underlying liver disease.

[a]First Department of Internal Medicine, Medical School, National and Kapodistrian University, Athens (Magdalini Adamantou, Nedia Georgia Petridou, Panagiotis Kalligiannakis, Christos Chologkitas, Michail Kalpoutzakis, Maria Christina Kavalaki, Dimitrios Glaros, Evangelinos Michelis, Apostolos Papageorgiou, Evangelos Cholongitas); [b]4th Department of Internal Medicine, "Hippocration" General Hospital of Thessaloniki, Aristotelion University of Thessaloniki, Thessaloniki (Ioannis Goulis, Theodora Oikonomou); [c]Academic Department of Gastroenterology, "Laiko" General Hospital of Athens, National and Kapodistrian University of Athens, Athens (George V. Papatheodoridis, Evangelos Cholongitas); Greece

Patients and methods

Study population

We retrospectively enrolled consecutive adult patients with stable DeCi admitted to 2 LT centers in Greece ("Hippokration" General Hospital of Thessaloniki and "Laiko" General Hospital of Athens) for pre-LT waitlist evaluation between January 2014 and December 2023. Exclusion criteria were: a) age <18 years; b) acute liver failure; c) need for combined kidney and liver transplantation; d) non-cirrhotic portal hypertension; and e) previous LT. The presence of HCC was not an exclusion criterion provided that there was underlying cirrhosis. Cirrhosis was established by biopsy or imaging, together with findings related to portal hypertension, e.g., thrombocytopenia or gastroesophageal varices. DeCi was defined as a history of complications, such as ascites, variceal bleeding and encephalopathy, in patients with known cirrhosis. The patients did not suffer from a complication of cirrhosis—i.e., variceal bleeding, encephalopathy, infection such as spontaneous bacterial peritonitis (SBP)—at baseline or during the last month before their admission. On admission, the following demographic and clinical characteristics were recorded in each patient: age, sex, cause of the underlying liver disease, previous history of complications (i.e., variceal bleeding, encephalopathy, SBP), medication for diuretic therapy (duration and dosage), and concomitant extra-hepatic diseases (e.g., diabetes mellitus, coronary artery disease). The presence of HCC was also recorded.

Laboratory variables, including platelet count, creatinine, electrolytes (sodium, potassium), protein, albumin, bilirubin (total and direct), INR, ferritin and natriuresis (with urine collection to calculate 24-h urinary sodium) were prospectively recorded. The severity of liver disease and the prognosis of the included patients were evaluated by estimating the CTP [4], MELD [5], and MELD-Na score [6], as well as the most recently proposed scores MELD 3.0 [9], GEMA, and GEMA-Na [10].

We followed the included patients, and their outcome (survival, death, or LT) was evaluated at the end of follow up. Survival was measured from the baseline (on admission) to date of death or LT, or last follow up. The study protocol conformed to the ethical guidelines of the 1995 Declaration of Helsinki. Informed consent was obtained from all participants prior to their enrollment in the study.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median with ranges, for normally and non-normally distributed values, respectively, while categorical variables were expressed as frequencies or percentages. Comparisons between patients were performed using Student's *t* or Mann-Whitney *U* tests, as appropriate, for continuous variables and the chi-square test for categorical variables. Multivariable Cox's proportional hazard model was used to identify independent factors associated with the outcome (death and/or LT) over

time, and cumulative overall survival was calculated to estimate the hazard ratios (HR). Factors with P<0.05 in the univariate Cox regression analysis were entered into the multivariate model. The discriminative ability of the prognostic scores to predict the outcome of patients with DeCi was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). This has the true-positive and false-positive rates on the vertical and horizontal axes, respectively. As the AUC approaches 1.0, the model approaches 100% sensitivity and specificity [13]. A P-value <0.05 was considered statistically significant. Statistical analysis was conducted using SPSS software (version 28.0 IBM) and comparison of ROC curves was performed using the MedCalc statistical software.

Results

A total of 694 patients with stable DeCi were evaluated: 489 (70.4%) males, mean age 55.3±11 years. Their baseline characteristics are shown in Table 1. The mean value of CTP score was 8.2±3 (range: 5-14). The etiology of cirrhosis was viral hepatitis in 201 (29%) patients and alcohol-related cirrhosis in 215 (31%) patients. A previous history of variceal bleeding, hepatic encephalopathy, SBP and HCC were recorded in 25%, 32%, 14% and 13% patients, respectively (Table 1). The median values of MELD, MELD-Na, MELD 3.0, GEMA and GEMA-Na were 14 (6-40), 16 (6-40), 15 (6-40), 14 (6-37) and 17 (8-37), respectively. The median follow-up time was 12 months (range: 4-52). During follow up, 197 (28.5%) patients died and 144 (21%) patients underwent LT, while 353 (50.5%) were still alive at the end of follow up.

