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Risk Factors and Outcomes of Acute Respiratory Distress Syndrome in Critically Ill Patients with Cirrhosis

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Abstract

Aim: Prior randomized controlled trials of acute respiratory distress syndrome (ARDS) excluded critically ill patients with cirrhosis. Data regarding risk factors for ARDS development and outcomes from ARDS in patients with cirrhosis are scarce. We sought to characterize outcomes from ARDS in patients with cirrhosis.

Methods: An observational cohort of patients with cirrhosis admitted to an intensive care unit (ICU) at a high-volume liver transplant center between January 1, 2012 and December 31, 2014 were reviewed. ARDS cases were identified according to the Berlin definition. Potential risk factors were examined in multivariable logistic regression analysis for ARDS development. Outcomes including in-hospital mortality were compared between ARDS and non-ARDS patients.

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AUTHOR CONTRIBUTIONS

Philip Yang was involved in study concept and design, acquisition of data, interpretation of data, drafting of the manuscript, critical revision of manuscript for important intellectual content, and study supervision. He is the guarantor of the article.

Perry Formanek was involved in study concept and design, acquisition of data, interpretation of data, critical revision of manuscript for important intellectual content, and study supervision.

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Results: 559 patients met inclusion criteria and 45 (8.1%) developed ARDS. Differences between ARDS and non-ARDS patients included sepsis, Model for End-Stage Liver Disease – Sodium score, and Sequential Organ Failure Assessment score. In-hospital mortality was higher in cirrhotic patients with ARDS compared to those without ARDS (82.2% vs. 27.6%, $p<0.001$). In multivariable analysis, acute on chronic liver failure (ACLF) (OR 8.69, 95% CI 2.28–33.18, $p<0.01$) and shock on ICU admission (OR 3.13, 95% CI 1.57–6.24, $p=0.001$) were associated with ARDS development, whereas etiology of cirrhosis or alcohol use were not.

Conclusions: ACLF and shock on ICU admission were risk factors for ARDS development, whereas etiology of cirrhosis and alcohol were not. Mortality from ARDS was markedly increased in patients with cirrhosis. Early recognition and treatment for infection may be important for improving the high mortality in this group of patients.

Keywords

Acute respiratory distress syndrome; Alcohol; Cirrhosis; Sepsis; Shock

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a severe form of non-cardiogenic pulmonary edema and hypoxic respiratory failure identified in patients who meet the Berlin Definition¹. The Berlin Definition is comprised of several parameters including respiratory failure that is not fully explained by hydrostatic pulmonary edema, onset within one week of a predisposing condition, bilateral opacities on chest imaging, and a partial pressure of arterial blood-to-fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio below 300 mm Hg¹. Incidence rates for ARDS is around 10.4% among all intensive care unit (ICU) admissions, with hospital mortality between 35% and 46%². Major efforts are currently underway to identify at-risk patients with a more focused approach on many sub-phenotypes of ARDS³. However, data regarding ARDS in patients with cirrhosis are limited despite increasing survivorship of these patients^{4, 5}. This is in part due to prior randomized clinical trials from the National Heart, Lung, Blood Institute's ARDS Network excluding patients with severe liver disease or cirrhosis^{6, 7}. More studies on ARDS in patients with liver cirrhosis are needed to inform the management of this complex cohort of patients.

Many predisposing conditions contribute to the development of ARDS, with the most common being sepsis, but also including pneumonia, aspiration, multiple transfusions, and pancreatitis^{8–10}. Risk modifiers including alcohol use disorder and tobacco use also contribute to the risk for ARDS development^{9, 11, 12}. Alcohol use disorder is one of the most common etiologies for cirrhosis development¹³ as well as a risk modifier for ARDS development in the Lung Injury Prediction Score^{9, 14}. Patients with decompensated cirrhosis have a dysregulated innate immune response with elevated levels of the pro-inflammatory cytokines IL-6 and IL-8¹⁵ that contribute to severe lung injury in those at-risk^{16, 17}. The handful of predisposing conditions and risk modifiers in ARDS are common in patients with cirrhosis, and are further complicated by baseline immune dysfunction and additional respiratory complications from pulmonary edema and pleural effusions¹⁸. This predisposition to respiratory failure can contribute to acute-on-chronic liver failure (ACLF), where requirement for mechanical ventilation has been shown to be a poor prognostic

indicator^{19, 20}. These factors contribute to a complex phenotype with little information regarding risk factors and outcomes unique to patients with cirrhosis and ARDS.

