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Original Article

Easy prognostic assessment of concomitant organ failure in critically ill patients undergoing mechanical ventilation

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ABSTRACT

Background: Acute respiratory distress syndrome (ARDS) is a life-threatening disease. We evaluated the prognostic utility of Model for End-stage Liver Disease excluding INR (MELD-XI) score for predicting mortality in a

Abbreviations: MELD, Model for End-stage Liver Disease score; MELD-XI, MELD excluding INR; APACHE2, Acute Physiology And Chronic Health Evaluation 2; ARDS, Acute Respiratory Distress Syndrome; ICU, Intensive Care Unit; PBW, Predicted Bodyweight; HR, Hazard Ratio; OR, Odds Ratio; 95%CI, 95% Confidence Interval; AUC, Area Under the Curve

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ICU
Risk stratification
Risk score
ARDS

cohort of critically ill patients on mechanical ventilation.
Methods: In total, 11,091 mechanically ventilated patients were included in our post-hoc retrospective analysis, a subgroup of the VENTILA study (NCT02731898). Evaluation of associations with mortality was done by logistic and Cox regression analysis, an optimal cut-off was calculated using the Youden Index. We divided the cohort in two sub-groups based on their MELD-XI score at the optimal cut-off (12 score points).
Results: Peak-, plateau- and positive end-expiratory pressure were higher in patients with MELD-XI > 12. Patients with MELD-XI > 12 had higher driving pressures (14 ± 6 cmH2O versus 13 ± 6; p < 0.001). MELD-XI was associated with 28-day mortality after correction for relevant cofounders including SAPS II and ventilation pressures (HR 1.04 95%CI 1.03–1.05; p < 0.001. Patients with MELD-XI > 12 evidenced both increased hospital (46% versus 27%; p < 0.001) and 28-day mortality (39% versus 22%).
Conclusions: MELD-XI is independently associated with mortality and constitutes a useful and easily applicable tool for risk stratification in critically ill patients receiving mechanical ventilation.
Trial registration: NCT02731898, registered 4 April 2016.

1. Introduction

Critically ill patients suffering from acute respiratory distress syndrome (ARDS) undergoing mechanical ventilation suffer from high mortality. Initial risk stratification to ensure optimal treatment as soon as possible is paramount but tricky. Several elaborate scores to predict risk and assess critically ill patients are available including Simplified Acute Physiology Score 2 (SAPS2) [1,2]. However, these scores are relatively complex and therefore often calculated retrospectively or only for scientific purposes. Hence, new reliable and straightforward tools for risk stratification are needed.

MELD-XI is a derivate of Model for End-stage Liver Disease (MELD) score omitting INR from the equation and consists of creatinine and bilirubin, which increases its use in medical patients often on vitamin K antagonists [3]. MELD was initially developed to predict mortality in patients suffering from liver and renal failure and is widely used to allocate organs to patients on the waiting list for liver transplantation but was shown to predict outcomes in other diseases including heart failure [4–6]. MELD-XI was recently described by our group and others to predict mortality in critically ill patients admitted to ICU, patients suffering from heart failure undergoing left ventricular assist device implantation or patients undergoing heart transplantation [6–9].

High volume and pressure mechanical ventilation in patients receiving mechanical ventilation were shown to cause lung injury and protective ventilation strategies were developed [10–13]. Studies evaluating MELD-XI in patients undergoing mechanical ventilation are lacking. The VENTILA study included mechanically ventilated patients suffering from various etiologies [14]. We aimed to assess MELD-XI for its predictiveness in mechanically ventilated patients and possible correlations of MELD-XI with parameters of mechanical ventilation, including airway pressures.

2. Methods

2.1. Study subjects

We retrospectively evaluated a sub-group of patients of VENTILA study groups from 2004, 2010 and 2016. The present study included all patients with available creatinine and bilirubin concentration. Primary end-point was mortality on day 28. Secondary endpoints included ICU and hospital mortality.

