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Model for End-Stage Liver Disease-Lactate and Prediction of Inpatient Mortality in Patients With Chronic Liver Disease

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BACKGROUND AND AIMS: Compared to other chronic diseases, patients with chronic liver disease (CLD) have significantly higher inpatient mortality; accurate models to predict inpatient mortality are lacking. Serum lactate (LA) may be elevated in patients with CLD due to both tissue hypoperfusion as well as decreased LA clearance. We hypothesized that a parsimonious model consisting of Model for End-Stage Liver Disease (MELD) and LA at admission may predict inpatient mortality in patients with CLD.

APPROACH AND RESULTS: We examined all patients with CLD in two large and diverse health care systems in Texas (North Texas [NTX] and Central Texas [CTX]) between 2010 and 2015. We developed (n = 3,588) and validated (n = 1,804) a model containing MELD and LA measured at the time of hospitalization. We further validated the model in a second cohort of 14 tertiary care hepatology centers that prospectively enrolled nonelective hospitalized patients with cirrhosis (n = 726). MELD-LA was an excellent predictor of inpatient mortality in development (concordance statistic [C-statistic] = 0.81, 95% confidence interval [CI] 0.79-0.82) and both validation cohorts (CTX cohort, C-statistic = 0.85, 95% CI 0.78-0.87; multicenter cohort C-statistic = 0.82, 95% CI 0.74-0.88). MELD-LA performed especially well in patients with specific cirrhosis diagnoses (C-statistic = 0.84, 95% CI 0.81-0.86) or sepsis (C-statistic = 0.80, 95% CI 0.78-0.82). For MELD score 25, inpatient mortality rates were 11.2% (LA = 1 mmol/L), 19.4% (LA = 3 mmol/L), 34.3% (LA = 5 mmol/L), and >50% (LA > 8 mmol/L). A linear increase (P < 0.01) was seen in MELD-LA and increasing number of organ failures. Overall, use of MELD-LA improved the risk prediction in 23.5% of patients compared to MELD alone.

CONCLUSIONS: MELD-LA (bswh.md/meldla) is an early and objective predictor of inpatient mortality and may serve as a model for risk assessment and guide therapeutic options. (Hepatology 2020;72:1747-1757).

Liver disease accounts for approximately 2 million deaths per year worldwide; furthermore, chronic liver disease (CLD)–related morbidity and mortality are underestimated and expected

Abbreviations: BSWH, Baylor Scott and White Health; CI, confidence interval; CLD, chronic liver disease; C-statistic, concordance statistic; CTX, Central Texas Division; HE, hepatic encephalopathy; ICU, intensive care unit; LA, lactate; MELD, Model for End-Stage Liver Disease; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; NLR, neutrophil to lymphocyte ratio; NRI, net reclassification index; NTX, North Texas Division.

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to increase.[1] A significant number of encounters for patients with CLD occur in the inpatient setting. Compared to other chronic diseases, CLD demonstrates significantly higher inpatient mortality; however accurate models to predict inpatient mortality are lacking.[2] Model for End-Stage Liver Disease (MELD), the most commonly used predictive model, is an excellent predictor of mortality for stable outpatients[3] but does not perform well in the inpatient setting.[4] MELD, which comprises bilirubin, international normalized ratio, and creatinine, does not consider other conditions that are associated with poor prognosis such as poor tissue perfusion, especially in critically ill patients. Other prognostic scoring systems have been used, based either on categorizing the degree of liver disease (Child-Pugh score)[5] or on overall clinical severity (Acute Physiology and Chronic Health Evaluation II [APACHE II][6]). However, these other scoring systems often are cumbersome to use, include subjective measures of disease severity, are applicable only in the intensive care setting (e.g., APACHE score), or may be more reflective of clinical course (e.g., number of organ failures) rather than predictive at the time of initial hospitalization.[7,8] Simple, objective prognostic tools such as neutrophil to lymphocyte ratio (NLR) have been studied[9]; however, this system lacks specificity to liver disease and may be confounded by variables such as nutritional status, type of liver disease,[10] and age. Having accurate, early, and objective prediction of mortality with parsimonious variables is important for risk assessment, guiding therapeutic options, allocating resources, and potentially mitigating premature mortality.

Elevated serum lactate (LA) levels have been associated with poor outcomes[11] and may help predict mortality in patients with CLD. Among patients with CLD, LA may be elevated due to both tissue hypoperfusion in the critically ill patient as well as decreased LA clearance in the setting of advanced liver and renal disease.[12] It may therefore capture an element of disease severity not captured by MELD score alone. LA predicts mortality in relevant subsets of patients including those with trauma,[13] pneumonia,[14] decompensated heart failure,[15] and gastrointestinal bleeding.[16] LA is a predictor of mortality in critically ill patients with CLD[17]; however, its role in overall (both intensive care unit [ICU] and non-ICU) patients with CLD is unknown. The addition of LA to existing prediction models may improve their prognostic value.[18]

The primary aim of the study was to develop and validate a parsimonious model to predict inpatient mortality in patients with CLD based on objective surrogates of disease severity present at admission, namely MELD score and serum LA.

