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Outcomes of Acute Respiratory Distress Syndrome in Mechanically Ventilated Patients With Cirrhosis

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Objective: To better describe the outcomes of acute respiratory distress syndrome in mechanically ventilated patients with cirrhosis.

Design: Single-center, retrospective study of mechanically ventilated patients with cirrhosis between 2008 and 2015.

Setting: ICU at a large academic medical and transplant center.

Patients: One hundred eighty-one mechanically ventilated patients with cirrhosis.

Interventions: Demographic and clinical data were reviewed, and acute respiratory distress syndrome was identified per Berlin criteria. We compared demographic and clinical characteristics on ICU admission in patients with and without acute respiratory distress syndrome. The primary endpoint was hospital mortality (including discharge to hospice). Mortality risk was stratified by Chronic Liver

Failure-Sequential Organ Failure Assessment and Model for End-Stage Liver Disease.

Measurements and Main Results: The mean age in 181 eligible patients was 53 ± 11 years; 67% were male; and 91% were Caucasian. In all, $n = 35$ (19%) of mechanically ventilated patients had acute respiratory distress syndrome. They were more frequently female (46% vs 30%; $p = 0.08$), with suspected infection (86% vs 53%; $p < 0.001$), and had higher mean Model for End-Stage Liver Disease (32 vs 24; $p < 0.001$) and Chronic Liver Failure-Sequential Organ Failure Assessment (15 vs 11; $p < 0.001$) than patients without acute respiratory distress syndrome. Hospital mortality was higher in patients with (40%) versus without (22%) acute respiratory distress syndrome ($p = 0.03$). In the risk-adjusted analysis (for Model for End-Stage Liver Disease, Chronic Liver Failure-Sequential Organ Failure Assessment and age), acute respiratory distress syndrome was not independently associated with hospital mortality (odds ratio, 0.80; CI, 0.3–2.5; $p = 0.7$).

Conclusions: Acute respiratory distress syndrome is common in mechanically ventilated patients with cirrhosis but is not independently associated with increased mortality.

Key Words: adult respiratory distress syndrome; cirrhosis; intensive care; mechanical ventilation

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Drs. Boente and Ghabril helped with acquisition, analysis, and interpretation of the data; drafting of the manuscript; and critical revision of the manuscript. They had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Ghabril is the guarantor of the content of the article, including the data and analysis. Dr. Bosslet helped with analysis and interpretation of the data and critical revision of the manuscript. Dr. Sheikh helped with acquisition of the data and analysis.

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Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome of acute lung injury characterized by disruption of the endothelial-epithelial lining resulting in capillary leak leading to an excess fluid collection in both the interstitium and alveoli in the absence of left heart disease (1–4). The consequences of ARDS include impaired gas exchange and decreased lung compliance, ultimately leading to life-threatening hypoxemic respiratory failure. Despite significant advances in the understanding of the pathophysiologic process of the disease and treatment strategies, mortality in ARDS remains greater than 40% (4).

Another disease entity associated with poor short- and long-term prognosis is decompensated liver cirrhosis. ICU admission due to complications of cirrhosis carry hospital mortality rates ranging from 43% to 87% (5–7). ARDS is estimated to occur in 8%

of patients with cirrhosis in the ICU and associated with increased mortality in critically ill patients with cirrhosis compared to those without cirrhosis (8, 9). The risk factors for developing ARDS in critically ill patients with cirrhosis include acute-on-chronic liver failure (most commonly associated with infection) and shock (8).

We previously reported that mechanically ventilated patients with cirrhosis with a Model for End-stage Liver Disease (MELD) greater than or equal to 33 had 61–64% 7-day mortality, where mechanical ventilation was independent predictor of mortality (10). Although there have been numerous studies investigating outcomes in pulmonary and extrapulmonary ARDS, there are little data evaluating the incidence and impact of ARDS in mechanically ventilated patients with cirrhosis. Furthermore, ARDS is anecdotally associated with increased perceived risk of mortality in patients with cirrhosis, but it is unclear if ARDS predicts mortality independent of commonly used models in the most critically ill patients with cirrhosis.

The aims of this study were to: 1) assess the incidence and clinical recognition of ARDS in mechanically ventilated patients with cirrhosis at a large academic transplant center; 2) compare characteristics and outcomes in patients with and without ARDS; and 3) assess the risk associated with ARDS after adjusting for other predictors of mortality.