We aim to examine the predisposing conditions and risk modifiers for development of ARDS that are important in patients with cirrhosis, and to investigate the outcomes after development of ARDS in this phenotype. We hypothesize that sepsis is the predisposing condition and alcohol use is the risk modifier of most importance. We also hypothesize that the in-hospital mortality is high in patients with decompensated cirrhosis who develop ARDS compared to their counterparts without ARDS.

METHODS

Patient Selection and Environment:

An observational cohort of consecutive patients with cirrhosis who were admitted to an ICU at Loyola University Medical Center (LUMC) between January 1, 2012 and December 31, 2014 were reviewed retrospectively. LUMC is a large, academic tertiary care medical center with a high-volume liver transplant program. Eligibility criteria included the following: 16 years of age or older, clinical diagnosis of cirrhosis and admission to an ICU. Cases of cirrhosis were determined by two prior encounters with diagnosis of cirrhosis, and the diagnosis was confirmed via chart review by two physicians (PY, PF). For patients who had multiple recorded admissions that met the eligibility criteria, only the most recent admission was included for analysis.

ARDS Case Identification:

Two blinded physician reviewers (PY, PF) independently reviewed the electronic medical record following the Berlin definition for ARDS¹. The two physician reviewers had experience and underwent further training in applying the Berlin Definition by a pulmonary and critical care physician with expertise in ARDS research (MA). In the cases of discordant patient assessment between the two physician reviewers, adjudication was performed by a third expert reviewer (MA). Substantial interobserver reliability between the two reviewers was observed, with κ -coefficient 0.66 (95% confidence interval [CI] 0.56–0.78). Adjudication was performed in 28 cases. Common reasons for discordance included differing classification of pulmonary edema between reviewers, and not meeting the one-week time criteria for the Berlin Definition of ARDS.

Outcome Measurements:

The primary outcome was development of ARDS. Secondary outcomes were 28-day ventilator-free days (defined as number of days alive and breathing spontaneously without the aid of a ventilator for at least 48 hours in a 28-day period from ICU admission)²¹, 28-day ICU-free days (defined as number of days alive and outside the ICU in a 28-day period from ICU admission), most recent known transplant status, and in-hospital death.

Candidate Variables:

Potential risk modifiers and predisposing conditions for development for ARDS were selected *a priori*, which included age, sex, sepsis, alcohol use disorder, tobacco use,

diabetes^{11, 12, 22}, presence of shock (cardiovascular component of Sequential Organ Failure Assessment [SOFA] score = 2, which is requirement for vasoactive agents such as dopamine, dobutamine, epinephrine, or norepinephrine), renal dysfunction (renal component of SOFA score = 2, which is serum creatinine concentration ≥ 2.0 mg/dL or urine output <500 mL/day), coagulopathy (coagulation component of SOFA score = 2, which is platelet count $<100,000/\mu\text{L}$)²³, etiology of cirrhosis^{15–18, 24}, Charlson Comorbidity Index²⁵, and Model for End-Stage Liver Disease – Sodium (MELD-Na) score²⁶, and ACLF (yes or no)¹⁹. Etiology of cirrhosis was abstracted from the EMR by the physician reviewers. For patients who had alcoholic and another etiology of cirrhosis listed concurrently in the chart, only those with alcohol use disorder listed as the sole etiology of cirrhosis were categorized as having alcoholic cirrhosis. For the patients who developed ARDS, the SOFA scores were also compared between the time of admission to ICU and the time of ARDS diagnosis.

Statistical Analysis:

Baseline characteristics were presented as medians with interquartile ranges and compared using Wilcoxon-Mann-Whitney or Kruskal-Wallis nonparametric tests with continuous variables. A comparison of two or more proportions was performed using chi-square test. Logistic regression was used to assess the risk for ARDS development.

The candidate variables listed previously were entered into a univariable logistic regression. Candidate variables with $p < 0.2$ in the univariable analysis were examined in a multivariable logistic regression analysis²⁷, and the area under the receiver operating characteristic curve (AUC) was calculated with the multivariable model. Cirrhosis type as a dichotomous variable for alcoholic cirrhosis (yes or no) and MELD-Na score were forced into the final model because they were the primary aims of this study. Infection-related ACLF (yes or no) according to the study on the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) database¹⁹ was added into the final model to examine its association with ARDS. ACLF in the NACSELD database was defined as two or more organ failures among West Haven hepatic encephalopathy grade III or IV, shock (mean arterial pressure <60 mmHg or reduction of 40 mmHg in systolic blood pressure from baseline), need for mechanical ventilation, or need for renal replacement therapy¹⁹. Hosmer-Lemeshow test was used to assess the goodness-of-fit for the model. Comparisons for the secondary outcomes were also made by ARDS severity.