Methods

DEVELOPMENT COHORT

Baylor Scott and White Health (BSWH) is one of the largest integrated health care systems in the United States. Data from patients in the North Texas Division (NTX) region were used for model development, while those from the Central Texas Division (CTX) region were used for primary validation. During the study period, these two health care populations had minimal overlap.

The NTX of BSWH serves the Dallas-Fort Worth Metroplex and surrounding communities (including 16 hospitals with a catchment area of 7 million individuals and over 130,000 annual hospitalizations).

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The Dallas-Fort Worth Metroplex is the largest metropolitan area in Texas and the fourth largest metropolitan area (out of 382) in the United States.

VALIDATION COHORT 1

The CTX of BSWH serves the Austin/Round Rock, Hill Country, College Station, Waco, and Temple regions and surrounding communities (including 14 hospitals with a catchment area of 2.7 million individuals and over 60,000 annual hospitalizations). Compared to NTX, the area encompasses a more rural population and does not have direct access to liver transplantation within its region.

VALIDATION COHORT 2

The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) consists of 14 tertiary care hepatology centers in the United States and Canada that prospectively enrolled nonelective hospitalized patients with cirrhosis.[19,20]

CASE ASCERTAINMENT

We examined all CLD-related hospitalizations from 2010 to 2015 among adult patients (≥18 years) in the BSWH system. Discharge diagnoses were classified in accordance with the *International Classification of Diseases*, Ninth Revision (ICD-9). Based on prior studies, we classified a hospitalization as a CLD-related hospitalization if it was associated with (1) a primary diagnosis of CLD (e.g., cirrhosis) as the underlying reason for hospitalization or (2) a secondary related complication associated with CLD (e.g., sepsis or hepatic encephalopathy [HE]) as the underlying reason for hospitalization in combination with a primary diagnosis of CLD (e.g., alcoholic cirrhosis or viral hepatitis).[2]

Of all patients with such hospitalizations, we examined all patients who had laboratory evaluation to calculate MELD (bilirubin, creatinine, international normalized ratio) as well as serum LA measured within 24 hours of admission. Similar criteria were applied to the two validation cohorts.

Statistical Methods

Patients' characteristics, clinical variables, and outcomes in the development and validation cohorts were summarized by mean and standard deviation (or median with interquartile range) for continuous variables and percent or proportion for categorical variables. Differences between the two cohorts were assessed by *t* tests or Kruskal-Wallis rank sum tests for continuous variables and chi-squared test for categorical variables.

PREDICTIVE MODEL BUILDING

Using the development data set, we modeled in-hospital mortality as the dependent variable in a multivariable logistic regression model to determine risk factors predictive of mortality. The primary variables of interest *a priori* were MELD score and serum LA. However, we considered other factors that may be associated with inpatient mortality. Independent variables considered in the initial model included sex, age, race, MELD score,[21] LA,[11] Charlson's comorbidity index,[22] alcoholic hepatitis,[23] HE,[24] ascites,[25] varices,[26] malignancy, cirrhosis,[27] and interaction between MELD and LA. We applied a backward variable selection algorithm to the initial model and obtained a reduced model that retained MELD, LA, age, HE, cirrhosis, and alcoholic hepatitis as significant predictors of mortality. We assessed further models with a subset of variables from the reduced model and evaluated their performance. For each model, we obtained Brier scores and concordance statistics (C-statistics) to compare model prediction accuracy and goodness of fit.[28-30] We also obtained Akaike information and Bayesian information criteria to assess the quality of each model relative to others and guide in determination of the most parsimonious model.[30,31] Supporting Table S1 summarizes prediction accuracy, goodness of fit, and selection criteria for the different models evaluated. The model with MELD and LA provided the best trade-off between goodness of fit, simplicity, and objective data and was considered for further evaluation. Though age was important, it did not markedly improve overall performance (Supporting Fig. S1). We investigated for interaction between MELD and LA and found no significant statistical interaction.

We observed a nonlinear relationship between the two predictors (MELD and LA) and risk of mortality. Hence, we developed the final model with restrictive cubic splines with four knots on the continuous predictors to account for nonlinearity.[32]

Based on the estimates from the final model, we developed a nomogram with point scoring system for ease of application.[33,34] For each predictor, "points" were assigned and rescaled to range from 0 to 25. The points from each predictor were then summed to obtain "total points," which ranged from 0 to 40. The total points were used to obtain the corresponding probability of death (bswh.md/meldla).

MODEL VALIDATION AND PERFORMANCE

The predictive model was validated against two independent data sets (CTX and NACSELD). We obtained C-statistics to quantify the discrimination ability of the model. Measures of discrimination assess the extent to which a model predicts a higher probability of having an event among patients who will compared to those who will not have the event. We also obtained a Brier score as a measure of accuracy of the prediction model. The Brier score ranges from 0 to 1, with 0 implying excellent calibration of the predictive model and 1 implying suboptimal calibration.[28] The performance of the model was also compared to models that considered MELD alone or LA alone. We further evaluated performance of the final model on a subset of patients that included those with alcohol-related hepatitis only and patients admitted to the ICU.