MATERIALS AND METHODS

This study was performed at Indiana University Hospital, a large tertiary medical and transplant center, with Institutional Review Board (IRB) approval (IRB approval No. 1606251640). We performed a search of an administrative database using *International Classification of Diseases*, 9th Edition, codes for cirrhosis and mechanical ventilation between 2008 and 2015. Exclusion criteria included do not resuscitate or limited code status prohibiting intubation; severe congestive heart failure, defined as an ejection fraction of less than 30%; severe lung disease with a 1-second forced expiratory volume (FEV1) less than 35% predicted; or metastatic cancer (**Supplemental Table 4**, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>). The characterization of study subjects included retrospective calculation of MELD and Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) scores on day 1 of ICU care (**Supplemental Table 3**, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>).

Data Collection

The diagnosis of cirrhosis was confirmed by histology, radiographic evidence on ultrasound or CT, or clinical findings of portal hypertension. Supportive laboratory data included platelet count, albumin, international normalized ratio (INR), and bilirubin. We identified patients meeting diagnostic criteria for ARDS according to The Berlin Definition (1). Demographic and clinical data collected included the etiology of cirrhosis, the cause for mechanical ventilation, the need for vasoactive medications, suspected etiology of ARDS, severity of ARDS based on a calculation of the PaO_2 divided by the FiO_2 scored according to Berlin criteria for classifying ARDS severity, and disposition at discharge. Study data were collected and managed

using REDCap 7.4.23 (University of Minnesota, St. Paul, MN) electronic data capture tools hosted at Indiana University (11).

Outcome Measures

The primary outcome of the study was hospital mortality (including discharge to hospice), and the secondary endpoint was 90-day mortality. We compared demographic and clinical characteristics on ICU admission in mechanically ventilated patients with cirrhosis with and without ARDS. We assessed the interaction of ARDS and well-established clinical models (MELD and CLIF-SOFA) to predict hospital and 90-day mortality. Finally, we performed post hoc analysis comparing outcomes in clinically recognized versus unrecognized ARDS.

Statistical Analysis

Descriptive statistics were performed to characterize patient groups and are reported as numbers (percentage), mean and SD, or median and interquartile range. Simple and multiple logistic regression analyses were performed to assess the association of ARDS with the study endpoints although controlling for liver and other organ disease severity, as well as other predictors of those endpoints in the study cohort. Area under the receiver operating characteristic (AUROC) curve analysis was used to assess the performance of CLIF-SOFA and MELD in predicting mortality in patients with and without ARDS. A p value of less than 0.05 was considered significant for all analyses. Statistical analysis was performed using SPSS version 24.0 (IBM, Armonk, NY) and Stata version 15 (Statacorp, College Station, TX).

RESULTS

The study cohort comprised of 181 mechanically ventilated patients with cirrhosis who met predefined eligibility criteria. Thirty-five of these patients (19%) met the Berlin definition criteria for ARDS.

Baseline demographics and clinical characteristics are described in **Table 1**. The patients were predominately Caucasian (91%). There was a higher proportion of females in the ARDS cohort (46% vs 30%; $p = 0.08$). Patients with ARDS were more likely to be on vasopressors (54% vs 21%) and had more pronounced laboratory derangements with significantly higher values for bilirubin, INR, lactate, and lower $\text{PaO}_2:\text{FiO}_2$ at admission to the ICU. Both MELD and CLIF-SOFA were significantly higher in patients with ARDS on ICU admission.

The etiology of ARDS was frequently multifactorial and was most commonly related to sepsis (54%), pneumonia (46%), and aspiration (29%) (**Supplemental Table 1**, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>). The severity of ARDS based on $\text{PaO}_2:\text{FiO}_2$ was mild in two patients (6%), moderate in 20 patients (57%), and severe in 13 patients (37%). The majority of patients with ARDS received mechanical ventilation for primary respiratory failure (66%) or sepsis (20%) (**Supplemental Table 2**, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>). Patients without ARDS were more likely to receive mechanical ventilation for nonrespiratory problems including altered mental status (33%) and gastrointestinal hemorrhage (30%); only 18% had respiratory failure due to a primary respiratory

TABLE 1. Demographic and Clinical Variables in the Study Cohort of Mechanically Ventilated Patients With Cirrhosis (n = 181), Comparing Those With and Without Acute Respiratory Distress Syndrome

