DR. JASMOHAN S BAJAJ (Orcid ID : 0000-0003-4928-3681)
DR. FLORENCE WONG (Orcid ID : 0000-0001-9263-8869)
DR. RAJENDER K. REDDY (Orcid ID : 0000-0002-4898-7778)
DR. SUMEET K ASRANI (Orcid ID : 0000-0001-9174-5670)

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Model for End-stage Liver Disease-Lactate and Prediction of Inpatient Mortality in Patients with Chronic Liver Disease

Naveed Sarmast MD, MPH[1*]
Gerald O. Ogola, PhD[2*]
Maria Kouznetsova PhD, MPh[2]
Michael Leise MD[3]
Ranjeeta Bahirwani MD[1]
Rakhi Maiwall MBBS MD[4]
Elliot Tapper MD[5]
James Trotter MD[1]
Jasmohan Bajaj MD[6]
Leroy R Thacker PhD[6]
Puneeta Tandon[7]
Florence Wong[8]
Rajender Reddy[9]
Jacqueline G O'Leary[10]
Andrew Masica MD, MSCI[2]
Ariel M Modrykamien MD[1]

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Patrick S Kamath MD[3]
Sumeet K. Asrani MD, MSc^[1]

1. Baylor University Medical Center, Baylor Scott and White, Dallas, TX, United States.
2. Center for Clinical Effectiveness, Baylor Scott and White, Dallas, TX, United States.
3. Mayo Clinic, Rochester, MN, United States.
4. Institute of Liver and Biliary Sciences, New Delhi, India.
5. University of Michigan, Ann Arbor, Michigan, United States.
6. Virginia Commonwealth University, Richmond, Virginia.
7. University of Alberta, Canada
8. University of Toronto, Canada
9. University of Pennsylvania, Pennsylvania, United States
10. Dallas VA Medical Center, Dallas, TX.

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***both authors contributed equally**

^Corresponding author and reprint requests
Sumeet K. Asrani MD, MSc
3410 Worth Street, Suite 860
Dallas, TX 75246
Fax: (214) 820-0993
Tel: (214) 820-8500
Email: sumeet.asrani@bswhealth.org

Abbreviations:

CLD: Chronic Liver Disease

MELD: Model for End Stage Liver Disease

LA: Lactate

BSWH: Baylor Scott and White Health

NTX: North Texas division

CTX: Central Texas division

C-Statistic: Concordance Statistic

NACSELD: The North American Consortium for the Study of End-Stage Liver Disease

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Abstract

Background & Aims: As 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 lactate 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 & Results: We examined all CLD patients in two large and diverse healthcare systems in Texas (North Texas, NTX and Central Texas, CTX) between 2010-2015. We developed (n=3,588) and validated (n=1,804) a model containing MELD and LA measured at time of hospitalization. We further validated the model in a second cohort of 14 tertiary care hepatology centers that prospectively enrolled non-elective hospitalized patients with cirrhosis (n=726). MELD-LA was an excellent predictor of inpatient mortality in development (c-statistic =0.81, 95% CI 0.79-0.82) and both validation cohorts (CTX cohort, c=0.85, 95% CI 0.78-0.87; multicenter cohort c=0.82, 95% CI 0.74-0.88). MELD-LA performed especially well in patients with specific cirrhosis diagnoses (c=0.84, 95% CI 0.81-0.86) or sepsis (c=0.80, 95% CI 0.78-0.82). For MELD score 25, inpatient mortality was 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 the patients as compared to MELD model alone.

Conclusion: MELD-LA is an early and objective predictor of inpatient mortality and may serve as a novel model for risk assessment and guide therapeutic options.

Liver disease accounts for approximately 2 million deaths per year worldwide; furthermore, chronic liver disease (CLD) related morbidity and mortality is underestimated and expected to increase (1). A significant number of encounters for patients with CLD occur in the inpatient setting. As compared to other chronic diseases, patients with CLD have 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) however does not

perform well in the inpatient setting (4). MELD, which comprises of 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, either based on categorizing the degree of liver disease, (Child-Pugh score (5), or on overall clinical severity (APACHE II (6)). However these other scoring systems often are either 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 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 both due to tissue hypoperfusion in the critically ill patient as well as decreased lactate clearance in setting of advanced liver and renal disease (12). It may therefore capture an element of disease severity not captured by MELD score alone. Lactate predicts mortality in relevant subsets of patients including trauma (13), pneumonia (14), decompensated heart failure (15), and gastrointestinal bleeding (16). Lactate is a predictor of mortality in critically ill CLD patients (17) however its role in overall (both ICU and non-ICU) CLD patients is unknown. The addition of lactate to existing prediction models may improve their prognostic value (18).