We assessed the calibration to quantify the extent to which absolute risk (predicted versus observed) is correctly estimated by a model (e.g., MELD-LA) compared to the old model (MELD). We calculated the absolute net reclassification index (NRI).[35] The absolute NRI calculates the absolute number of patients correctly reclassified and consists of the net reclassification of patients with the event (correctly identify patients with inpatient mortality) and net reclassification of patients without the event (correctly identify patients alive) divided by the total number of patients. It ranges from −100% to 100% and represents the percent of patients incorrectly or correctly reclassified. In addition, we compared the performance to other competing models that are available at the time of admission to include MELD-Na and NLR.

Data were analyzed using SAS, version 9.4 (SAS Institute Inc., Cary, NC), and R[34,36] statistical programs, with $P < 0.05$ considered statistically significant. The study was approved by the institutional IRB and exempt from human subject review.

Results

BASELINE DEMOGRAPHICS

Between 2010 and 2015, there were 14,733 CLD-related hospitalizations in the development data set. Of those, 5,614 (38%) patients had LA measured on admission and 3,588 (24%) had both LA and parameters for calculating MELD. Table 1 summarizes the characteristics of patients in the development and primary validation cohorts. The overall mean age was 58.2 years (SD, 13.1), 43% were women, 16.5% were African American, and 16.3% were of Hispanic ethnicity. The most common cause of hospitalization was sepsis, alcoholic cirrhosis, and hepatitis C. The mean MELD score was 18.2 (SD, 8.4), and the median LA was 2.4 mmol/L (interquartile range 1.5-3.9). Overall inpatient mortality was 17.2%.

RELATION BETWEEN MELD AND LA

A nonlinear relationship existed between the two continuous predictors (MELD and LA) and risk of inpatient mortality. The adjusted risk of mortality was constant for patients with MELD 6-15 and then increased linearly for those with MELD > 15. Similarly, the adjusted risk of mortality increased linearly with LA levels, but the rate of change was higher for LA ≤10 mmol/L compared to patients with LA >10 mmol/L (Fig. 1).

The impact of LA varied by severity of liver disease as captured by the MELD score (Fig. 2). As an example, for a MELD of 15, associated inpatient mortality was 15%, 47%, and 62% for LA 5, 15, and 25 mmol/L, respectively. For a MELD of 25, associated inpatient mortality was 32%, 70%, and 81% for LA 5, 15, and 25 mmol/L, respectively.

TABLE 1. Baseline Characteristics of Hospitalized Patients With Measured LA and MELD Score at Admission in the Development (NTX) and Validation (CTX and NACSELD) Cohorts

	Total NTX and CTX (n = 5,392)	NTX (n = 3,588)	CTX (n = 1,804)	*P* (NTX to CTX)	NACSELD (n = 726)	*P* (NTX to NACSELD)
Age (years)	58.2 ± 13.1*	58.1 ± 13.2*	58.4 ± 13.0*	0.475‡	57.5 ± 11.1	0.264‡
Female sex	2316 (43.0%)	1538 (42.9%)	778 (43.1%)	0.855§	258 (35.5%)	<0.0003§
Race				<0.001§		<0.001§
White	3221 (59.7%)	2050 (57.1%)	1171 (64.9%)		517 (71.2%)	
Black	890 (16.5%)	660 (18.4%)	230 (12.7%)		78 (10.7%)	
Hispanic	877 (16.3%)	561 (15.6%)	316 (17.5%)		60 (8.3%)	
Other	404 (7.5%)	317 (8.8%)	87 (4.8%)		71 (9.8%)	
Payer, n (%)				<0.001§		<0.001§
Commercial	1628 (30.2%)	1276 (35.6%)	352 (19.5%)		186 (25.6%)	
Medicaid	391 (7.3%)	159 (4.4%)	232 (12.9%)		66 (9.1%)	
Medicare	2476 (45.9%)	1638 (45.7%)	838 (46.5%)		339 (46.7%)	
Self pay/ uninsured	700 (13.0%)	475 (13.2%)	225 (12.5%)		81 (11.2%)	
Other	197 (3.7%)	40 (1.1%)	157 (8.7%)		54 (7.4%)	
Charlson's index	5.7 (2.9)	5.7 (2.9)	5.6 (3.0)	0.135‡	n/a	n/a
Alcoholic hepatitis	323 (6.0%)	194 (5.4%)	129 (7.2%)	0.011§	51 (7.3%)	0.085§
HE	1765 (32.7%)	1295 (36.1%)	470 (26.1%)	<0.001§	124 (17.3%)	<0.001§
Ascites	1512 (28.0%)	1096 (30.5%)	416 (23.1%)	<0.001§	200 (27.6%)	0.108§
Varices	2384 (44.2%)	1686 (47.0%)	698 (38.7%)	<0.001§	309 (42.6%)	0.029§
Neoplasm	358 (6.6%)	262 (7.3%)	96 (5.3%)	0.006§	n/a	n/a
Disposition				<0.001§		<0.001§
Expired	927 (17.2%)	705 (19.6%)	222 (12.3%)		35 (4.8%)	
Home	2,457 (45.6%)	1,641 (45.7%)	816 (45.2%)		570 (78.5%)	
Hospice	392 (7.3%)	284 (7.9%)	108 (6.0%)		33 (4.6%)	
Transfer to higher care	147 (2.7%)	92 (2.6%)	55 (3.0%)		0 (0.0%)	
Transfer to home health	493 (9.1%)	263 (7.3%)	230 (12.7%)		0 (0.0%)	
Transfer to SNF or rehab	633 (11.7%)	392 (10.9%)	241 (13.4%)		70 (9.6%)	
Other	343 (6.4%)	211 (5.9%)	132 (7.3%)		18 (2.5%)	
Bilirubin	1.6 (0.8, 3.4)†	1.7 (0.8, 3.9)†	1.3 (0.7, 2.7)†	<0.001¶	2.5 (1.3, 5.5)†	<0.001¶
Creatinine	1.3 (0.9, 2.2)†	1.4 (1.0, 2.5)†	1.1 (0.8, 1.8)†	<0.001¶	1.1 (0.8, 1.6)†	<0.001¶
INR	1.4 (1.2, 1.8)†	1.4 (1.2, 1.8)†	1.3 (1.1, 1.7)†	<0.001¶	1.5 (1.3, 1.9)†	<0.001¶
Lactate	2.4 (1.5, 3.9)†	2.6 (1.7, 4.3)†	2.0 (1.3, 3.1)†	<0.001¶	2.2 (1.6, 3.2)†	<0.001¶
MELD score	18.2 ± 8.4*	19.2 ± 8.4*	16.2 ± 7.9*	<0.001‡	18.7 ± 7.3*	<0.001‡