2.2. Statistical analysis

Continuous variables are expressed as mean (± standard deviation) and compared using student's T test. Categorical data are expressed as numbers (percentage). Chi-square test was applied to calculate differences between groups. Both univariable and multivariable logistic regression analysis to adjust for confounding factors for 28-day-mortality were done. Both univariable and multivariable Cox regression analysis to adjust for confounding factors for hospital mortality were done. For the multivariable regression model, confounders with a p-value < 0.15 in the univariate analysis were included, then a backward variable elimination was performed. Elimination criterion was a p-value of > 0.10. A p-value of < 0.05 was considered statistically significant. SPSS version 22.0 (IBM, USA) and MedCalc version 14.8 (MedCalc Software, USA) were used for statistical analysis.

2.3. Calculation of MELD-XI and SAPS2 score and MELD-XI clearance

MELD-XI score was calculated as follows: MELD-XI = 5.11 × ln (serum bilirubin in mg/dL) + 11.76 × ln (serum creatinine in mg/dL) + 9.44. Serum creatinine and bilirubin values utilized were those reported on day of admission, creatinine and bilirubin concentration below 1 were set to 1 and creatinine above 4 was set to 4 to avoid

Table 1
Baseline demographic, laboratory and clinical data.

Parameter	Total cohort n = 11,091 Mean	SD	MELD ≤ 12 n = 5527 Mean	SD	MELD > 12 n = 5564 Mean	SD	p-value
Age (years)	60	± 17	58	± 18	62	± 17	< 0.001
Weight (kg)	75	± 20	74	± 19	77	± 20	< 0.001
Height (cm)	168	± 10	168	± 9	168	± 10	< 0.001
PBW	62	± 9	62	± 9	62	± 9	< 0.001
BMI	27	± 6	26	± 6	27	± 7	< 0.001
SAPSII (points)	47	± 19	42	± 17	52	± 19	< 0.001
Creatinine (mg/dL)	2	± 2	1	± 0	2	± 2	< 0.001
Bilirubin (mg/dL)	2	± 5	1	± 0	3	± 7	< 0.001
ICU stay (days)	12	± 14	12	± 13	12	± 14	0.16
Hospital stay (days)	26	± 27	26	± 27	26	± 27	0.95
Ventilation (day)	8	± 9	8	± 9	9	± 9	0.005

SAPSII – Simplified Acute Physiology Score II; PBW – predicted body weight; BMI – body mass index; ICU – intensive care unit.

negative values. Initial SAPS2 scores were calculated by the treating physician within 24 h after admission as reported before [1]. We calculated a MELD-XI clearance up to day 7; MELD-XI clearance day X: [(MELD day 1 – MELD day X)/MELD day 1].

3. Results

3.1. Study population

In total, 11,091 critically ill patients were investigated. Median MELD-XI was 12 points, and the cohort was split into two subgroups, above (n = 5564) and below (n = 5527) MELD-XI of 12 points. Patients with a MELD-XI > 12 points were older (62 ± 17 years vs. 58 ± 17 years; $p < 0.001$), and clinically sicker as mirrored by higher SAPS2 scores (52 ± 19 vs 42 ± 17; $p < 0.001$). Baseline characteristics are given in Table 1. Admission diagnoses are given in Suppl Table 1.