Methods:

Aims: 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 lactate.

Setting

Development cohort: Baylor Scott and White Health (BSWH) is one of the largest integrated healthcare systems in the U.S. Data from patients in North Texas division (NTX) region was used for model development while that from Central Texas division (CTX) region was used for primary validation. During the study period, both these healthcare populations had minimal overlap.
The North Texas division (NTX) of BSWH serves the Dallas-Fort Worth Metroplex and surrounding communities (including 16 hospitals with the catchment area of 7 million individuals and over 130,000 annual hospitalizations). 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 central Texas division (CTX) of BSWH serves the Austin/Round Rock, Hill Country, College Station, Waco, and Temple regions and surrounding communities (including 14 hospitals with the catchment area of 2.7 million individuals and over 60,000 annual hospitalizations). As compared to North Texas, 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 non-elective hospitalized patients with cirrhosis. (19, 20).

Case Ascertainment: We examined all CLD related hospitalizations from 2010 to 2015 amongst adult patients (≥18 years) in BSWH system. Discharge diagnoses were classified in accordance with the International Classification of Diseases (ICD-9). Based on prior studies, we classified a hospitalization as a CLD related hospitalization if it was associated with (a) a primary diagnosis of CLD (e.g. cirrhosis) as underlying reason for hospitalization or (b) a secondary related complication associated with CLD (e.g. sepsis or hepatic encephalopathy) as underlying reason for hospitalization in combination with a primary diagnosis of CLD (e.g. alcoholic cirrhosis or viral hepatitis)(2).
Of all patients with above hospitalizations, we examined all patients that had laboratory evaluation to calculate MELD (bilirubin, creatinine, International Normalized Ratio) as well as serum lactate 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-square test for categorical variables.

Predictive model building: Using the development dataset, we modeled in-hospital mortality as 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 lactate. 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), lactate (11), Charlson's comorbidity index (22), alcoholic hepatitis (23), hepatic encephalopathy (HE) (24), ascites (25), varices (26), malignancy, cirrhosis (27) and interaction between MELD and lactate. We applied backward

variable selection algorithm to the initial model and obtained reduced model that retained MELD, lactate, age, HE, cirrhosis, and alcoholic hepatitis as significant predictors of mortality. We assessed further models with subset of variables from the reduced model and evaluated their performance. For each model, we obtained Brier scores and c-statistics to compare model prediction accuracy and goodness of fit (28-30) We also obtained Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) to assess the quality of each model relative to others and guide in determination of the most parsimonious model (30, 31). **Supplemental table 1** summarizes prediction accuracy, goodness of fit and selection criteria for different models evaluated. The model with MELD and lactate 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 (**Supplemental figure 1**). We investigated for interaction between MELD and lactate and found no significant statistical interaction.

We observed a nonlinear relationship between the two predictors (MELD and lactate) and risk of mortality. Hence, we developed the final model with restrictive cubic splines with 4-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 re-scaled 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 corresponding probability of death.

Model validation and performance: The new predictive model was validated against two independent datasets (CTX and NACSELD). We obtained concordance statistics (c-statistics) to quantify the discrimination ability of the new model. Measures of discrimination assess the extent to which a model

predicts a higher probability of having an event among patients who will as compared to those that will not have the event. We also obtained Brier score as a measure of accuracy of the prediction model. Brier score ranges from 0 to 1, with value of 0 implies excellent calibration of the predictive model and 1 implies suboptimal calibration (28). The performance of the new model was also compared to models that considered MELD alone or lactate alone. We further evaluated performance of the final model on subset of patients that included alcohol related hepatitis patients only, and patients admitted to ICU.

We assessed the calibration to quantify the extent to which absolute risk (predicted versus observed) is correctly estimated by a new model (e.g. MELD-LA) as 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 was analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R (34, 36) statistical programs, with p-value <0.05 considered statistically significant.