Clinical Variable	ARDS (n = 35)	Non-ARDS (n = 146)	p
Mean age, yr, mean ± SD	52 ± 12	54 ± 11	0.4
Male, %	54	70	0.08
Race, %			0.14
White	89	91	
Black	11	7	
Hispanic	None	None	
Other	None	1	
Cirrhosis etiology, %			0.18
Alcohol	26	29	
Viral	14	23	
Alcohol and viral	23	16	
Nonalcoholic fatty liver disease	11	19	
Autoimmune	11	4	
Idiopathic/others	15	9	
Reason for mechanical ventilation, %			< 0.001
Primary respiratory failure	66	18	
Gastrointestinal hemorrhage	6	30	
Sepsis	20	7	
Altered mental status	8	33	
Elective	None	12	
Mean ventilator days, d, mean ± SD	10 ± 9	4 ± 6	< 0.001
Need for tracheostomy, %	8.6	0.7	0.04
Vasopressor use ICU day 1, %	54	21	0.03
Mean laboratory data, ICU day 1, mean ± SD			
Bilirubin, mg/dL	10.6 ± 8.5	5.3 ± 6	< 0.001
Creatinine, mg/dL	2.2 ± 1.4	2.0 ± 1.5	0.4
International normalized ratio	3.0 ± 2	2.0 ± 0.7	0.004
Serum sodium, mmol/L	137 ± 6.4	135 ± 6.5	0.13
WBC count, 1,000/mL	11 ± 7	12 ± 8	0.8
Lactate mmol/L	5.4 ± 4.2	4.1 ± 4.1	0.2
Bicarbonate mEq/L	21 ± 6.4	21 ± 8.4	0.9
PaO ₂ :FiO ₂	145 ± 75	316 ± 170	< 0.001
Model for End-Stage Liver Disease score, mean ± SD	32 ± 10	24 ± 9	< 0.001
Chronic Liver Failure-Sequential Organ Failure Assessment score, mean ± SD	15 ± 4	11 ± 4	< 0.001
Mean length of stay, d, mean ± SD			
Hospital	27 ± 20	18 ± 13	0.001
ICU	14 ± 13	7 ± 6	< 0.001

ARDS = acute respiratory distress syndrome.

The data are reported as mean ± SD or percentages.

Boldface values indicate $p < 0.05$.

TABLE 2. Hospital Mortality in Patients With and Without Acute Respiratory Distress Syndrome With and Without Stratification by Chronic Liver Failure-Sequential Organ Failure Assessment and Model for End-Stage Liver Disease Using the 75th Percentile Thresholds

Hospital Mortality	ARDS, % (n = 35)	Non-ARDS, % (n = 146)	p
All patients	40	22	0.03
Chronic Liver Failure-Sequential Organ Failure Assessment			
≥ 14	56	55	0.9
< 14	8	13	0.6
Model for End-Stage Liver Disease			
≥ 33	73	54	0.2
< 33	15	15	0.9

ARDS = acute respiratory distress syndrome.

problem. Patients with ARDS had higher rates of suspected and confirmed infections, predominantly related to higher rates of Gram-negative bacterial infections. When echocardiography was available, patients with ARDS also had higher rates of diastolic dysfunction (Supplemental Table 2, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>).

Hospital Course and Outcomes

Overall mortality was 25%; 35 (19%) died in the hospital and 11 (6%) were discharged to hospice care (Table 3). Patients with ARDS

TABLE 3. Summary of Multiple Logistic Regression Analysis for Predictors of Hospital and 90-Day Mortality

Hospital Mortality		
Variable	OR (95% CI)	p
ARDS	0.8 (0.3–2.5)	0.7
CLIF-SOFA	1.2 (1.1–1.4)	< 0.001
MELD	1.12 (1.1–1.2)	< 0.001
Sepsis as the reason for mechanical ventilation	8 (1.8–35.3)	0.006
90-d Mortality		
Variable	OR (95% CI)	p
ARDS	1.1 (0.37–3.2)	0.9
CLIF-SOFA	1.3 (1.2–1.5)	< 0.001
MELD	1.16 (1.1–1.2)	< 0.001
Age	1.04 (1.0–1.07)	0.04
Sepsis as the reason for mechanical ventilation	2.3 (0.5–10.8)	0.3

ARDS = acute respiratory distress syndrome, CLIF-SOFA = Chronic Liver Failure-Sequential Organ Failure Assessment, MELD = Model for End-Stage Liver Disease, OR = odds ratio.

Results are described as an OR, its 95% CI, and associated p value.

had higher hospital mortality (combined endpoint of death or discharge to hospice) (40% vs 22%) and 90-day mortality (51% vs 30%) (Table 2) than those without ARDS. Although ARDS was associated with increased hospital and 90-day mortality, no mortality difference was observed after stratification of the cohort using the 75th percentile value for MELD (≥ 33) and CLIF-SOFA (≥ 14) (Table 3). Similar findings were noted for ARDS and 90-day mortality.