The Institutional Review Boards of Loyola University Chicago approved this study. Analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Selection and Baseline Characteristics:

A total of 822 adult patients with cirrhosis were admitted to an ICU during the study period. After selecting the most recent ICU admission, 559 unique patients remained in the analysis cohort. Forty-five patients (8.1%) met criteria for ARDS. The median time from hospital admission to ARDS development was 2.6 days (interquartile range [IQR] 0.40–4.0). The most common predisposing condition for ARDS was sepsis (84.4%, $n=38$), followed by

pneumonia (n=3), aspiration (n=1), trauma (n=1), and soft tissue infection (n=1). Twenty-five ARDS patients had positive cultures, and of these, sixteen patients had positive cultures from multiple sources. Most common sources of positive cultures were blood (n=14), followed by ascites fluid (n=7) and urine (n=7). Most commonly identified organisms were *Enterococcus faecium* or *Enterococcus faecalis* (n=7), *Pseudomonas aeruginosa* (n=5), *Escherichia coli* (n=4), and *Klebsiella pneumoniae* (n=4). Notable differences between the ARDS and non-ARDS patients included sepsis diagnosis, MELD-Na score, and multiple organ dysfunctions per SOFA criteria (Table 1). There were no differences between the ARDS and non-ARDS patients with regard to the Charlson Comorbidity Index and the etiology of cirrhosis. The proportion of patients with an alcohol use disorder or tobacco use were also not different between the ARDS and non-ARDS patients (Table 1). Hepatocellular carcinoma (with or without treatment or transplant) was identified in 7% (n=39) of the cohort, and the case-rate was not different between ARDS and non-ARDS patients (p=0.93).

In patients who developed ARDS, respiratory, cardiovascular, and central nervous system components of the SOFA scores increased significantly from the time of ICU admission to the time of ARDS diagnosis (p=0.001, p<0.001, p=0.03 for respiratory, cardiovascular, and central nervous system components, respectively; Table 1). ACLF was present in much greater proportion in patients with ARDS than in patients without ARDS (Table 1). In patients with ARDS, sepsis was present in all patients with ACLF. At the time of ARDS diagnosis, the proportion with mild, moderate, and severe ARDS cases was 31.1% (N=14), 42.2% (N=19), and 26.6% (N=12), respectively. Nine patients with mild ARDS and 12 patients with moderate ARDS subsequently progressed to a higher severity of ARDS. A total of 30 patients met criteria for severe ARDS at some point during the admission.

Outcome Measurements:

The median 28-day ICU-free days was markedly lower in ARDS patients compared to those without ARDS (0 [IQR 0–0] vs. 22 [IQR 0–25], p<0.001). ARDS patients also had significantly lower 28-day ventilator-free days compared to non-ARDS patients (Table 2). In-hospital death occurred in 82.2% of ICU patients with cirrhosis who developed ARDS, compared to 27.6% of patients without ARDS (p<0.001). The proportion of in-hospital death did not differ between the different severities of ARDS (Table 2). Of those who died, the proportion of patients who died from an infectious etiology was not different between ARDS and non-ARDS groups (p=0.08). In the patients with ARDS, neither an increase in cardiovascular SOFA score (p=0.48) nor an increase in renal SOFA score (p=0.13) was associated with in-hospital death. Among patients receiving invasive mechanical ventilation, median tidal volume to ideal body weight ratio was not different between ARDS and non-ARDS patients (7.83 cc/kg [IQR 6.76–8.76] vs. 7.89 cc/kg [IQR 7.04–8.91], p=0.89). Only one patient from the ARDS cohort received a liver transplant compared to 72 patients from the cohort without ARDS (p<0.001).

Predisposing Conditions and Risk Modifiers for ARDS:

In the univariable logistic regression analysis of the predisposing conditions and risk modifiers for development of ARDS, increased odds was noted from sepsis (OR 9.77, 95% CI 4.06–23.48, p<0.001), presence of shock on admission (OR 5.36, 95% CI 2.84–10.13,

$p < 0.001$), and renal dysfunction (OR 2.28, 95% CI 1.23–4.21, $p = 0.009$). Neither alcohol use disorder (OR 0.99, 95% CI 0.53–1.83, $p = 0.99$) nor alcohol cirrhosis (OR 1.63, 95% CI 0.62–4.29, $p = 0.985$) was associated with ARDS development. In the multivariable analysis adjusted for sex, diabetes, sepsis, cirrhosis type, ACLF, cardiovascular dysfunction, renal dysfunction, and MELD-Na score, ACLF had an OR of 8.69 (95% CI 2.28–33.18, $p < 0.01$) and presence of shock on ICU admission had an OR of 2.24 (95% CI 1.11–4.51, $p = 0.03$) for the development of ARDS (Figure 1). Sepsis was no longer associated with ARDS development when ACLF was added into the model. Similar to the results of univariable analysis, neither alcoholic cirrhosis nor history of alcohol use disorder was associated with ARDS development in the multivariable analysis. No collinearity occurred between any of the independent variables and no interaction terms were found to be significant in the multivariable model. Specifically, no interactions were found between ACLF and other variables related to the components of ACLF, including sepsis, cardiovascular SOFA score 2, and renal SOFA score 2 ($p > 0.05$ for all). The model had good fit by the Hosmer-Lemeshow goodness-of-fit test ($p = 0.18$).