The comparison between males and females is presented in Table 2. Interestingly, females had significantly lower MELD and MELD-Na scores compared to males, attributable to the significantly lower serum creatinine, since all the other components of prognostic scores, such as bilirubin, INR and Na, were similar between males and females. However, GEMA, GEMA-Na and MELD 3.0 scores were not different between males and females (Table 2), indicating that these scores were able to eradicate the creatinine-derived disparity between the 2 sexes. Finally, fewer women than men underwent LT during the follow-up period (23.5% vs. 39.2%, respectively, P=0.025).

Table 1 Baseline clinical and laboratory characteristics of 694 patients with cirrhosis admitted for evaluation for liver transplantation

Variable	Patients, n=694
Age, mean±SD (years)	55.3±11
Sex, male n (%)	489 (70.4)
Etiology of cirrhosis, n (%)	
Viral hepatitis	201 (29)
Alcohol	215 (31)
NASH/cryptogenic	124 (18)
Other	154 (22)
History of complications, n (%)	
GI bleeding	173 (25)
Encephalopathy	222 (32)
SBP	97 (14)
HCC, n (%)	90 (13)
Total bilirubin, median (range) (mg/dL)	1.9 (0.24-40)
Albumin, mean±SD (g/dL)	3.3±0.6
INR, mean±SD	1.51±0.5
Sodium, mean±SD (mEq/L)	136±13
Creatinine, mean±SD (mg/dL)	0.88±0.3
Platelets, median (range) ($\times 10^3/\mu L$)	85 (20-368)
Ferritin, median (range) (ng/mL)	140 (5-3398)
Natriuresis, median (range) (mEq/24h)	66 (1.5-380)
CTP score, mean±SD	8.2±3
MELD, mean±SD	15±6
MELD-Sodium, mean±SD	17±6
MELD 3.0, mean±SD	16±7
GEMA, mean±SD	15±5
GEMA-Sodium, mean±SD	18±6

CTP, Child-Turcotte-Pugh; GI bleeding, gastrointestinal bleeding; HCC, hepatocellular carcinoma; INR, international normalized ratio; NASH, nonalcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; SD, standard deviation; MELD, model for end-stage liver disease; GEMA, gender-equity model for liver allocation

Characteristics of patients who survived or died/underwent LT

The patients who survived, n=353 (50.5%), group 1, compared to those who died or underwent LT during follow up, n=341 (49.5%), group 2, had significantly higher baseline platelet counts (93 [range: 40-368] vs. 81 [range: 20-340] $\times 10^3/\mu L$, P<0.001), Na (137±3.8 vs. 135±5 mEq/L, P<0.001), albumin (3.5±0.7 vs. 3.2±0.5 g/dL, P<0.001), and natriuresis (85 [range: 3-380] vs. 61 [range: 1.5-210] mEq/24h, P=0.004), but lower bilirubin (1.3 [range: 0.24-23] vs. 2.4 [range: 0.29-40] mg/dL, P<0.001), INR (1.4±0.3 vs. 1.6±0.6, P=0.002) and ferritin (107 [range: 5-2500] vs. 184 [range: 9-3398] ng/mL, P<0.001). In addition, all prognostic scores (CTP, MELD, MELD-Na, MELD 3.0, GEMA, GEMA-Na) were significantly lower in group 1, compared to group 2 patients (Table 3).

Factors associated with the outcome: univariate and multivariate analysis

Univariate Cox regression analysis showed that SBP (HR 1.20, 95% confidence interval [CI] 1.01-1.03; P=0.04), INR (HR 1.21, 95%CI 1.098-1.324; P<0.001), creatinine (HR 1.47, 95%CI 1.14-1.91; P=0.003), total bilirubin (HR 1.065, 95%CI 1.045-1.086; P<0.001), Na (HR 0.991, 95%CI 0.98-0.997; P=0.004), albumin (HR 0.72, 95%CI 0.59-0.87; P<0.001) and ferritin (HR 1.1, 95%CI 1.0-1.21; P<0.001), were significant factors associated with the outcome (death or LT) (Table 4). In addition, CTP score (HR 1.22, 95%CI 1.15-1.30; P<0.001), MELD (HR 1.098, 95%CI