Results:

Baseline demographics

Between 2010-2015, there were 14,733 CLD related hospitalizations in the development dataset. Of those, 5,614 (38%) patients had a lactate measured on admission and 3,588 (24%) had both lactate 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 lactate was 2.4 mmol/L (IQR 1.5, 3.9). Overall inpatient mortality was 17.2%.

Relation between MELD and lactate

A nonlinear relationship existed between the two continuous predictors (MELD and lactate) 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 lactate levels, but the rate of change was higher for lactate ≤ 10 mmol/L as compared to patients with lactate > 10 mmol/L. (**Figure 1**)

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

MELD-LA model

MELD-LA was an excellent predictor of inpatient mortality in development cohort (c-statistic =0.81, 95% CI 0.79-0.82) **Figure 3** shows the relationship between probability of mortality and scores obtained from model developed by MELD and lactate (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 (**Supplemental Figure 2**). **Table 3** summarizes the findings for select cutoffs of MELD and lactate based on the MELD-LA score.

Consideration of alternate models

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

Neutrophil to lymphocyte ratio: The performance and predictive accuracy of neutrophil to lymphocyte ratio was suboptimal (c-statistics = 0.62 and Brier score = 0.146).

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

Validation cohort 1, CTX: There were fewer absolute number of hospitalizations, however patient demographics were similar between the development and validation cohort (**Table 1**). Inpatient mortality was significantly lower (12.3% vs 19.6%, $p<0.001$). The median LA was lower (2.0 mmol/L vs. 2.6 mmol/L, $p=<0.001$), and the mean MELD score was lower (16.2 vs. 19.2, $p=<0.001$). 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 datasets.

Validation cohort 2, NACSELD: Of 3,057 patients in 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=0.82, 95% CI 0.74-0.88), similar to the current validation group. Performance for MELD score was c= 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 = 0.74 95% CI 0.72-0.76), those only with alcohol related hepatitis (c=0.77, 95% CI 0.67-0.88) or a specific cirrhosis diagnosis (c=0.84, 95% CI 0.81-0.86) or sepsis (c=0.80, 95% CI 0.78-0.82) was excellent. Lactate may be influenced by presence of patients with cancer. After exclusion, results for MELD-LA still had excellent performance (c=0.80, 95% CI 0.78-0.82).

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

independent, large, and diverse validation datasets. The independent impact of LA varied based on disease severity, as adjudicated by the MELD score. MELD-LA model outperformed MELD alone, lactate alone, MELD-Na based models and the neutrophil-lymphocyte ratio. Based on risk reclassification analysis, the MELD-LA model improved risk prediction for 23.5% of patients as compared to MELD alone. Clinically, this would have impacted risk prediction for 798 patients during the study duration. Additionally, our study showed that the same lactate 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 a MELD of 15. In addition, MELD-LA correlated with increasing number of organ failures. MELD-LA 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 highest at risk prior to identification of triggers. There are several potential applications and implications of MELD-LA. First, it may help stratify patients that may need higher levels of care or earlier interventions. Though many surrogates of critical illness exist (frailty, ascites, hepatic encephalopathy), these may be subjective at the time of presentation and are more reflective of current state of health. With lactate being a predictor of all-cause mortality in critically ill patients (37), the inclusion of lactate 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 lactate cutoffs for hospitalized patients ***without*** liver disease may not apply to chronic liver disease patients (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 that are non-responders 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. Lactate's prognostic utility has been well established in literature (13-16) as well as in selected subsets with cirrhosis (39), however this study sheds light on the unique relationship between lactate and all comers with liver disease. Lactic acidosis, a persistent elevation of blood lactate, is most commonly related to tissue hypoperfusion and hypoxia (40). However in chronic liver disease patients, the co-presence of lactate elevation not associated with hypoperfusion, may be contributing. The liver is intimately involved in lactate clearance, with 40% to 60% being removed by gluconeogenesis (41). Due to impairment in tissue oxygenation and hepatocellular damage in CLD patients, gluconeogenesis is impaired, decreasing lactate clearance (41). In settings that may involve hemodynamic permutations (e.g. sepsis), the issue is exacerbated and CLD patients may be more prone to lactic acidosis. Hence, among patients with CLD, LA may be elevated both due to tissue hypoperfusion and hypoxia (in hepatic and extra hepatic endothelial beds) as well as due to a decreased lactate clearance in 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 network. 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 healthcare systems. We further validated our findings in a prospective study of cirrhotics across 14 centers with lower inpatient mortality rates. Referral bias and spectrum bias was 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 that are either already in the ICU or may