*Mean ± standard deviation.
†Median (interquartile range).
‡Student *t* test.
§Chi-squared test.
¶Kruskal-Wallis rank sum test.
Abbreviation: INR, international normalized ratio; n/a, not available; SNF, skilled nursing facility.

MELD-LA MODEL

MELD-LA was an excellent predictor of inpatient mortality in the development cohort (C-statistic = 0.81, 95% confidence interval [CI] 0.79-0.82). Figure 3 shows the relationship between probability of mortality and scores obtained from the model developed by MELD-LA. There was a linear increase in risk of mortality with increasing MELD-LA. The risk prediction calculator from the final model is provided as a nomogram with a point scoring system (Supporting Fig. S2). Table 2 summarizes the findings

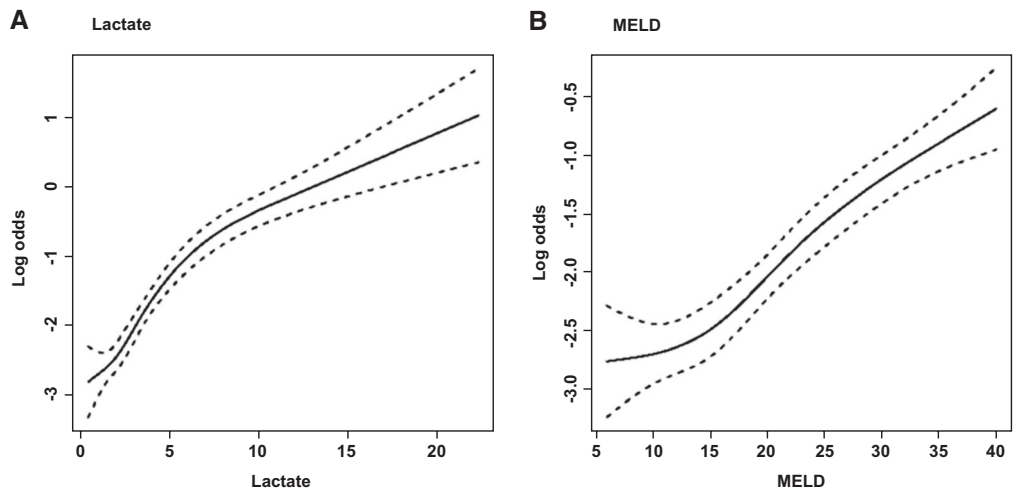

FIG. 1. (A) Relationship between LA and log odds of inpatient mortality. (B) Relationship between MELD score and log odds of inpatient mortality.

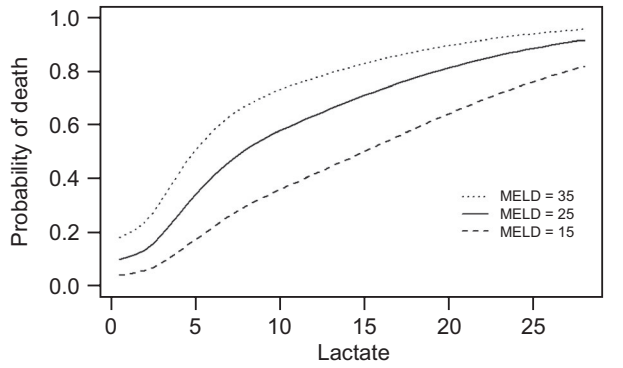

FIG. 2. In-hospital mortality by LA and ranges of MELD values.