Table 2 Clinical and laboratory characteristics compared between males and females in our cohort of 694 patients with cirrhosis

Variables	Males (n=489, 70.4%)	Females (n=205, 29.6%)	P-value
Age, mean±SD (years)	55±10	54±13	0.55
Albumin, mean±SD (g/dL)	3.3±1.2	3.2±0.5	0.36
Bilirubin, median (range) (mg/dL)	2.2 (0.24-40)	2 (0.29-33)	0.17
INR, mean±SD	1.5±0.4	1.5±0.7	0.81
Sodium, mean±SD (mEq/L)	134±14	135±11	0.51
Creatinine, mean±SD (mg/dL)	1.1±0.5	0.8±0.3	<0.001
Natriuresis, median (range) (mEq/24h)	66 (5-380)	56 (3-210)	0.34
CTP score, mean±SD	8.3±2	7.9±2	0.14
MELD, mean±SD	15±7	14±5	0.02
MELD-Sodium, mean±SD	17.6±6	16±6	0.03
MELD 3.0, mean±SD	16±7	16±7	0.89
GEMA, mean±SD	15±5.5	15±5	0.93
GEMA-Sodium, mean±SD	18±6	17.8±5.5	0.56

CTP, Child-Turcotte-Pugh; GEMA, gender-equity model for liver allocation; GI bleeding, gastrointestinal bleeding; INR, international normalized ratio; MELD, model for end-stage liver disease; GEMA, gender-equity model for liver allocation; SBP, spontaneous bacterial peritonitis; SD, standard deviation

Table 3 Clinical and laboratory characteristics of patients who survived (Group 1) or died/underwent liver transplantation (Group 2)

Variables	Group 1 (n=353, 50.5%)	Group 2 (n=341, 49.5%)	P-value
Age, mean±SD (years)	54.7±10	55.6±11	0.64
Sex, male, n (%)	215 (61)	274 (80)	0.12
History of complications, n (%)			
GI bleeding	79 (22)	94 (27.5)	0.16
Encephalopathy	114 (33)	108 (31)	0.92
SBP	56 (16)	41 (12)	0.25
Albumin, mean±SD (g/dL)	3.5±0.7	3.2±0.5	<0.001
Protein, mean±SD (g/dL)	7.1±0.7	7.3±0.5	0.06
Bilirubin, median (range) (mg/dL)	1.3 (0.24-23)	2.4 (0.29-40)	<0.001
INR, mean±SD	1.4±0.3	1.6±0.6	0.002
Sodium, mean±SD (mEq/L)	137±3.8	135±5	<0.001
Creatinine, mean±SD (mg/dL)	0.9±0.4	0.81±0.3	0.36
Platelets, median (range) ($\times 10^3/\mu L$)	93 (40-368)	81 (20-340)	<0.001
Ferritin, median (range) (ng/mL)	107 (5-2500)	184 (9-3398)	<0.001
Natriuresis, median (range) (mEq/24h)	85 (3-380)	61 (1.5-210)	0.004
CTP score, mean±SD	7.5±2	8.5±2	<0.001
MELD, mean±SD	13±5	15.7±6	<0.001
MELD-Sodium, mean±SD	15±5.5	18.5±6.6	<0.001
MELD 3.0, mean±SD	14.3±5.7	17.8±7	<0.001
GEMA, mean±SD	13.5±4.5	16.2±5.8	<0.001
GEMA-Sodium, mean±SD	16±5	19±6.2	<0.001

CTP, Child-Turcotte-Pugh; GEMA, gender-equity model for liver allocation; GI bleeding, gastrointestinal bleeding; INR, international normalized ratio; MELD, model for end-stage liver disease; GEMA, gender-equity model for liver allocation; SBP, spontaneous bacterial peritonitis; SD, standard deviation

1.075-1.12; P<0.001), MELD-Na (HR 1.102, 95%CI 1.079-1.125; P<0.001), MELD 3.0 (HR 1.075, 95%CI 1.056-1.094; P<0.001), GEMA (HR 1.109, 95%CI 1.084-1.13; P<0.001) and GEMA-Na (HR 1.107, 95%CI 1.083-1.13; P<0.001) were associated with

Table 4 Clinical and laboratory characteristics of 694 patients with stable decompensated cirrhosis associated with the outcome (death or liver transplantation) (univariate analysis)