DISCUSSION

In this study of a large cohort of critically ill patients with cirrhosis, we demonstrate that patients with cirrhosis who develop ARDS are unique from the patients included in prior studies on ARDS. There are three important findings from our study. First, the mortality from ARDS in patients with cirrhosis was markedly higher than previously reported in non-cirrhotic disease cohorts^{1, 2}, and most cirrhotic patients who developed ARDS died in-hospital regardless of the severity of ARDS. Second, the etiology of cirrhosis and history of alcohol use disorder did not carry a significant risk for development of ARDS, in contrast to prior studies identifying alcohol use disorder as a risk factor for ARDS^{14, 28}. Third, mortality did not differ significantly among the different severities of ARDS in our study, which is contrary to the results published in prior studies^{1, 2} that showed increasing mortality with increasing severities of ARDS.

Our case rate of ARDS at 8.1% was comparable to the 10.4% incidence of ARDS reported in an international multicenter epidemiologic study². In the fully adjusted model, sepsis was not associated with development of ARDS, but this was likely because all patients with sepsis also had an infection-related ACLF which carried the highest odds risk for ARDS development. In ARDS patients with positive cultures, the most common organisms identified in our cohort were similar to those reported in prior literature for other cohorts of patients with ARDS²⁹. However, the most common sources of positive cultures in our cohort were slightly different from prior studies showing that lung was the most common site of infection in ARDS patients³⁰. The median time from hospital admission to ARDS development was 2.6 days, which was comparable to the time of onset of ARDS previously reported in literature^{31, 32}.

However, the risk modifiers for development of ARDS in our cohort of patients with cirrhosis were different from the findings reported in prior studies of other cohorts of patients with ARDS. For example, the proportion of alcohol use disorder was similar between ARDS and non-ARDS patients, and alcoholic cirrhosis as well as alcohol use

disorder did not carry an increased odds risk for development of ARDS in our patient cohort. Prior studies examining alcohol use disorder showed an increased risk for ARDS development in patients with sepsis¹⁴. Similar to our study, the authors showed in their cohort of septic shock patients that the association of chronic hepatic dysfunction was most strongly associated with mortality from ARDS. However, the authors did not examine the role of the etiology of cirrhosis in the development of ARDS. We demonstrate that the etiology of cirrhosis was not a major determinant for ARDS development. More studies are needed to investigate the interaction between alcohol use disorder and alcoholic cirrhosis on the development of ARDS.

ARDS was associated with significant morbidity and mortality in our cohort of critically ill patients with cirrhosis, resulting in lower median 28-day ICU-free days and lower median 28-day ventilator-free days compared to the patients without ARDS. Mortality was extremely high, with in-hospital death occurring in 82.2% of patients who developed ARDS, compared to only 27.6% in patients without ARDS. The mortality associated with ARDS was significantly higher than a recently published mortality rate ranging from 34.9% for mild ARDS to 46.1% for severe ARDS². The mortality in our study was more comparable to, but still higher than, a recent study showing a 62% mortality in patients with cirrhosis who developed ARDS³³. Interestingly, mortality did not differ significantly among the different severities of ARDS in our study, which is contrary to the results published in the Berlin Definition¹ and other studies² that showed increasing mortality with increasing severities of ARDS. One contributing factor is that patients with cirrhosis tend to rapidly progress in severity of ARDS, which was the case in the large majority of our patients. The progression in the severity of hypoxemia in ARDS and the high mortality rate appear to be unique to this phenotype and should be further examined separately from other phenotypes of ARDS. Another consideration is that the lung protective ventilation strategy was not followed in many patients, as demonstrated by the tidal volume-to-ideal body weight ratios that were comparable between ARDS and non-ARDS patients. However, the data presented herein do not clarify whether this occurred due to physiologic or pulmonary mechanic limitations in patients with cirrhosis or due to practice behaviors.