have acute on chronic liver failure (12, 17). Performance amongst those already in the ICU was similar in our study to previous 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 lactate rather than arterial lactate in the expanded cohort. The former is easier to obtain and readily available and there appears to be strong correlation between arterial and venous lactate (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 a serum lactate level greater than 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, different threshold and definitions of response to therapy may be required for this population.

Our study has limitations. Inpatient mortality rates were high among patients that had serum lactate measured. As expected those that underwent lactate measurement were systematically different than those that did not undergo measurement. The mean age of those that 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% vs. 78.0%) and ICU hospitalization was lower (23% vs 55%, $p<0.01$). Inpatient mortality was also lower at 4.9%. However, validation in two separate cohorts with lower mortality (CTX, 12.3% and 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 that would need to be incorporated at the system level. A future prospective validation is needed whereby lactate is measured in all patients with chronic liver disease 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 are 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 novel parsimonious and objective model to identify inpatients with CLD at highest at risk for mortality regardless of ICU status. Early prediction may allow for earlier identification of CLD patients that may benefit from escalation of care and can also assist in determining starting early goal directed therapy. Alternatively, it may identify patients highest at risk for mortality and aid in discussion of prognosis. Further independent validation in prospective studies with unbiased lactate 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 intensive care unit is highly encouraged.

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California, San Diego; University of California, San Francisco; University of Colorado, Denver; University of Pennsylvania, Philadelphia; University of Rochester, NY; University of Texas, Houston; University of Toronto, Ontario; Virginia Commonwealth University; and Yale University Medical Center, New Haven

Figures

Figure 1a. Relationship between lactate and log odds of inpatient mortality

Figure 1b. Relationship between MELD score and log odds of inpatient mortality

Figure 2. In-hospital mortality by lactate and ranges of MELD values.

Figure 3. MELD-Lactate score and probability of inpatient mortality.

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

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Table 1: Baseline characteristics of hospitalized patients with measured lactate and MELD score at admission in the development (NTX) and validation cohorts (CTX and NACSELD).

	Total NTX and CTX (N=5392)	NTX (N=3588)	CTX (N=1804)	P value (NTX to CTX)	NACSELD (n=726)	P value (NTX to NACSELD)
Age (years)	58.2 ± 13.1‡	58.1± 13.2‡	58.4 ± 13.0‡	0.475[1]	57.5 ± 11.1	0.264[1]
Female Sex	2316 (43.0%)	1538 (42.9%)	778 (43.1%)	0.855[2]	258 (35.5%)	<0.0003[2]
Race				< 0.001[2]		< 0.001[2]
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[2]		< 0.001[2]
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[1]	n/a	n/a
Alcoholic hepatitis	323 (6.0%)	194 (5.4%)	129 (7.2%)	0.011[2]	51 (7.3%)	0.085[2]
Hepatic Encephalopathy	1765 (32.7%)	1295 (36.1%)	470 (26.1%)	< 0.001[2]	124 (17.3%)	< 0.001[2]
Ascites	1512 (28.0%)	1096 (30.5%)	416 (23.1%)	< 0.001[2]	200 (27.6%)	0.108[2]
Varices	2384 (44.2%)	1686 (47.0%)	698 (38.7%)	< 0.001[2]	309 (42.6%)	0.029[2]
Neoplasm	358 (6.6%)	262 (7.3%)	96 (5.3%)	0.006[2]	n/a	n/a
Disposition				< 0.001[2]		< 0.001[2]
Expired	927 (17.2%)	705 (19.6%)	222 (12.3%)		35 (4.8%)	
Home	2457 (45.6%)	1641 (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,	1.7 (0.8,	1.3 (0.7,	<	2.5 (1.3,	< 0.001[3]