Variables	Hazard ratio	P-value	95%CI
Age	1.004	0.50	1.098-1.324
Sex (n, %)	1.15	0.62	0.92-1.22
SBP	1.20	0.04	1.098-1.324
Albumin	0.72	<0.001	0.59-0.87
Bilirubin	1.065	<0.001	1.045-1.086
INR	1.21	<0.001	1.098-1.324
Sodium	0.991	0.004	0.98-0.997
Creatinine	1.47	0.003	1.14-1.91
Platelets	1.0	0.29	1.0-1.0
Ferritin	1.1	<0.001	1.0-1.21
Natriuresis/24hs	0.99	0.24	0.99-1.001
CTP score	1.22	<0.001	1.15-1.30
MELD	1.098	<0.001	1.075-1.12
MELD-Sodium	1.102	<0.001	1.079-1.125
MELD 3.0	1.075	<0.001	1.056-1.094
GEMA	1.109	<0.001	1.084-1.13
GEMA-Sodium	1.107	<0.001	1.083-1.13

CI, confidence interval; CTP, Child-Turcotte-Pugh; GEMA, gender-equity model for liver allocation; INR, international normalized ratio; MELD, model for end-stage liver disease; GEMA, gender-equity model for liver allocation; SBP, spontaneous bacterial peritonitis; SD, standard deviation

the outcome (Table 4). Multivariate Cox regression analysis excluding the components of the prognostic scores (i.e., INR, bilirubin, creatinine, Na, and albumin), showed that GEMA-Na (HR 1.10, 95%CI 1.073-1.128; P<0.001) was the only factor independently associated with death/LT. Excluding the patients who underwent LT, GEMA-Na (HR 1.12, 95%CI 1.085-1.155; P<0.001) was again independently associated with mortality. Finally, excluding the patients with HCC, GEMA-Na was the only independent factor significantly associated with death/LT (HR 1.106, 95%CI 1.077-1.136; P<0.001) and mortality (HR 1.13, 95%CI 1.093-1.168; P<0.001).

Discriminative ability of prognostic scores including GEMA and GEMA-Na

The discriminative abilities of the prognostic scores were evaluated. Based on the area under the curve, GEMA-Na had the best discriminative ability to predict the outcome (death or LT) (AUC 0.698, 95%CI 0.647-0.750), followed by GEMA (AUC 0.692, 95%CI 0.640-0.744), MELD-Na (AUC 0.686, 95%CI 0.634-0.738) and MELD 3.0 (AUC 0.684, 95%CI 0.631-0.736) (Fig. 1A). However, these differences were not significant. Similarly, excluding the patients who underwent LT, GEMA-Na had the best discriminative ability for mortality (0.715, 95%CI 0.661-0.770) followed by GEMA (AUC 0.710, 95%CI 0.654-0.766), MELD 3.0 (AUC 0.704, 95%CI 0.648-0.760) and MELD-Na (AUC 0.701, 95%CI 0.645-0.757) (Fig. 1B). These differences were again not significant.

Performance of GEMA and GEMA-Na in different subgroups of patients

Interestingly, GEMA-Na was the only independent factor associated with the outcome in several subgroups, such as those with: a) MELD score ≥15 (HR 1.132, 95%CI 1.086-1.1042; P<0.001) with AUC 0.69; b) CTP score ≥7 (HR 1.105, 95%CI 1.073-1.138; P<0.001) with AUC 0.71; c) a previous history of SBP (HR 1.183, 95%CI 1.111-1.260; P<0.001) with AUC 0.81; d) viral-related cirrhosis (HR 1.12, 95%CI 1.072-1.171; P<0.001) with AUC 0.68; e) height <165 cm (HR 1.158, 95%CI 1.092-1.228; P<0.001) with AUC 0.74; and f) moderate/severe ascites (HR 1.339, 95%CI 1.157-1.549; P<0.001) with AUC 0.65. In those with MELD score <15, MELD-Na score was independently associated with the outcome (HR 1.123, 95%CI 1.043-1.289; P=0.002), while in patients with alcohol-related cirrhosis, GEMA was independently associated with the outcome (HR 1.171, 95%CI 1.10-1.247; P<0.001).

Discussion

In our study we investigated for the first time the association between GEMA and GEMA-Na scores and the long-term outcomes of patients with DeCi admitted for LT evaluation, and we compared the predictive ability of these new scores with that of the MELD-based scores (MELD, MELD-Na and the recently proposed MELD 3.0). Based on our findings, GEMA-Na showed the best performance in the entire cohort, as well as in several subgroups of patients with DeCi.