A recent study by Gacouin, et al³³ has also explored the mortality associated with cirrhosis in patients who had ARDS according to the older American-European Consensus Conference Definition³⁴, and has concluded that cirrhosis was a poor prognostic factor in patients with ARDS. However, this study showed a similar mortality between cirrhotic patients who developed ARDS and those without ARDS. It also showed that the non-pulmonary SOFA scores were higher in cirrhotic patients than in non-cirrhotic patients whereas the pulmonary SOFA scores did not differ, suggesting that the increased mortality was related to extrapulmonary organ failures rather than hypoxemia. Our study shows several contrasting findings. First, cirrhotic patients who developed ARDS actually had markedly higher mortality than those without ARDS in our study. Also, neither an increase in cardiovascular or renal SOFA score nor a higher severity of ARDS were associated with increased in-hospital mortality in our cohort. This suggests that the increased mortality from ARDS in patients with cirrhosis may be intrinsically related to the presence of ARDS, rather than the severity of hypoxemia or extrapulmonary organ dysfunction. Further studies will be needed to reconcile these contrasting findings, and to elucidate the contribution of

respiratory versus extrapulmonary organ failure for mortality in cirrhotic patients with ARDS.

There are several limitations to this study. First, this was a retrospective observational study. Accurate evaluation of ARDS and the data collection for predisposing conditions and risk modifiers for this cohort was limited by the diagnostic studies and recorded data for each patient. For example, we were unable to distinguish whether patients with history of alcohol use disorder or alcoholic cirrhosis were still actively using alcohol at the time of inclusion. This may indirectly affect the development of ARDS through other causes such as aspiration, as well as the secondary outcome of most recent transplant status. This study was also a single-center study, which limits the generalizability of this data to cirrhotic patients in other institutions or geographic regions. The absolute number of ARDS cases identified was also relatively small, which may have resulted in insufficient power to detect important risk factors for ARDS development. Future studies will be necessary to identify the effect of early sepsis treatment and fluid management on outcomes for ARDS in this phenotype. The role of fluid management in ARDS will be particularly important in setting of patients with cirrhosis who tend to inappropriately increase only noncentral blood volume in response to fluid resuscitation with crystalloids^{35, 36}. In addition, there is evidence to support the use of albumin to prevent certain complications in patients with cirrhosis³⁵, highlighting that they respond differently to fluid resuscitation compared to other critically ill patients. Therefore, the optimal strategy for fluid management for ARDS, especially in cirrhotic patients with hydrostatic edema, is another area of research that may impact the high mortality shown in our study.

Case-rates of in-hospital death from ARDS was very high in patients with cirrhosis regardless of the PaO₂/FiO₂ at onset, and infection-related ACLF and presence of shock on admission were the strongest risk factors for development of ARDS in this cohort. We demonstrate substantial differences in risk factors and outcomes in the cirrhosis phenotype from other patient phenotypes in ARDS that were previously studied. Focused and tailored interventions for prevention and early diagnosis of decompensated cirrhotic patients on the wards with infections may be an important intervention for prevention of ARDS and improvement of health outcomes.

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REFERENCES

1. Ranieri V, Rubenfeld G, Thompson B, et al. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA. 2012;307: 2526–33. [PubMed: 22797452]
2. Bellani G, Laffey J, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016;315: 788–800. [PubMed: 26903337]
3. Matthay M, McAuley D, Ware L. Clinical trials in acute respiratory distress syndrome: challenges and opportunities. Lancet Respir Med. 2017;5: 524–34. [PubMed: 28664851]