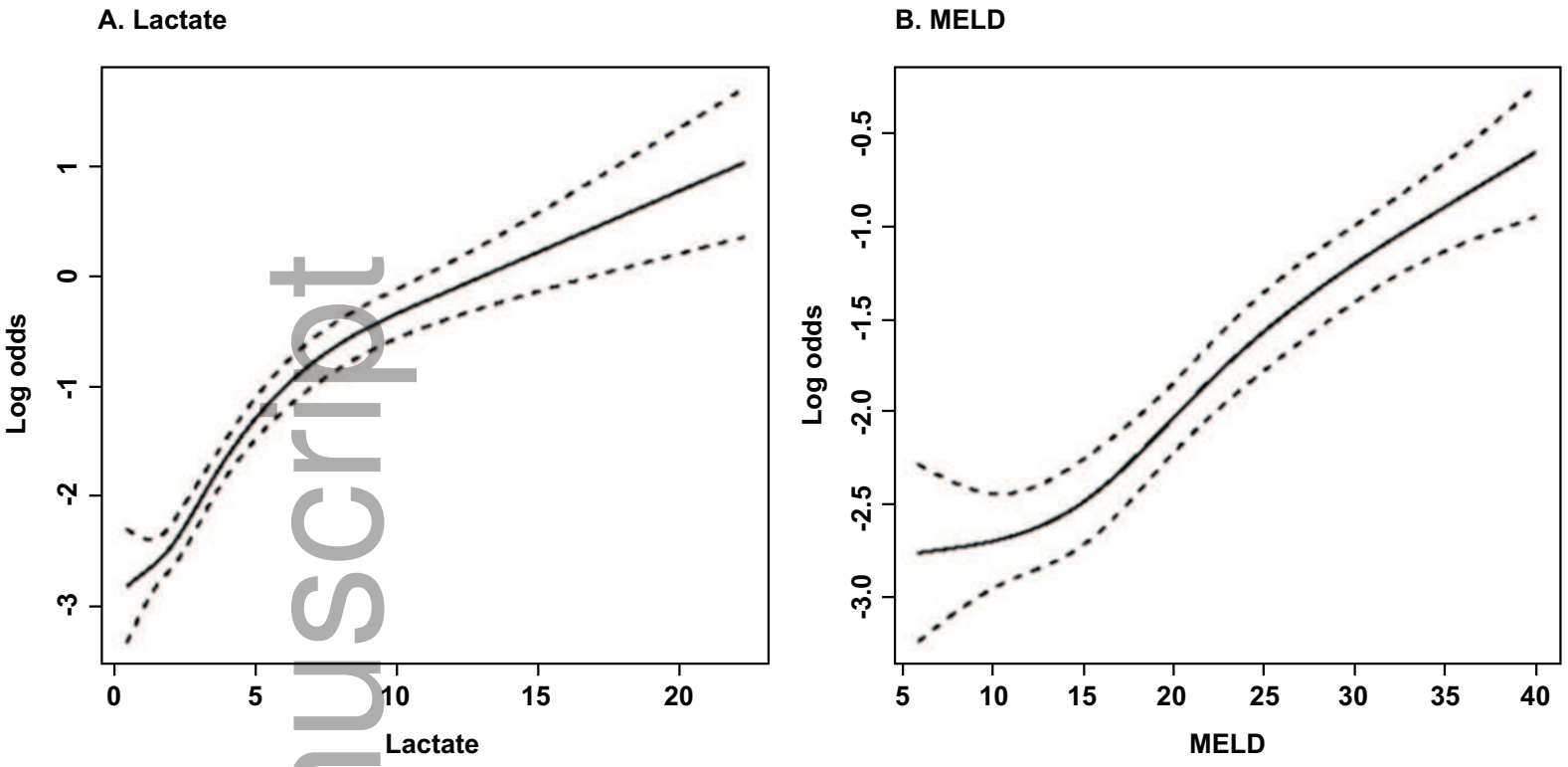
	3.4)§	3.9)§	2.7)§	0.001[3]	5.5)§	
Creatinine	1.3 (0.9, 2.2)§	1.4 (1.0, 2.5)§	1.1 (0.8, 1.8)§	< 0.001[3]	1.1 (0.8, 1.6)§	< 0.001[3]
INR	1.4 (1.2, 1.8)§	1.4 (1.2, 1.8)§	1.3 (1.1, 1.7)§	< 0.001[3]	1.5 (1.3, 1.9)§	< 0.001[3]
Lactate	2.4 (1.5, 3.9)§	2.6 (1.7, 4.3)§	2.0 (1.3, 3.1)§	< 0.001[3]	2.2 (1.6, 3.2)§	< 0.001[3]
MELD score	18.2 ± 8.4‡	19.2 ± 8.4‡	16.2 ± 7.9‡	< 0.001[1]	18.7 ± 7.3‡	< 0.001[1]