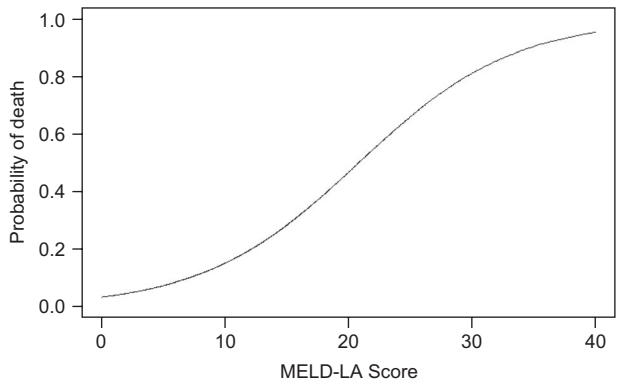

FIG. 3. MELD-LA score and probability of inpatient mortality.

TABLE 2. Probability of Inpatient Mortality by MELD and LA Levels Based on the MELD-LA Score (Nomogram Is Provided in Supporting Fig. S2)

	LA												
MELD	0.5	1	2	3	4	5	6	7	8	10	12	15	20+
6	3.6%	3.9%	4.9%	7.2%	10.6%	14.4%	18.2%	21.9%	25.2%	30.8%	35.9%	44.2%	58.5%
10	3.8%	4.1%	5.2%	7.6%	11.1%	15.1%	19.1%	22.8%	26.3%	32.0%	37.3%	45.6%	59.9%
15	4.5%	5.0%	6.2%	9.0%	13.2%	17.7%	22.2%	26.4%	30.2%	36.3%	41.9%	50.4%	64.4%
20	6.8%	7.4%	9.2%	13.3%	18.9%	24.9%	30.6%	35.6%	39.9%	46.8%	52.6%	61.0%	73.6%
25	10.3%	11.2%	13.8%	19.4%	26.9%	34.3%	40.9%	46.5%	51.1%	58.0%	63.6%	71.1%	81.4%
30	14.2%	15.4%	18.7%	25.7%	34.6%	42.9%	49.9%	55.6%	60.1%	66.6%	71.5%	78.0%	86.3%
35	18.5%	20.0%	24.0%	32.2%	42.1%	50.7%	57.8%	63.2%	67.4%	73.2%	77.5%	83.0%	89.6%
40	23.6%	25.3%	30.1%	39.2%	49.6%	58.3%	65.0%	70.0%	73.7%	78.8%	82.4%	86.9%	92.2%

Color coding for severity of mortality: Green: <10%; Yellow: 10-<20%; Orange: 20-<40%; Bright Red: 40-<60%; Dark Red: >60%.

for select cutoffs of MELD and LA based on the MELD-LA score.

CONSIDERATION OF ALTERNATE MODELS

MELD-Na

The performance of the MELD-Na model (C-statistic = 0.73 95% CI 0.71-0.75) in our data was not better than that of the MELD score (C-statistic = 0.74 95% CI 0.72-0.75). A model combining MELD-Na with LA (C-statistic = 0.80, 95% CI 0.78-0.82) did not improve performance when compared to the MELD-LA model (C-statistic = 0.81, 95% CI 0.79-0.83).

NLR

The performance and predictive accuracy of the NLR were suboptimal (C-statistics = 0.62 and Brier score = 0.146).

We compared MELD-LA at admission to subsequent development of organ failure over the clinical course. There was a linear increase ($P < 0.01$) in MELD-LA score with increasing number of organ failures (Fig. 4).

Validation Cohort 1, CTX

There was a lower absolute number of hospitalizations; however, patient demographics were similar between the development and validation cohorts (Table 1). Inpatient mortality was significantly lower (12.3% versus 19.6%, $P < 0.001$). The median LA was lower (2.0 versus 2.6 mmol/L, $P \leq 0.001$), and the mean MELD score was lower (16.2 versus 19.2, $P \leq 0.001$). Despite being a less sick cohort, the performance of MELD-LA was similarly excellent with a C-statistic of 0.85 (95% CI 0.78-0.87). The Brier score was also similar between cohorts (0.084), suggesting minimal variation in performance between the two data sets.

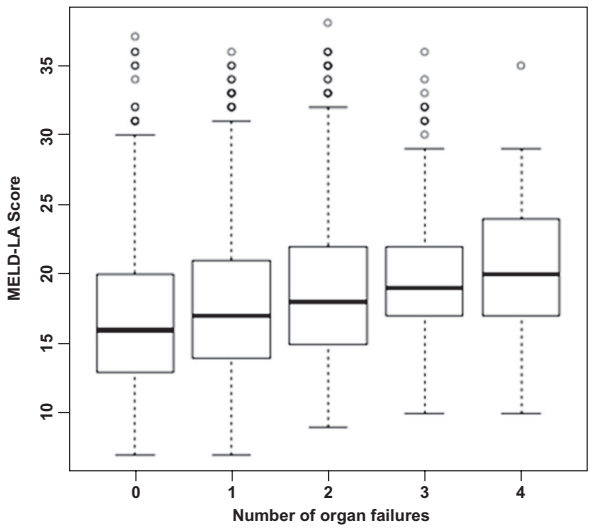

FIG. 4. Relationship between derived MELD-LA score and number of organ failures among ICU patients ($P < 0.01$).