4. Schmidt M, Barritt A, Orman E, Hayashi P. Decreasing mortality among patients hospitalized with cirrhosis in the United States from 2002 through 2010. *Gastroenterology*. 2015;148: 967–77. [PubMed: 25623044]
5. Kanwal F, Tansel A, Kramer J, Feng H, Asch S, El-Serag H. Trends in 30-Day and 1-Year Mortality Among Patients Hospitalized With Cirrhosis From 2004 to 2013. *Am J Gastroenterol*. 2017;112: 1287–97. [PubMed: 28607480]
6. Brower R, Matthay M, Morris A, Schoenfeld D, Thompson B, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342: 1301–8. [PubMed: 10793162]
7. Papazian L, Forel J, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363: 1107–16. [PubMed: 20843245]
8. Hudson L, Milberg J, Anardi D, Maunder R. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1995;151: 293–301. [PubMed: 7842182]
9. Thakur LK M, Thakur S, Pieper M et al. Alcohol consumption and development of acute respiratory distress syndrome: a population-based study. *Int J Environ Res Public Health*. 2009;6: 2426–35. [PubMed: 19826554]
10. TenHoor T, Mannino D, Moss M. Risk factors for ARDS in the United States: analysis of the 1993 National Mortality Followback Study. *Chest*. 2001;119: 1179–84. [PubMed: 11296187]
11. Trillo-Alvarez C, Cartin-Ceba R, Kor D, et al. Acute lung injury prediction score: derivation and validation in a population-based sample. *Eur Respir J*. 2011;37: 604–9. [PubMed: 20562130]
12. Iribarren C, Jacobs D, Sidney S, Gross M, Eisner M. Cigarette smoking, alcohol consumption, and risk of ARDS: a 15-year cohort study in a managed care setting. *Chest*. 2000;117: 163–8. [PubMed: 10631215]
13. Heidelbaugh J, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. *Am Fam Physician*. 2006;74: 756–62. [PubMed: 16970019]
14. Moss M, Parsons P, Steinberg K, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. *Crit Care Med*. 2003;31: 869–77. [PubMed: 12626999]
15. Jalan R, Gines P, Olson J, et al. Acute-on chronic liver failure. *Journal of Hepatology*. 2012;57: 1336–48. [PubMed: 22750750]
16. Donahoe M Acute respiratory distress syndrome: A clinical review. *Pulmonary Circulation*. 2011;1: 192–211. [PubMed: 22034606]
17. Gustot T, Durand F, Lebrec D, Vincent J, Moreau R. Severe sepsis in cirrhosis. *Hepatology*. 2009;50: 2022–33. [PubMed: 19885876]
18. Hemprich U, Papadakos P, Lachmann B. Respiratory failure and hypoxemia in the cirrhotic patient including hepatopulmonary syndrome. *Curr Opin Anaesthesiol*. 2010;23: 133–8. [PubMed: 20019600]
19. Bajaj J, O’Leary J, Reddy K, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology*. 2014;60: 250–6. [PubMed: 24677131]
20. Asrani S, Simonetto D, Kamath P. Acute-on-Chronic Liver Failure. *Clin Gastroenterol Hepatol*. 2015;13: 2128–39. [PubMed: 26188138]
21. Schoenfeld D, Bernard G, Network A. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med*. 2002;30: 1772–7. [PubMed: 12163791]
22. Gajic O, Dabbagh O, Park P, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med*. 2011;183: 462–70. [PubMed: 20802164]
23. Vincent J, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22: 707–10. [PubMed: 8844239]
24. Huffmyer J, Nemergut E. Respiratory Dysfunction and Pulmonary Disease in Cirrhosis and Other Hepatic Disorders. *Respir Care*. 2007;52: 1030–6. [PubMed: 17650360]

25. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40: 373–83. [PubMed: 3558716]
26. Leise M, Kim W, Kremers W, Larson J, Benson J, Therneau T. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. *Gastroenterology.* 2011;140: 1952–60. [PubMed: 21334338]
27. Mickey R, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol.* 1989;129: 125–37. [PubMed: 2910056]
28. Moss M, Bucher B, Moore F, Moore E, Parsons P. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA.* 1996;275: 50–4. [PubMed: 8531287]
29. Yang S, Liao K, Chen C, Lin W. Positive blood culture is not associated with increased mortality in patients with sepsis-induced acute respiratory distress syndrome. *Respirology.* 2013;18: 1210–6. [PubMed: 23692513]
30. Sheu C, Gong M, Zhai R, et al. The influence of infection sites on development and mortality of ARDS. *Intensive Care Med.* 2010;36: 963–70. [PubMed: 20229040]
31. Shari G, Kojicic M, Li G, et al. Timing of the onset of acute respiratory distress syndrome: a population-based study. *Respir Care.* 2011;56: 576–82. [PubMed: 21276315]
32. Liao K, Chen C, Hsiue T, Lin W. Timing of acute respiratory distress syndrome onset is related to patient outcome. *J Formos Med Assoc.* 2009;108: 694–703. [PubMed: 19773207]
33. Gacouin A, Locufier M, Uhel F, et al. Liver Cirrhosis is Independently Associated With 90-Day Mortality in ARDS Patients. *Shock.* 2016;45: 16–21. [PubMed: 26674451]
34. Bernard G, Artigas A, Brigham K, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149: 818–24. [PubMed: 7509706]
35. Polli F, Gattinoni L. Balancing volume resuscitation and ascites management in cirrhosis. *Curr Opin Anaesthesiol.* 2010;23: 151–8. [PubMed: 20124894]
36. Møller S, Bendtsen F, Henriksen J. Effect of volume expansion on systemic hemodynamics and central and arterial blood volume in cirrhosis. *Gastroenterology.* 1995;109: 1917–25. [PubMed: 7498657]
37. Martin G, Mannino D, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *NEngl JMed.* 2003;348: 1546–54.