3.2. Survival analysis: 28-day-mortality

Overall 28-day-mortality was 31%. MELD-XI was associated with 28-day mortality in logistic regression (OR 1.066 95%CI 1.059–1.072; $p < 0.001$). AUC for prediction of 28-day-mortality was 0.63 (95%CI 0.62–0.64), the optimal cut-off using Youden Index was 12 points. Predictiveness was lower compared to AUC of SAPS II (AUC 0.69 95%CI 0.685–0.702; $p < 0.001$) but higher compared to bilirubin (AUC 0.57 95%CI 0.56–0.58; $p < 0.001$ vs MELD-XI) and creatinine (AUC 0.62 95%CI 0.61–0.63; $p = 0.04$) alone. MELD-XI score was associated with hospital mortality even after correction for relevant clinical confounders including age in years, SAPS II in points, driving pressure in cmH2O, tidal volume/predicted body weight (PBW) in ml/kg, presence of acidosis, paO2/FiO2 in mmHg in a multivariable regression (HR 1.04 95%CI 1.03–1.05; $p < 0.001$; Table 2). Patients with MELD-XI > 12 evidenced increased hospital (46% versus 27%; $p < 0.001$), ICU (39% versus 22%; $p < 0.001$) and 28-day mortality (39% versus 22%).

3.3. Survival analysis: hospital mortality

Further, MELD-XI was independently associated with hospital mortality after correction for SAPS2 (change per score-point: HR 1.023 95%CI 1.03 95%CI 1.019–1.028; $p < 0.001$). AUC for prediction of hospital mortality was 0.64 (95%CI 0.63–0.65), the optimal cut-off was >12 points. Compared to SAPS II (AUC 0.695 95%CI 0.686–0.703; $p < 0.001$ vs. MELD-XI) MELD-XI lacked predictiveness. MELD-XI score was associated with hospital mortality even after correction for relevant clinical confounders including age in years, SAPS II in points, driving pressure in cmH2O, tidal volume/PBW in ml/kg, presence of acidosis, paO2/FiO2 in mmHg in a multivariable regression (HR 1.02 95%CI 1.02–1.03; $p < 0.001$). In the MELD-XI > 12 cohort in-hospital-mortality was significantly higher compared to the MELD ≤ 12 group (46% vs 27%; HR 1.74 95%CI 1.63–1.86; $p < 0.0001$; Fig. 1).

3.4. MELD-XI clearance

We calculated a MELD-XI clearance for up to day 7: MELD-XI clearance was associated with 28-day-mortality but at low predictiveness (Suppl Table 2). Of note, this was similar evaluating MELD-XI clearance only in patients with MELD-XI > 12 (AUC 0.56 95%CI 0.55–0.57).

3.5. MELD-XI in different admission diagnoses

MELD-XI was associated with hospital mortality regardless of main admission diagnosis, but optimal cut-offs varied (Table 3).

3.6. Correlation analysis and association with respiratory parameters

Parameters of mechanical ventilation are given in Table 4. In patients with MELD-XI > 12 pH was lower (7.32 ± 0.31 versus 7.37 ± 0.10; $p < 0.001$). Peak-, plateau- and positive end expiratory pressure were higher in patients with MELD-XI > 12. Patients with MELD-XI > 12 had higher driving pressures (14 ± 6 cmH2O versus 13 ± 6; $p < 0.001$). MELD-XI correlated weakly with airway ventilation pressures (Table 5).

4. Discussion

In summary, in this large, international cohort of critically ill patients, MELD-XI was independently associated with mortality. We calculated an optimal MELD-XI cut-off of 12 points for prediction of mortality. In comparison to SAPS II, MELD-XI lacked predictiveness, but given its easy availability, it could play an independent, important role in initial risk stratification of critically ill patients. Of note, the concept to assess MELD-XI clearance provided no additional information with regards to the prediction of mortality.

MELD-XI correlated weakly with airway pressures in mechanically ventilated patients and patients in the MELD-XI > 12 group evidenced higher ventilation pressures. These findings might primarily reflect higher pressures in sicker patients given the robust association of MELD-XI with both outcome and clinical sickness assessed by SAPS II scores. However, higher airway pressure, especially PEEP might increase contribute to higher hepatic and renal venous blood pressure and aggravate impaired hepatic/renal perfusion and hence contribute to increased bilirubin or creatinine concentration in critically ill patients.