Patients with ARDS had prolonged need for mechanical ventilation and longer ICU and hospital length of stay (Table 1). Patients with ARDS were less likely to be discharged to home in comparison to those without ARDS (23% vs 51%; $p = 0.008$).

Predictors of Mortality

In the unadjusted analysis, ARDS was associated with hospital mortality (odds ratio [OR], 2.4; 95% CI, 1.1–5.2; $p = 0.03$) and 90-day mortality (OR, 2.5; 95% CI, 1.2–5.2; $p = 0.02$). However, ARDS was not associated with mortality on multiple logistic regression analysis after adjusting for MELD, CLIF-SOFA, and other clinical factors (Table 3). The independent predictors of hospital and 90-day mortality were CLIF-SOFA (OR, 1.25; 95% CI, 1.1–1.4; $p < 0.001$), MELD (OR, 1.12; 95% CI, 1.1–1.2; $p < 0.01$), and sepsis as the primary reason for mechanical ventilation (OR, 8.02; 95% CI, 1.8–35.3; $p = 0.006$). Age (OR, 1.04; 95% CI, 1.0–1.07; $p = 0.043$) was also found to be an independent predictor of 90-day mortality.

Impact of ARDS on Predictive Models for Mortality

Both MELD and CLIF-SOFA performed well in predicting hospital (Fig. 1) and 90-day mortality in the overall cohort as demonstrated by the AUROC curve analysis (Supplemental Table 5, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>). The C-statistic for MELD and CLIF-SOFA in predicting hospital mortality in the cohort was 0.8 and 0.78, respectively (Fig. 1; and Supplemental Table 5, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>). The C-statistic for MELD and CLIF-SOFA in predicting hospital mortality in patients with ARDS was 0.89 and 0.77, respectively (Fig. 2; and Supplemental Table 5, Supplemental Digital Content 1, <http://links.lww.com/CCX/A83>).

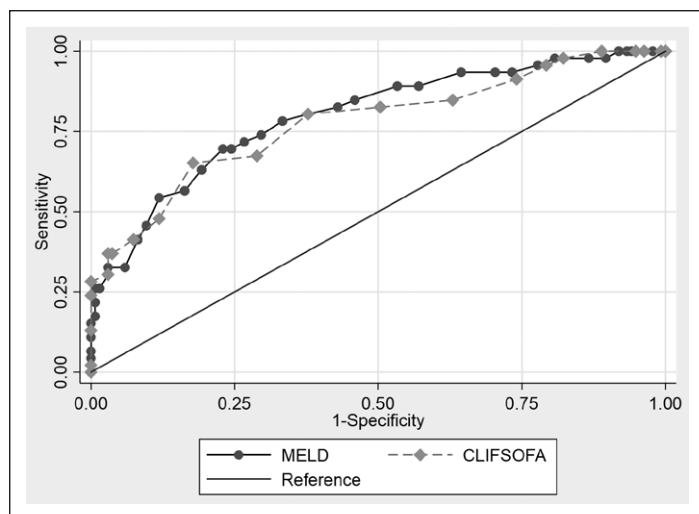


Figure 1. Area under the receiver operator characteristic curve for the association of Model for End-Stage Liver Disease (MELD) and Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) with hospital mortality in all mechanically ventilated patients with cirrhosis (acute respiratory distress syndrome [ARDS] and non-ARDS).

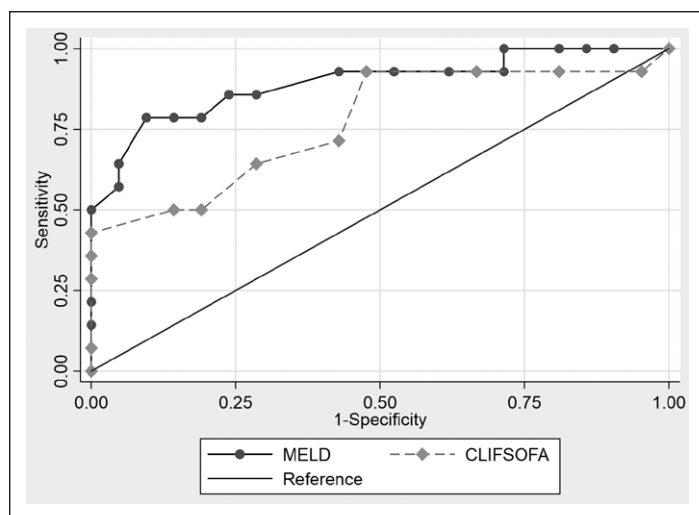


Figure 2. Area under the receiver operator characteristic curve for the association of Model for End-Stage Liver Disease (MELD) and Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) with hospital mortality in mechanically ventilated patients with cirrhosis and acute respiratory distress syndrome.