‡ - mean ± standard deviation; § median (interquartile range); 1 - Student t-test; 2 - Chi-squared test; 3 - Kruskal-Wallis rank sum test; n/a: not available

Table 2. Probability of inpatient mortality by MELD and Lactate Levels based on the MELD-LA score. Nomogram is provided in Supplemental figure 2.

	Lactate												
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%**

	Lactate												
MELD	0.5	1	2	3	4	5	6	7	8	10	12	15	20+
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%



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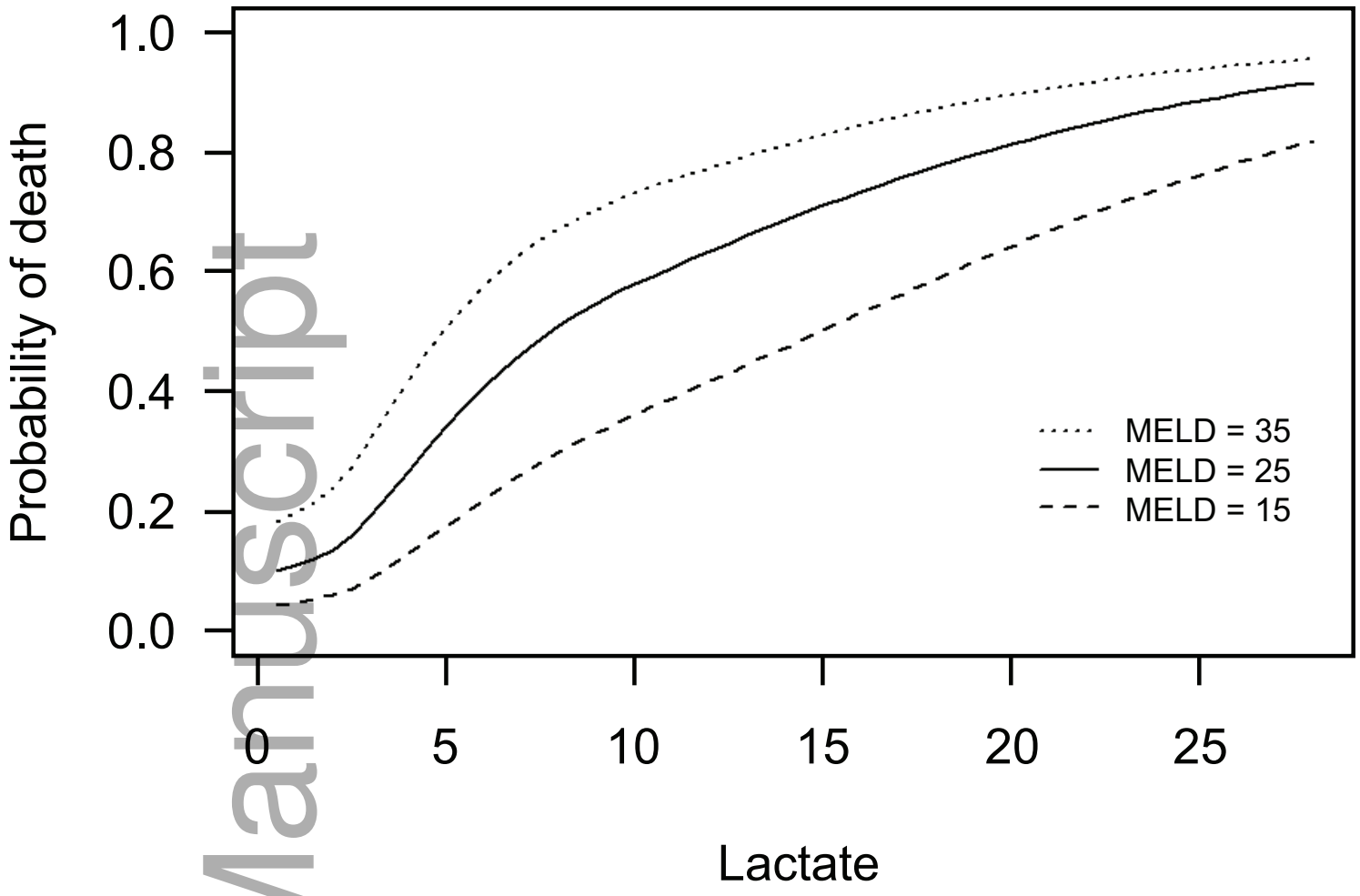