Compared to SAPS II, MELD-XI evidenced lower predictiveness. However, elaborate scores such as SAPS II are complicated and time-consuming to calculate whereas MELD-XI consists of only two biomarkers and could even be automatically calculated and stated alongside creatinine and bilirubin on lab read-outs. Therefore, MELD-XI might play an important role in initial risk assessment in critically ill patients on mechanical ventilation. In this regard we confirm previous results of single-center studies, which was the intention of this investigation [6,9]. In addition, this study evaluated explicitly critically ill patients on mechanical ventilation; to our knowledge this is the first analysis of MELD-XI in this specific sub-group of critically ill patients.

We further compared baseline MELD-XI values to MELD-XI clearance with regards to the prediction of mortality. Interestingly, and contrary to our anticipation, we found a lower in predictiveness of

Table 2
shows univariable and multivariable logistic regression analysis of MELD-XI and relevant cofounders with 28-day-mortality.

	Unvariable			Multivariable		
Parameter	OR	95%CI	p-value	OR	95%CI	p-value
MELD-XI	1.066	1.059–1.072	<0.001	1.04	1.03–1.05	<0.001
SAPS II	1.039	1.037–1.42	<0.001	1.032	1.029–1.035	<0.001
PaO2/FiO2 (mmHg)				1.27	1.20–1.36	<0.001
≤100	1.61	1.44–1.80	<0.001			
100–150	2.05	1.81–2.32	<0.001			
>150	1					
Driving pressure (cmH2O)	1.04	1.03–1.05	<0.001			
Tidal volume/ PBW (ml/ kg)	0.981	0.961–1.003	<0.001			
pH < 7.35	1.67	1.54–1.81	<0.001	1.20	1.09–1.32	<0.001
Age (years)	1.019	1.016–1.021	<0.001	1.009	1.006–1.012	<0.001

SAPSII - Simplified Acute Physiology Score II; PBW – predicted body weight; BMI – body mass index.

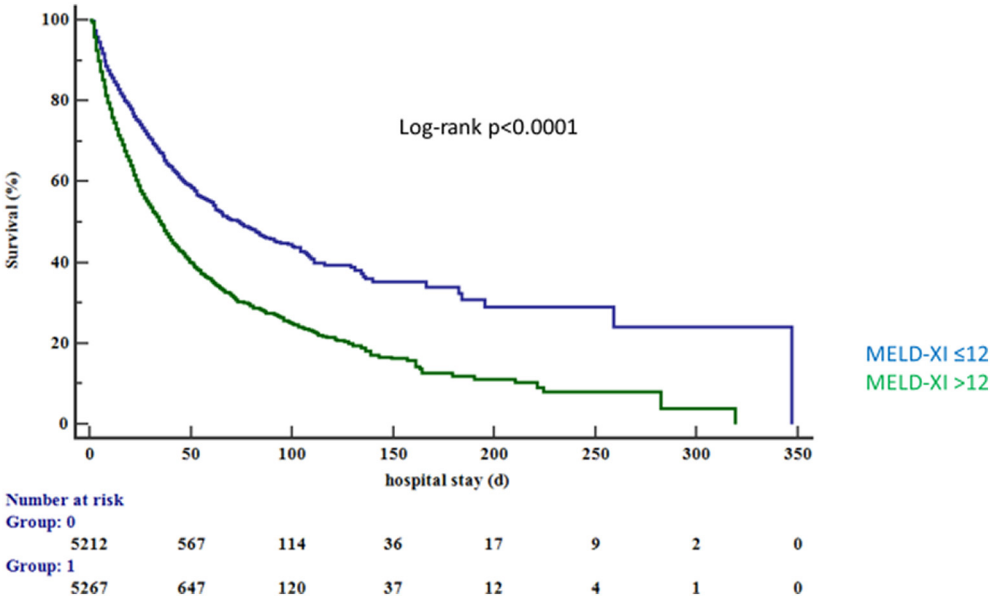

Fig. 1. In the MELD-XI > 12 cohort in-hospital-mortality was significantly higher compared to the MELD ≤ 12 group (log-rank p < 0.0001). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
shows association of MELD-XI with 28-day-mortality in distinct admission diagnoses.