Validation Cohort 2, NACSELD

Of 3,057 patients in the NACSELD multicenter study, 726 subjects met study criteria and had complete data for ascertainment of study outcome (Table 1). Inpatient mortality was 4.8%. MELD-LA was an excellent predictor of inpatient mortality (C-statistic = 0.82, 95% CI 0.74-0.88), similar to the current validation group. Performance for the MELD score was C-statistic = 0.76 (95% CI 0.67-0.83).

Subsets

We examined the performance within relevant subsets. Performance may vary by disease severity. Performance among ICU admissions (C-statistic = 0.74 95% CI 0.72-0.76), those only with alcohol-related hepatitis (C-statistic = 0.77, 95% CI 0.67-0.88), or those with a specific cirrhosis diagnosis (C-statistic = 0.84, 95% CI 0.81-0.86) or sepsis (C-statistic = 0.80, 95% CI 0.78-0.82) was excellent. LA may be influenced by the presence of patients with cancer. After exclusion, the performance of the MELD-LA still was excellent (C-statistic = 0.80, 95% CI 0.78-0.82).

Calibration

Finally, we examined the absolute NRI to quantify differences in observed versus predicted events. Overall, use of MELD-LA improved the risk prediction in 23.5% of the patients compared to MELD alone. This implies that risk stratification at the time of admission by MELD-LA would have impacted 798 patients during the study. Net reclassification was higher than incorporation of MELD-Na (+18.2%) or simply examination of LA alone (+5.1%). The net reclassification of our model compared to the NLR was +27%, implying that MELD-LA would have reclassified 990 patients compared to the NLR.

Discussion

A disproportionate amount of treatment and care for CLD and cirrhosis is provided in the inpatient setting; mortality for CLD remains significant and persistently higher than that for other chronic diseases.[2] The MELD score is an imperfect predictor of inpatient mortality. We sought to develop and validate a parsimonious and objective model to predict inpatient mortality in patients with CLD. Both MELD score and serum LA were associated with an increased risk of mortality. MELD-LA assessed at the time of hospitalization was an excellent predictor of inpatient mortality both in development and in two independent, large, and diverse validation data sets. The independent impact of LA varied based on disease severity, as adjudicated by the MELD score. MELD-LA outperformed MELD alone, LA alone, MELD-Na-based, models and the NLR. Based on risk reclassification analysis, MELD-LA improved risk prediction for 23.5% of patients compared to MELD alone. Clinically, this would have impacted risk prediction for 798 patients during the study. Additionally, our study showed that the same LA levels were associated with higher levels of mortality, dependent on the disease severity; e.g., a lactate of 3 mmol/L carried a worse prognosis in a patient with a MELD of 30 than in a patient with a MELD of 15. In addition, MELD-LA correlated with increasing number of organ failures. MELD-LA (bswh.md/meldla) may serve as a putative model for risk stratification at the time of hospitalization.

Incorporation of MELD-LA has several advantages. Addition of LA may capture an element of disease severity not entirely encompassed by the MELD score. It is agnostic of subjective factors (ICU care), patient demographics, or underlying disease process. It is easily measured at the time of hospitalization and may help identify subjects at highest risk prior to identification of triggers. There are several potential applications and implications of MELD-LA. First, it may help stratify patients who may need higher levels of care or earlier interventions. Though many surrogates of critical illness exist (frailty, ascites, HE), these may be subjective at the time of presentation and are more reflective of the current state of health. With LA being a predictor of all-cause mortality in critically ill patients,[37] the inclusion of LA and its elevation may more accurately represent both liver disease and systemic damage occurring in CLD. Second, a majority of patients with CLD present with sepsis and septic shock. Traditional LA cutoffs for hospitalized patients *without* liver disease may not apply to patients with CLD.[38] Hence, guidelines for sepsis management of critically ill patients for CLD may need further refinement to tangibly impact outcomes. Finally, MELD-LA scores at admission and during the hospital course may identify patients who are nonresponders to therapy. This may allow for earlier discussion regarding introduction of palliative care.