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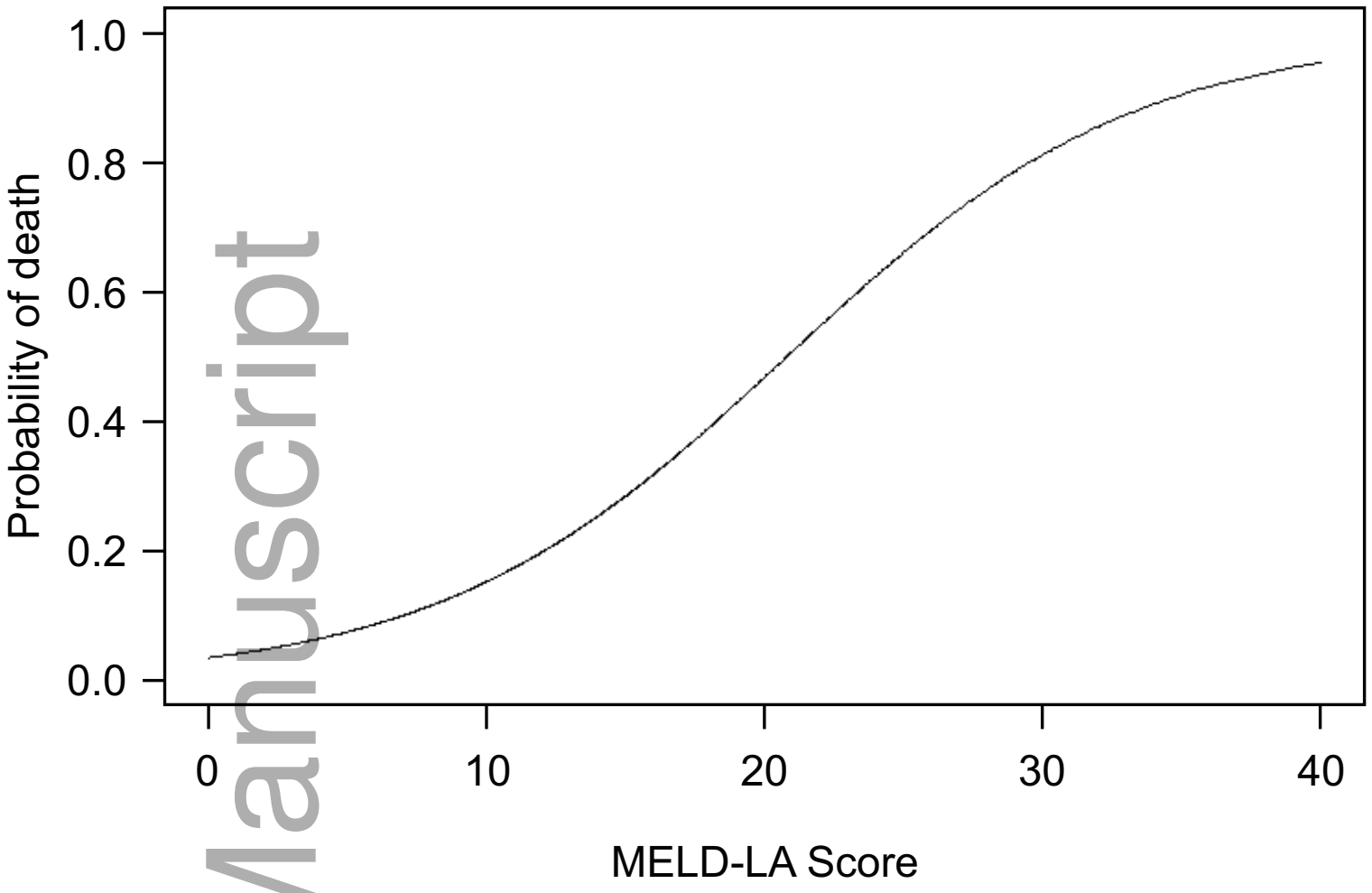