Main admission diagnosis	n =	OR	95%CI	p-value	Optimal cut-off	AUC
ARDS	431	1.051	1.021–1.082	< 0.001	11	0.61
Aspiration	303	1.049	1.009–1.091	0.02	14	0.60
Cardiac arrest	690	1.026	1.004–1.049	0.02	21	0.54
Acute heart failure	524	1.065	1.037–1.094	< 0.001	16	0.64
COPD	454	1.056	1.018–1.085	0.004	12	0.60
Neurologic disease	2290	1.049	1.035–1.063	< 0.001	10	0.59
Other acute respirator failure	617	1.063	1.039–1.088	< 0.001	9	0.59
Pneumonia	1188	1.061	1.042–1.079	< 0.001	14	0.61
Postoperative	2489	1.074	1.058–1.091	< 0.001	12	0.66
Sepsis	6959	1.068	1.052–1.085	< 0.001	17	0.64
Trauma	510	1.089	1.048–1.130	< 0.001	14	0.66
Aspiration	303	1.049	1.009–1.091	0.02	14	0.60

ARDS – acute respiratory distress syndrome; COPD – chronic obstructive pulmonary disease.

MELD-XI clearance compared to baseline MELD-XI. This is in contrary to clearance concepts in other biomarkers, most importantly lactate in which lactate clearance was at least non-inferior and even superior in specific applications [15,16]. However, this lack of predictiveness of MELD-XI might be influenced by the distinct behavior of bilirubin/creatinine concentrations compared to lactate concentration. Whereas lactate concentration is relatively volatile and reflects tissue hypoperfusion relatively "online", creatinine and bilirubin primarily reflect already established end-organ damage. To our knowledge, we are the first to evaluate the concept MELD-XI clearance. Based on these results, MELD-XI clearance is not useful to predict mortality in critically ill patients.

The findings of this study are in accordance with previous studies evaluating different cohorts of critically ill patients: We could previously show that MELD-XI is independently associated with mortality

Table 5
shows correlation analysis of MELD-XI with parameters of mechanical ventilation.

MELD-XI versus	r =	p =
pH (mmHg)	−0.23	< 0.001
paCO2 (mmHg)	−0.07	< 0.001
PaO2_FiO2_1	−0.14	< 0.001
Peak pressue (mmHg)	0.11	< 0.001
Plateau pressue (mmHg)	0.13	< 0.001
PEEP (mmHg)	0.07	< 0.001
Tidal volume	0.03	< 0.001

FiO2 – fraction of inspired oxygen; PEEP – positive end-expiratory pressure.

Table 4
shows baseline parameters of mechanical ventilation.

Parameter	Total cohort n = 11,091 Mean	SD	MELD ≤ 12 n = 5527 Mean	SD	MELD > 12 n = 5564 Mean	SD	p-value
pH	7.34	± 0.12	7.37	± 0.10	7.32	± 0.13	< 0.001
paCO2 (mmHg)	40.7	± 12.7	41.3	± 12.6	40.1	± 12.7	< 0.001
PaO2_FiO2_1	238.0	± 123.8	253.3	± 127.5	223,0	± 118,2	< 0.001
Peak pressure (mmHg)	25.2	± 7.7	24,6	± 7.9	25.8	± 7.5	< 0.001
Plateau pressure (mmHg)	19.8	± 6.0	19.2	± 5.9	20.5	± 6.0	< 0.001
PEEP	6.4	± 3.0	6.1	± 2.9	6.6	± 3.1	< 0.001
Tidal volume	505.9	± 113.8	502.5	± 112.4	509.3	± 115,2	0.002
Tidal volume/PBW ml/kg	8.3	± 2.0	8.2	± 1.9	8,3	± 2,1	0.07
Driving pressure	13.5	± 5.9	13.0	± 5.7	13.9	± 6.0	< 0.001