Inclusion of LA adds a physiologic explanation for severity of disease and increased mortality risk. LA's prognostic use has been well established in the literature[13-16] as well as in selected subsets with cirrhosis[39]; however, this study sheds light on the unique relationship between LA and all comers with liver disease. Lactic acidosis, a persistent elevation of blood LA, is most commonly related to tissue hypoperfusion and hypoxia.[40] However, in patients with CLD, the copresence of LA elevation not associated with hypoperfusion may be contributing. The liver is intimately involved in LA clearance, with 40%-60% being removed by gluconeogenesis.[41] Due to impairment in tissue oxygenation and hepatocellular damage in patients with CLD, gluconeogenesis is impaired, decreasing LA clearance.[41] In settings that may involve hemodynamic permutations (e.g., sepsis), the issue is exacerbated and patients with CLD may be more prone to lactic acidosis. Hence, among patients with CLD, LA may be elevated due to both tissue hypoperfusion and hypoxia (in hepatic and extrahepatic endothelial beds) as well as to decreased LA clearance in the setting of advanced liver disease.[12]

Our study has several strengths. We were able to capture a broad spectrum of patients admitted for complications of CLD in one of the largest metropolitan health networks. Additionally, we were able to validate our model and show external generalizability in an independent cohort that was more rural and less critically ill with minimal overlap between the health care systems. We further validated our findings in a prospective study of patients with cirrhosis across 14 centers with lower inpatient mortality rates. Referral bias and spectrum bias were minimized by considering all hospitalized patients and not simply including tertiary centers with liver transplantation. Our study adds to the existing literature looking at the role of LA in patients with cirrhosis. Prior studies have

explored its role limited to critically ill patients, especially those who are either already in the ICU or may have acute on chronic liver failure.[12,17] Performance among those already in the ICU was similar in our study to what was seen in the literature. We were able to expand and start the measurement from the time of hospitalization regardless of ICU status and explored a wider range of LA measurements. We included MELD score rather than prior subjective models.[5,17] We also included serum LA rather than arterial LA in the expanded cohort. The former is easier to obtain and readily available, and there appears to be a strong correlation between arterial and venous LA[42]; however, this correlation has not been studied in liver patients. In addition, patterns of LA distribution described in the study may have implications for management of septic shock in patients with CLD. Consensus guidelines suggest that a serum LA level >2 mmol/L after adequate fluid resuscitation identifies unselected patients with septic shock.[38] Given the higher median LA on admission in patients with CLD, a different threshold and different definitions of response to therapy may be required for this population.

Our study has limitations. Inpatient mortality rates were high among patients who had serum LA measured. As expected, those who underwent LA measurement were systematically different from those who did not undergo measurement. The mean age of those who did not have measurement was slightly younger at 57.2 years (SD, 12.7). Sepsis as a cause for admission was significantly lower (44.2% versus 78.0%), and ICU hospitalization was lower (23% versus 55%, $P < 0.01$). Inpatient mortality was also lower at 4.9%. However, validation in two separate cohorts with lower mortality (CTX, 12.3%; NACSELD, 4.8%) provides further credence. We were unable to assess whether LA would play a role among patients without cause for measurement. This would require collection in all patients with CLD, which would need to be incorporated at the system level. A future prospective validation is needed whereby LA is measured in all patients with CLD presenting to the emergency room to address this limitation. The model may overestimate mortality in unselected hospitalized patients with CLD. Use of ICD coding to determine CLD admissions lacks specificity and is subject to diagnosis bias at the time of admission. However, we included a broader definition of CLD to improve case ascertainment as previously done[2,43]; the highest accuracy was noted for patients with cirrhosis.

In summary, MELD-LA may serve as a parsimonious and objective model to identify inpatients with CLD at highest risk for mortality regardless of ICU status. Early prediction may allow for earlier identification of patients with CLD who may benefit from escalation of care and can also assist in starting early goal-directed therapy. Alternatively, it may identify patients at highest risk for mortality and aid in discussion of prognosis. Further independent validation in prospective studies with unbiased LA measurements and application in relevant subsets (e.g., alcohol-related hepatitis and risk-stratifying patients with acute on chronic liver failure), evaluation of change in scores over time, and comparison to alternate models in the ICU are highly encouraged.