The C-statistic for MELD was higher than that of CLIF-SOFA at predicting hospital mortality for patients with ARDS ($p = 0.01$).

DISCUSSION

In this study of a high-risk group of mechanically ventilated patients with cirrhosis, ARDS was common (19%) and was associated with significantly increased morbidity and mortality. Mechanically ventilated patients with cirrhosis and ARDS were twice as likely to die in the hospital and within 90 days when compared with those without ARDS. In addition, ARDS was associated with increased duration of mechanical ventilation, prolonged hospital and ICU length of stay, and decreased likelihood of being

discharged to home. Not surprisingly, the incidence of ARDS in our study was twice as high as that reported in all patients with cirrhosis requiring intensive care because we only studied a higher-risk group of mechanically ventilated patients (2, 8). However, we also found common association with sepsis and association with higher MELD and CLIF-SOFA scores, similar rates of severity of ARDS, although lower hospital mortality (40%) in our cohort relative to a reported mortality rate of 82% (8).

Others have reported that ARDS was associated with increased mortality in patients with cirrhosis when compared with patients without cirrhosis (9). However, ARDS was only associated with hospital mortality in our cohort of only patients with cirrhosis on univariate analysis. In the risk-adjusted analysis, ARDS was not an independent predictor of hospital or 90-day mortality. It was not surprising that both MELD and CLIF-SOFA independently predicted mortality. The MELD is a scoring system that is used to assess severity of chronic liver disease and was initially developed to predict 3-month mortality in hospitalized patients with cirrhosis. The score incorporates serum bilirubin, creatinine, and the INR with a score of 30–39 having an observed 52.6% mortality (12). The CLIF-SOFA score was designed to assess acute-on-chronic liver failure using a number of indices of end-organ failure including bilirubin, creatinine, presence and severity of hepatic encephalopathy, need for vasoactive medications, and severity of hypoxemia (13, 14). These findings suggest that at a given threshold of CLIF-SOFA and MELD, the driving factor for mortality is not ARDS, but rather the severity of end-organ impairment or septic shock. The clinical implication is that a diagnosis of ARDS in a critically ill patient with cirrhosis does not in itself define outcomes in mechanically ventilated patients with cirrhosis. Sepsis as a cause of mechanical ventilation was associated with increased risk of hospital mortality. This was not surprising because infection is associated with increased mortality in patients with cirrhosis (15).

Mortality risk stratification using the 75th percentile values for CLIF-SOFA (≥ 14) and MELD (≥ 33) measured at admission to the ICU provided valuable prognostic information with reasonable sensitivity and specificity. Overall accuracy of both models was similar, but MELD outperformed CLIF-SOFA at predicting mortality in patients with ARDS. This may be related to the fact that the respiratory failure component of CLIF-SOFA and the Berlin Criteria for ARDS share similar definitions based on $\text{PaO}_2/\text{FiO}_2$ ratio, whereas MELD does not include a respiratory failure component. Although both MELD and CLIF-SOFA can be used early in the course of care to help aide in shared decision-making among caregivers and surrogate decision-makers, our data support the preferential use of MELD in patients with ARDS in modeling mortality risk in this population.

This study does not attempt to describe the incidence of ARDS in cirrhosis, but rather the incidence of ARDS where it matters the most, in mechanically ventilated patients with cirrhosis. This study has several limitations. It is a single-center, retrospective study which lacks racial diversity (91% Caucasian). Although it represents one of the larger cohorts of ARDS in cirrhosis, the sample is still relatively small and may be underpowered. The Berlin criteria for ARDS has been demonstrated to be susceptible to subjective assessment and interobserver variability (16).

Finally, ARDS-specific interventions, for example, ventilator settings, were difficult to collate and analyze on a case-by-case basis. Hence, our data do not elucidate the impact of clinical recognition or specific interventions on outcomes of ARDS in this patient population, irrespective of etiology or severity. The strengths of the study include the detailed description of a unique cohort, the relatively large sample size for a study of this type and the information it provides on infection and ARDS outcomes in this population.

CONCLUSIONS

ARDS is common in mechanically ventilated patients with cirrhosis, and although it is associated with increased morbidity, it does not independently predict mortality in this patient group. In patients with cirrhosis and ARDS, MELD outperforms CLIF-SOFA in predicting hospital mortality. Our data add to the growing body of evidence that infection in patients with cirrhosis is a major driver of morbidity and mortality. Future studies are needed to prospectively study ARDS, validate our results, and identify strategies to identify and treat ARDS in patients with cirrhosis.

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