Figure 1.

Multivariable logistic regression for risk factors and predisposing conditions for ARDS development.

Candidate variables with $p < 0.2$ in the univariable analysis were examined in a multivariable logistic regression analysis. These included sepsis, male sex, diabetes, shock on admission, and renal dysfunction, all examined as dichotomous variables. Cirrhosis type as a dichotomous variable for alcoholic cirrhosis (yes or no) and MELD-Na score (as a continuous variable) were forced into the model because they were the primary aims of this study. ACLF was also added into the model to determine its association with ARDS. Results were as follows: sepsis (OR 2.59, 95% CI 0.94–7.13, $p = 0.07$), male sex (OR 1.58, 95% CI 0.80–3.15, $p = 0.19$), diabetes (OR 1.75, 95% CI 0.87–3.54, $p = 0.12$), alcoholic cirrhosis (OR 1.15, 95% CI 0.56–2.36, $p = 0.71$), shock on ICU admission (OR 2.24, 95% CI 1.11–4.51, $p = 0.03$), renal dysfunction (OR 0.68, 95% CI 0.31–1.51, $p = 0.34$), MELD-Na (OR 1.03, 95% CI 0.98–1.07, $p = 0.30$), and ACLF (OR 8.69, 95% CI 2.28–33.18, $p < 0.01$).

Table 1.

Patient characteristics

	Total (n=559)	No ARDS (n=514)	ARDS (n=45)	p-value
Age, median (IQR)	59.0 (52–67)	59.0 (51–67)	60.0 (52–65)	0.86
Sex, male, n (%)	349 (62.4)	325 (63.2)	24 (53.3)	0.19
Race, white, (%)	395 (70.8)	367 (71.5)	28 (62.2)	0.18
Charlson Comorbidity Index, median (IQR)	4.0 (3–4)	3.0 (3–4)	3.0 (3–4)	0.82
MELD-Na [†] score, median (IQR) (n=534)	24 (16–32)	23 (15–31)	28 (23–38)	<0.001
Acute on chronic liver failure, n (%)	244 (43.6)	202 (39.3)	42 (93.3)	<0.001
SOFA [‡] scores at ICU admission, median (IQR)				
Respiratory (n=339)	1 (0–2)	1 (0–2)	3 (1–3)	<0.001
Coagulation	2 (1–2)	2 (1–2)	2 (1–2)	0.54
Liver (n=548)	2 (1–3)	2 (1–3)	3 (2–4)	<0.001
Cardiovascular	0 (0–1)	0 (0–1)	1 (0–3)	<0.001
Central nervous system (n=369)	1 (0–3)	1 (0–2)	3 (0.5–3)	<0.001
Renal	1 (0–2)	1 (0–2)	2 (1–3)	0.002
SOFA [‡] scores at ARDS diagnosis, mean difference (SD) from Admission SOFA				
Respiratory	N/A	N/A	0.68 (1.26)	.001 *
Coagulation	N/A	N/A	0.09 (0.36)	0.22
Liver	N/A	N/A	0.02 (0.45)	0.99
Cardiovascular	N/A	N/A	1.11 (1.58)	<0.001
Central nervous system (n=31)	N/A	N/A	0.61 (1.56)	0.03
Renal	N/A	N/A	0.15 (0.56)	0.11
Diabetes [§] , n (%)	218 (39.0)	196 (38.1)	22 (48.9)	0.16
Sepsis, n (%)	245 (43.8)	206 (40.1)	39 (86.7)	<0.001
Sepsis with organ dysfunction and/or shock [¶] , n (%)	244 (43.7)	205 (39.9)	39 (86.7)	<0.001
Primary Cirrhosis type, n (%)				0.57
Alcohol	199 (35.7)	183 (35.6)	16 (35.7)	
Nonalcoholic steatohepatitis	88 (15.7)	77 (15.0)	11 (24.4)	
Viral hepatitis C	140 (25.0)	129 (25.1)	11 (24.4)	
Viral hepatitis B	14 (2.5)	13 (2.5)	1 (2.2)	
Autoimmune hepatitis	25 (4.5)	24 (4.7)	1 (2.2)	
Other	93 (16.6)	88 (17.1)	5 (11.1)	
Tobacco use, n (%)	300 (53.7)	275 (53.5)	25 (55.6)	0.79
Highest lactate (mmol/L), median (IQR) (n=414)	3.7 (2.1–6.6)	3.4 (2.0–6.0)	6.8 (4.1–11.8)	<0.001
Alcohol use disorder ^{††} , n (%)	237 (42.4)	218 (42.4)	19 (42.2)	0.98

[†] MELD-Na = Model for End-Stage Liver Disease – Sodium.