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REFERENCES

1) Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70:151-171.
2) Asrani SK, Kouznetsova M, Ogola G, Taylor T, Masica A, Pope B, et al. Increasing health care burden of chronic liver disease compared with other chronic diseases, 2004-2013. Gastroenterology 2018;155:719-729.e714.
3) Botta F, Giannini E, Romagnoli P, Fasoli A, Malfatti F, Chiarbonello B, et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. Gut 2003;52:134-139.
4) Durand F, Valla D. Assessment of prognosis of cirrhosis. Semin Liver Dis 2008;28:110-122.
5) 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.
6) Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-829.
7) Peng Y, Qi X, Guo X. Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Medicine (Baltimore) 2016;95:e2877.
8) Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: the model for end-stage liver disease—should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther 2005;22:1079-1089.
9) Rice J, Dodge JL, Bambha KM, Bajaj JS, Reddy KR, Gralla J, et al. Neutrophil-to-lymphocyte ratio associates independently with mortality in hospitalized patients with cirrhosis. Clin Gastroenterol Hepatol 2018;16:1786-1791.e1781.
10) Alkhouri N, Morris-Stiff G, Campbell C, Lopez R, Tamimi TA, Yerian L, et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2012;32:297-302.
11) Tuchschmidt J, Fried J, Swinney R, Sharma OP. Early hemodynamic correlates of survival in patients with septic shock. Crit Care Med 1989;17:719-723.
12) Edmark C, McPhail MJ, Bell M, Whitehouse T, Wendon J, Christopher KB. LiFe: a liver injury score to predict outcome in critically ill patients. Intensive Care Med 2016;42:361-369.
13) Raux M, Le Manach Y, Gauss T, Baumgarten R, Hamada S, Harrois A, et al. Comparison of the prognostic significance of initial blood lactate and base deficit in trauma patients. Anesthesiology 2017;126:522-533.
14) Gwak MH, Jo S, Jeong T, Lee JB, Jin YH, Yoon J, et al. Initial serum lactate level is associated with inpatient mortality in patients with community-acquired pneumonia. Am J Emerg Med 2015;33:685-690.
15) Kawase T, Toyofuku M, Higashihara T, Okubo Y, Takahashi L, Kagawa Y, et al. Validation of lactate level as a predictor of early mortality in acute decompensated heart failure patients who entered intensive care unit. J Cardiol 2015;65:164-170.
16) Shah A, Chisolm-Straker M, Alexander A, Rattu M, Dikdan S, Manini AF. Prognostic use of lactate to predict inpatient mortality in acute gastrointestinal hemorrhage. Am J Emerg Med 2014;32:752-755.
17) Drolz A, Horvatits T, Rutter K, Landahl F, Roedl K, Meersseman P, et al. Lactate improves prediction of short-term mortality in critically ill cirrhosis patients: a multinational study. Hepatology 2019;69:258-269.
18) Cardoso NM, Silva T, Basile-Filho A, Mente ED, Castro-e-Silva O. A new formula as a predictive score of post-liver transplantation outcome: postoperative MELD-lactate. Transplant Proc 2014;46:1407-1412.
19) O'Leary JG, Reddy KR, Garcia-Tsao G, Biggins SW, Wong F, Fallon MB, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018;67:2367-2374.
20) Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) experience. Hepatology 2012;56:2328-2335.
21) Roth JA, Chrobak C, Schadelin S, Hug BL. MELD score as a predictor of mortality, length of hospital stay, and disease burden: a single-center retrospective study in 39,323 inpatients. Medicine (Baltimore) 2017;96:e7155.
22) Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288-1294.
23) Orrego H, Blake JE, Blendis LM, Medline A. Prognosis of alcoholic cirrhosis in the presence and absence of alcoholic hepatitis. Gastroenterology 1987;92:208-214.
24) Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol 1999;30:890-895.

25) Ennaifer R, Elleuch N, Romdhane H, Hefaiedh R, Cheikh M, Chaabouni S, et al. Prognosis of refractory ascites in cirrhosis. Tunis Med 2016;94:12-15.
26) Sharara AI, Rockey DC. Gastroesophageal variceal hemorrhage. N Engl J Med 2001;345:669-681.
27) Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 2018;362:k2817.
28) Brier GW. Verification, of forecasts expressed in terms of probability. Mon Weather Rev 1950;78:1-3.
29) Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
30) Akaike H. A new look at the statistical model identification. In: Parzen E, Tanabe K, Kitagawa G, eds. Selected Papers of Hirotugu Akaike. New York, NY: Springer; 1974:215-222.
31) Schwarz G. Estimating the dimension of a model. Ann Statist 1978;6:461-464.
32) Harrell FE. Resampling, validating, describing, and simplifying the model. In: Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York, NY: Springer; 2001:87-103.
33) Banks J. Nomograms. In: Balakrishnan N, Everitt B, Piegorsch W, Ruggeri F, Teugels JL, eds. Wiley StatsRef: Statistics Reference Online. Hoboken, NJ: Wiley; 2014. https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118445112.stat02304
34) Lubsen J, Pool J, van der Does E. A practical device for the application of a diagnostic or prognostic function. Methods Inf Med 1978;17:127-129.
35) Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, et al. Discrimination and calibration of clinical prediction models: users' guides to the medical literature. JAMA 2017;318:1377-1384.
36) R Core Development Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2005.
37) Zhang Z, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis. Crit Care Med 2014;42:2118-2125.
38) Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:775-787.
39) Choudhury A, Jindal A, Maiwall R, Sharma MK, Sharma BC, Pamecha V, et al. Liver failure determines the outcome in patients of acute-on-chronic liver failure (ACLF): comparison of APASL ACLF research consortium (AARC) and CLIF-SOFA models. Hepatol Int 2017;11:461-471.
40) Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. Intensive Care Med 2007;33:1892-1899.
41) De Gasperi A, Mazza E, Corti A, Zoppi F, Prosperi M, Fantini G, et al. Lactate blood levels in the perioperative period of orthotopic liver transplantation. Int J Clin Lab Res 1997;27:123-128.
42) Theerawit P, Na Petvicharn C, Tangsujaritvijit V, Sutherasan Y. The correlation between arterial lactate and venous lactate in patients with sepsis and septic shock. J Intensive Care Med 2018;33:116-120.
43) Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. Gastroenterology 2013;145:375-382.e371-372.

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