PEEP – positive end-expiratory pressure; PBW – predicted body weight.

in critically ill patients admitted to ICU for various admission diagnosis [6,9]. Further, MELD-XI was recently proposed to predict risk in heart failure patients undergoing heart transplantation or left ventricular assist device implantation [7,8]. In patients suffering from infective endocarditis, MELD-XI was reported to predict poor outcomes [17]. In patients undergoing transcatheter aortic valve implantation, MELD-XI was associated with 30-day-survival [18]. This relatively broad spectrum of successful MELD-XI applications might reflect its reliable assessment of two and a half organ systems: In addition to creatinine as a parameter for renal function, bilirubin assessing hepatic disturbances MELD-XI could indirectly evaluate cardiac function via cardio-hepatic and cardio-renal interactions [19–21]. For future studies, the combination of lactate concentrations (being a “real-time” marker for hypoperfusion), MELD-XI (reflecting end-organ damage in two and a half vital organ systems) could further increase predictiveness of mortality compared to both tools in a stand-alone setting.

4.1. Limitations

Besides it's retrospective manner, this study has limitations. Due to missing values (creatinine and bilirubin need to be available), MELD-XI could not be calculated in all patients, which could prone our investigation to selection bias. Further, this study was initially not designed to investigate the MELD-XI/mechanical ventilation relation, and measurements were not necessarily simultaneously conducted. Comparison and combination of MELD-XI with lactate concentration were not possible as lactate concentrations are not available for this cohort. Still, this study constitutes to our knowledge the most extensive study investigating MELD-XI in critically ill patients.

5. Conclusions

MELD-XI is associated with mortality and constitutes a useful tool for risk stratification in intensive care medicine. We calculated an optimal cut-off of 12 for critically ill patients on mechanical ventilation. In multivariable analysis, MELD-XI provided information independently SAPS-2 and might find a role for early patient assessment due to its easy applicability.

Funding

No (industry) sponsorship has been received for this investigator-initiated study, with the exception of a local hospital fund.

Ethics approval and consent to participate

A study protocol was provided to participating centers. Every participating center obtained ethics approval according to local legislation. A copy of the ethics approval was sent to the study coordinator before start of the study.

Consent for publication

Written informed consent was obtained of all included subjects, unless the local ethics committee specifically allowed a waiver in this respect. The study was registered at http://www.clinicaltrials.gov/ (NCT02731898).

Availability of data and materials

All data relevant for this study will be given by the authors upon specific request without restriction.

CRediT authorship contribution statement

Bernhard Wernly: Formal analysis, Writing - original draft. **Fernando Frutos-Vivar:** Formal analysis, Validation. **Oscar Peñuelas:** Formal analysis, Validation. **Konstantinos Raymondos:** Formal analysis, Validation. **Alfonso Muriel:** Formal analysis, Validation. **Bin Du:** Validation. **Arnaud W. Thille:** Validation. **Fernando Ríos:** Validation. **Marco González:** Validation. **Lorenzo del-Sorbo:** Validation. **Maria del Carmen Marín:** Validation. **Bruno Valle Pinheiro:** Validation. **Marco Antonio Soares:** Validation. **Nicolas Nin:** Validation. **Salvatore M. Maggiore:** Validation. **Andrew Bersten:** Validation. **Malte Kelm:** Validation. **Pravin Amin:** Validation. **Nahit Cakar:** Validation. **Michael Lichtenauer:** Formal analysis, Validation. **Gee Young Suh:** Validation. **Fekri Abroug:** Validation. **Manuel Jibaja:** Validation. **Dimitros Matamis:** Validation. **Amine Ali Zeggwagh:** Validation. **Yuda Sutherasan:** Validation. **Antonio Anzueto:** Validation. **Andrés Esteban:** Formal analysis, Validation. **Christian Jung:** Formal analysis, Writing - original draft.

Declaration of Competing Interest

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.09.002.

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