[‡]SOFA = Sequential Organ Failure Assessment. For respiratory system, 0 = PaO₂/FiO₂ ≥ 400, 1 = PaO₂/FiO₂ < 400, 2 = PaO₂/FiO₂ < 300, 3 = PaO₂/FiO₂ < 200, 4 = PaO₂/FiO₂ < 100. For coagulation, 0 = platelets ≥ 150,000/μL, 1 = platelets <150,000/μL, 2 = platelets <100,000/μL, 3 = platelets <50,000/μL, 4 = platelets <20,000/μL. For liver, 0 = bilirubin <1.2 mg/dL, 1 = bilirubin 1.2–1.9 mg/dL, 2 = bilirubin 2.0–5.9 mg/dL, 3 = bilirubin 6.0–11.9 mg/dL, 4 = bilirubin >12.0 mg/dL. For cardiovascular, 0 = mean arterial pressure (MAP) ≥ 70 mmHg, 1 = MAP < 70 mmHg, 2 = dopamine <5 μg/kg/min or dobutamine any dose, 3 = dopamine 5.1–15 μg/kg/min or epinephrine/norepinephrine ≥ 0.1 μg/kg/min, 4 = dopamine >15 μg/kg/min or epinephrine/norepinephrine > 0.1 μg/kg/min. For central nervous system, 0 = Glasgow coma scale (GCS) 15, 1 = GCS 13–14, 2 = GCS 10–12, 3 = GCS 6–9, 4 = GCS <6. For renal, 0 = creatinine <1.2 mg/dL, 1 = creatinine 1.2–1.9 mg/dL, 2 = creatinine 2.0–3.4 mg/dL, 3 = creatinine 3.5–4.9 mg/dL or urine output <500 mL/day, 4 = creatinine >5.0 mg/dL or urine output <200 mL/day.

* Comparison between admission SOFA and SOFA at time of ARDS diagnosis.

[§]Type I and II Diabetes Mellitus with and without insulin requirement.

[¶]Sepsis with organ dysfunction/shock = Martin, et al³⁷ method or sepsis + vasopressor use, or sepsis + lactate ≥ 4 mmol/L.

^{††} Primary or secondary diagnosis of alcohol cirrhosis or administrative data for alcohol dependence.

Table 2.**Outcomes**

	Total (n=559)	No ARDS (n=514)	Mild ARDS (n=14)	Moderate ARDS (n=19)	Severe ARDS (n=12)	p-value
28-day ICU free days (days)	21 (0–24.9)	22 (0–25)	0 (0–0)	0 (0–0)	0 (0–0)	<0.001
28-day vent free days (days)	26 (0–28)	28 (0–28)	0(0–0)	0 (0–0)	0 (0–0)	<0.001
Most recent known transplant status, n (%)						
Transplanted, alive	84 (15.1)	83 (16.2)	0 (0)	1 (5.3)	0 (0)	0.01
Transplanted, deceased	19 (3.4)	18 (3.5)	1 (7.1)	0 (0)	0 (0)	
Listed, alive	17 (3.1)	16 (3.1)	0 (0)	0 (0)	1 (8.3)	
Listed, deceased	29 (5.2)	26 (5.1)	1 (7.1)	1 (5.3)	1 (8.3)	
Not listed/ineligible, alive	177 (31.7)	171 (33.3)	1 (7.1)	3 (15.7)	2 (16.7)	
Not listed/ineligible, deceased	230 (41.2)	198 (38.6)	11 (78.7)	13 (68.4)	8 (66.7)	
Other	2 (0.3)	1 (0.2)	0 (0)	1 (5.3)	0 (0)	
Disposition						
Home/AMA	251 (44.9)	249 (48.4)	0 (0)	1 (5.3)	1 (8.3)	<0.001
Inpatient Rehab	48 (8.6)	45 (8.8)	1 (7.1)	2 (10.5)	0 (0)	
LTCH [†]	13 (2.3)	11 (2.1)	0 (0)	1 (5.3)	1 (8.3)	
SNF [‡]	49 (8.8)	48 (9.3)	0 (0)	0 (0)	1 (8.3)	
Other	5 (0.9)	5 (1.0)	0 (0)	0 (0)	0 (0)	
Hospice	14 (2.5)	14 (2.7)	0 (0)	0 (0)	0 (0)	
In-Hospital Death	179 (32.0)	142 (27.6)	13 (93.0)	15 (79.0)	9 (75.0)	

[†]LTCH = long term care hospital

[‡]SNF = skilled nursing facility