The MELD-Na score was implemented in 2016 as a variant of the original MELD score, corrected for Na, and it is currently the most widely used prognostic score for stratifying patients on the LT waiting list worldwide [6]. It is based on objective laboratory variables that are associated with the severity of liver disease, and several studies have demonstrated its utility in prioritizing patients for LT in the context of the sickest-first policy [14]. However, since women tend to have a lower muscle mass, and hence lower serum creatinine levels and MELD scores compared to men with the same severity of liver disease, a major drawback of the MELD-based allocation system is that it can lead to sex-related inequities in access to LT [8,15]. Thus, in the MELD-based allocation system, women are underserved compared to men, undergoing longer waiting times for LT and a higher risk of death [16]. Our study confirmed these findings since, compared to men, women had significantly lower MELD and MELD-Na scores, attributable to the lower values of serum creatinine, while all the other components of MELD and MELD-Na scores, as well as other variables associated with the severity of liver disease, were similar between men and women. This may explain the finding that, in our transplant centers, which used the MELD-Na based allocation system, fewer women than men underwent LT during the follow-up

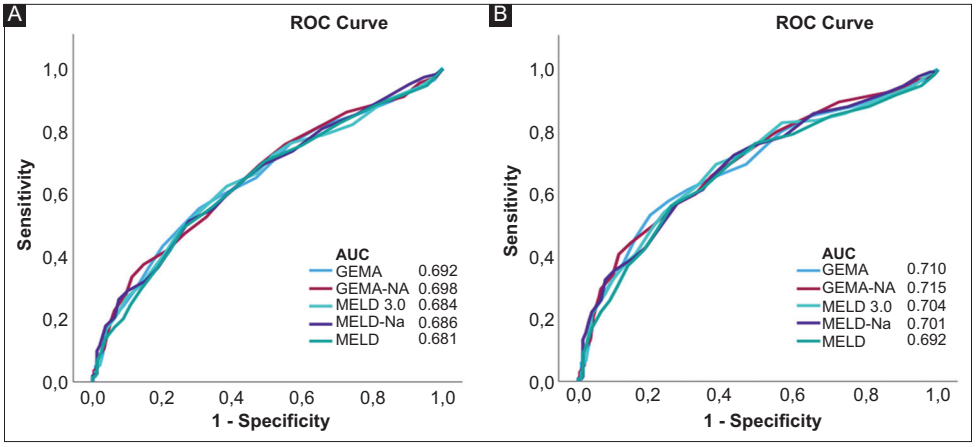

Figure 1 Receiver operator characteristic (ROC) curves for the discriminative ability of the prognostic scores in 694 patients with cirrhosis (A) to predict the outcome (death or liver transplantation), (B) to predict mortality
MELD, model for end-stage liver disease; Na, sodium; GEMA, gender-equity model for liver allocation

period (23.5% vs. 39.2%, respectively, P=0.025). In addition, the prognostic scores MELD 3.0, GEMA and GEMA-Na did not differ between men and women—as would be expected, since they were developed to overcome sex-related disparities.

In the original publication, the MELD 3.0 score showed better performance compared to MELD-Na, with the addition of 1.3 extra points to women [9], but its validation in several external cohorts revealed conflicting results [17-19]. In our study we were not able to confirm the superiority of MELD 3.0 over the MELD-Na score. The more recently proposed GEMA and GEMA-Na were developed in the United Kingdom [10], and they have been validated in 2 cohorts from Italy and Spain, with promising results regarding the risk of 3-month drop out from the LT waiting list [11,12]. However, the present study is the first to evaluate the prognostic association between GEMA and GEMA-Na and long-term outcomes (death and/or LT) using multivariate analysis, and to compare them with the other MELD-based prognostic scores. Thus, in our cohort with 12 (range: 4-52) months of follow up, GEMA-Na was found to be the only factor independently associated with the outcome (death and/or LT). In addition, because of the relatively long follow up, we had enough events to perform several subgroup analyses, which confirmed the independent association of GEMA-Na with the outcome in the case of those with the highest need for LT, such as those with MELD score ≥15, CTP ≥7 (i.e., CTP class B and C), or a previous history of SBP. Finally, GEMA-Na had the best discriminative ability, compared to the other scores, although the difference was not significant.