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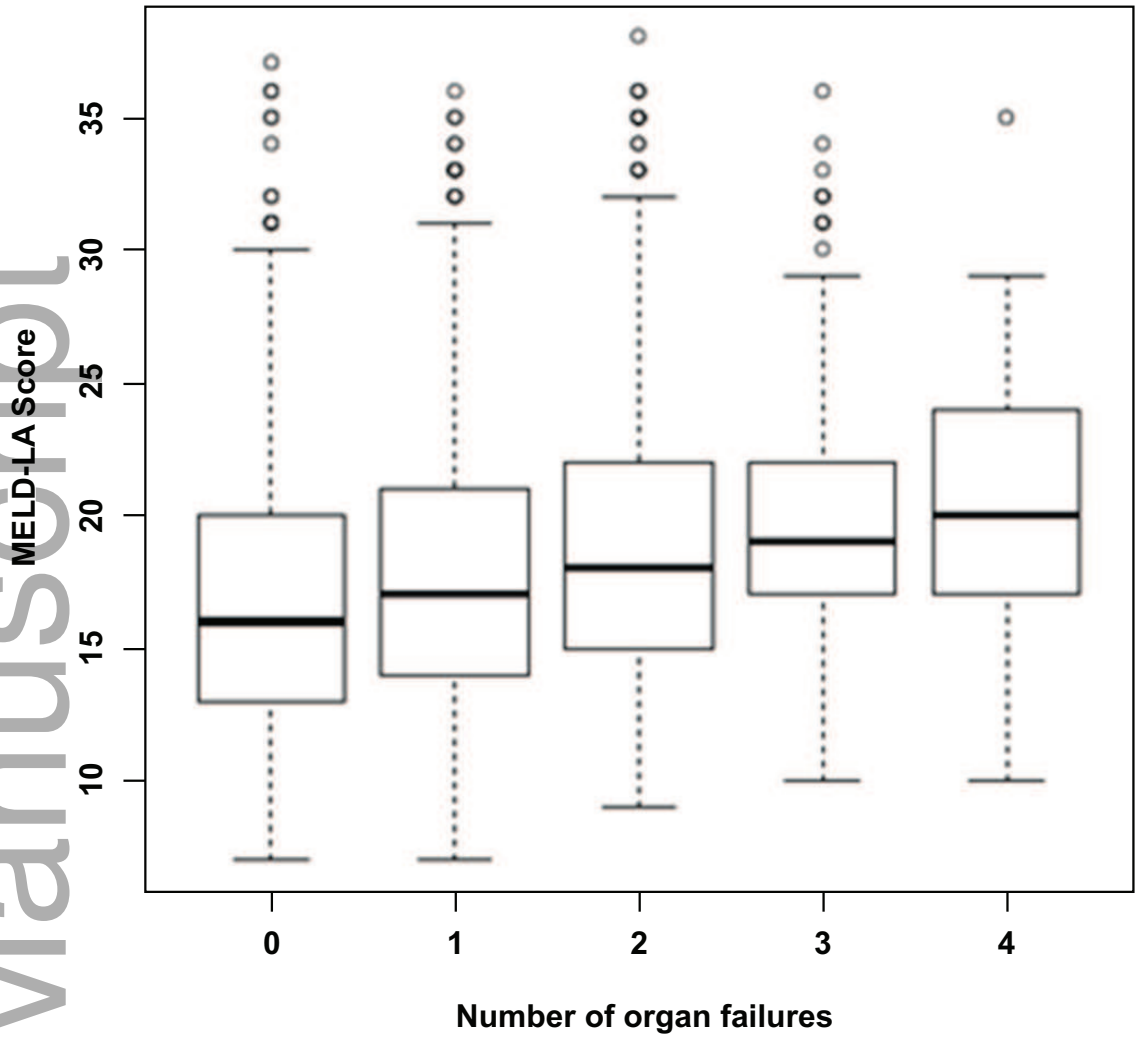

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