We acknowledge that there are some limitations, including our study's retrospective design. However, a large number of patients with DeCi were included, while their data were collected prospectively from the 2 LT centers in our country. In addition, we were not able to record information regarding the waiting time for LT, or the number of dropouts from the list due to deterioration of liver disease, in order to evaluate the performance of the prognostic scores on these issues. However, for the first time in the literature, the predictive association between GEMA and GEMA-Na scores and the long-term outcomes of LT candidates was assessed in comparison with other MELD-based scores.

In conclusion, our study (including all predictive models based on MELD and GEMA) showed for the first time that GEMA-Na was the only prognostic score independently associated with the outcome of patients with stable DeCi in the total cohort, as well as in several subgroups of LT candidates. However, further studies will be needed to validate these findings.

Summary Box

What is already known:

- The model for end-stage liver disease (MELD)-Sodium (MELD-Na) is widely used for stratification of patients on the waiting list for liver transplantation (LT)
- The MELD-Na based allocation system is associated with sex-related inequities, leading to higher mortality for women than for men on the waiting list for LT
- New prognostic scores, such as the MELD 3.0, the Gender-Equity Model for liver Allocation (GEMA) and GEMA-Na have been proposed to overcome this disparity

What the new findings are:

- For the first time in the literature, the predictive association between GEMA and GEMA-Na and the long-term outcomes of LT candidates was assessed, in comparison with the other MELD-based scores
- GEMA-Na was the only independent factor associated with the outcome (death/LT)
- GEMA-Na had the best performance in predicting the outcome in the total cohort, as well as in several subgroups of patients with cirrhosis

References

1. D'Amico G, Morabito A, D'Amico M, et al. New concepts on the clinical course and stratification of compensated and decompensated cirrhosis. *Hepatol Int* 2018;**12**:34-43.
2. Durand F, Valla D. Assessment of prognosis of cirrhosis. *Semin Liver Dis* 2008;**28**:110-122.
3. Cholongitas E, Germani G, Burroughs AK. Prioritization for liver transplantation. *Nat Rev Gastroenterol Hepatol* 2010;**7**:659-668.
4. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;**60**:646-649.
5. Wiesner R, Edwards E, Freeman R, et al; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003;**124**:91-96.
6. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008;**359**:1018-1026.
7. Cholongitas E, Marelli L, Shusang V, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. *Liver Transpl* 2006;**12**:1049-1061.
8. Cholongitas E, Marelli L, Kerry A, et al. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores—a systematic bias. *Am J Transplant* 2007;**7**:685-692.
9. Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: The model for end-stage liver disease updated for the modern era. *Gastroenterology* 2021;**161**:1887-1895.
10. Rodríguez-Perálvarez ML, Gómez-Orellana AM, Majumdar A, et al. Development and validation of the Gender-Equity Model for Liver Allocation (GEMA) to prioritise candidates for liver transplantation: a cohort study. *Lancet Gastroenterol Hepatol* 2023;**8**:242-252.
11. Marrone G, Giannelli V, Agnes S, et al. Superiority of the new sex-adjusted models to remove the female disadvantage restoring equity in liver transplant allocation. *Liver Int* 2024;**44**:103-112.
12. Rodríguez-Perálvarez ML, de la Rosa G, Gómez-Orellana AM, et al. GEMA-Na and MELD 3.0 severity scores to address sex disparities for accessing liver transplantation: a nationwide retrospective cohort study. *EClinicalMedicine* 2024;**74**:102737.
13. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;**148**:839-843.
14. Sacleux SC, Samuel D. A Critical Review of MELD as a Reliable Tool for Transplant Prioritization. *Semin Liver Dis* 2019;**39**:403-413.
15. Moylan CA, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. *JAMA* 2008;**300**:2371-2378.
16. Verna EC, Lai JC. Time for action to address the persistent sex-based disparity in liver transplant access. *JAMA Surg* 2020;**155**:545-547.
17. Yoo JJ, Kim SG, Kim YS, et al. Estimation of renal function in patients with liver cirrhosis: Impact of muscle mass and sex. *J Hepatol* 2019;**70**:847-854.
18. Duan F, Liu C, Zhai H, Quan M, Cheng J, Yang S. The Model for End-stage Liver Disease 3.0 is not superior to the Model for End-stage Liver Disease-Na in predicting survival: A retrospective cohort study. *Hepatol Commun* 2023;**7**:e0250.
19. Kim JH, Cho YJ, Choe WH, Kwon SY, Yoo BC. Model for end-stage liver disease-3.0 vs. model for end-stage liver disease-sodium: mortality prediction in Korea. *Korean J Intern Med* 2024;**39**:248-260.