# Model for end-stage liver disease and pneumonia: An improved scoring model for critically ill cirrhotic patients with pneumonia

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## ABSTRACT

***Background/Aims:*** *Critically ill patients with cirrhosis with pneumonia are at an increased risk for mortality. Only a few accurate predictive models are existing specific to these patients. The aim of the present study was to compare the existing prognostic models and to develop an improved mortality risk model for patients with cirrhosis and pneumonia.*

***Materials and Methods:*** *A total of 231 patients were enrolled in our study (70% training and 30% validation cohorts). All participants were followed up for at least 21 days. Model for End-stage Liver Disease and Pneumonia (MELD-P) was derived by the Cox proportional hazards model. The performances of prognostic scoring systems were compared by calculation of the area under the receiver operating characteristic (AUROC) curve.*

***Results:*** *MELD-P showed better discriminative capabilities than existing scoring systems. Four clinical variables, including loge bilirubin (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.01-1.73), loge international normalized ratio (HR 3.57, 95% CI 1.30-9.78), loge pulse oxygen saturation/fraction of inspired oxygen (HR 0.38, 95% CI 0.14-0.99), and vasopressors used (HR 3.72, 95% CI 1.85-7.49), were considered as independent prognostic values associated with 21-day mortality. MELD-P had AUROC curve values of 0.78 (95% CI 0.71-0.84) in predicting in-hospital mortality, 0.78 (95% CI 0.70-0.84) at 21-day, 0.88 (95% CI 0.82-0.93) at 14-day, and 0.87 (95% CI 0.81-0.92) at 7-day. A similar result was obtained in validation cohort.*

***Conclusion:*** *MELD-P, as the first model specifically designed to evaluate the risk of mortality in critically ill patients with cirrhosis and pneumonia, performs well on the mortality assessment of short-term mortality.*

***Keywords:*** *Cirrhosis, pneumonia, CURB65, PSI, MELD, MELD-Na*

## INTRODUCTION

Liver cirrhosis results from different mechanisms of liver injury that lead to irreversible necroinflammation and fibrogenesis (1). This change results in portal hypertension and liver synthesis dysfunction. Patients with cirrhosis are more susceptible to bacterial infection, and infection is one of the most frequent causes of acute decompensation of liver disease (2). Every year, 25%-35% of patients with cirrhosis are infected during hospitalization, and the incidence is 4-5-fold higher than that observed in the general population (3). Several factors are involved in the pathogenesis of bacterial infections in those patients, including gut microbiota interaction, intestinal permeability, bacterial translocation, and immune deficiency (4,5). Infections represent one of the crucial reasons for repeated hospitalizations, which increase healthcare costs in cirrhosis and impair health-related quality of life. Depending on a research, infections increased mortality 4-fold among patients with cirrhosis; 30% of the patients died within 1 month after infection, and another 30% of the patients would die within 1 year (6).

Pneumonia is the fourth most common infection in patients with cirrhosis, particularly in those with advanced diseases (7). It accounts for 13%-48% of all bacterial infections, and the mortality rate reaches 41% (8-11). Despite the use of newer antibiotics, better supportive care, improved diagnosis, and availing the use of various preventive strategies, pulmonary infection remains the major cause of mortality and morbidity in the intensive care

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units (ICUs) (12). Thus, early evaluation of the severity of illness and mortality of these patients is very crucial.

There are certain risk prognostic models available for liver failure or pneumonia. The pneumonia severity index (PSI) and the score comprising confusion, blood urea nitrogen, respiratory rate, blood pressure, and age >65 years (CURB65) are widely utilized for evaluating the severity of pneumonia (13,14). MELD and MELD-Na are also widely used scoring systems to assess the prognosis of liver failure (15-17). However, there is a lack of predictive models specialized in estimating the mortality of pneumonia in critically ill patients with cirrhosis. Therefore, the aim of the present study was to compare the accuracy of pneumonia scoring systems with liver failure scoring systems in critically ill patients with cirrhosis with pneumonia. Then, an improved prognostic model (Model for End-stage Liver Disease and Pneumonia (MELD-P)) was built to stratify patients with cirrhosis with pneumonia based on the severity of illness and to predict the probability of mortality. Our research mainly focused on the short-term mortality of critically ill patients with cirrhosis with pneumonia to diminish the impact on death by other factors.

## MATERIALS AND METHODS

### Study design

Patient dataset was extracted from a large, freely accessible database, which is known as the Medical Information Mart for Intensive Care III (MIMIC-III). The database was built by the Beth Israel Deaconess Medical Center (BIDMC), and the establishment was approved by the institutional review boards of the Massachusetts Institute of Technology. There are over 40,000 patients who stayed in the ICUs of BIDMC between 2001 and 2012, and all the information about patients used was anonymous. To obtain access to the database, the training course, which was set up by the National Institute of Health, was completed. Since all the information about patients in the database was anonymous and the institutional review boards of BIDMC and the Massachusetts Institute of Technology had approved the establishment of the MIMIC-III, informed consent and ethics committee approval were not necessary for this manuscript.

### Definition

Diagnosis of liver cirrhosis was based on clinical evidence of liver dysfunction, portal hypertension, ultrasound or computed tomography findings, and histopathology. Diagnosis of pneumonia was based on the physical signs, clinical evidence of infection, and chest X-ray. In addition, the pathogen of pneumonia was determined based on blood culture or sputum culture.

Patients who met the following criteria were excluded from the study: (1) age <18 years, (2) pregnancy, (3) stayed in the ICU not >24 h, (4) absence of data to calculate prognostic scores, (5) malignancy, (6) organ transplantation, (7) acquired immune deficiency syndrome, and (8) serious diseases in other organ systems (excluding complications of cirrhosis and pneumonia). All included patients met the diagnosis of cirrhosis and pneumonia. Everyone was followed up for at least 21 days. The primary end points were defined at 21-day, 14-day, 7-day, and in-hospital all-cause mortality.

### Scoring systems

CURB65, PSI, and MELD scoring systems were calculated according to the published formulas (15,16,18,19). MELD=9.57×loge (creatinine (mg/dL))+3.78×loge (bilirubin (mg/dL))+11.2×loge (INR)+6.43x (etiology: 0, if cholestatic or alcoholic; 1, otherwise). MELD-Na=MELD+1.59×(135-Na (mmol/L)).

### Date extraction

For comparing the performances of different prognostic models and remodeling the MELD to predict short-term mortality risk in patients with cirrhosis with pneumonia, clinical vital signs and laboratory parameters were extracted from the database. Vital signs included blood pressure, heart rate, respiratory rate, and temperature, which were collected from the clinical information system at the bedside. Laboratory parameters were also recorded including white blood cell and platelet counts; albumin, bilirubin, blood urea nitrogen, creatinine, glucose, lactate, potassium, and sodium levels; activated partial thromboplastin time; prothrombin time; international normalized ratio (INR); arterial blood gas; and 24-hour urine output. The mean values of each clinical parameter were extracted within 24 h after ICU admission. Patients who met the cirrhosis and pneumonia criteria within the first day after ICU admission were included in our study. All scoring systems were calculated based on the mean values for each parameter from the first 24 h of ICU for all patients.

### Statistical analysis

MedCalc (version 15.2.2; Ostend, Belgium) and SPSS (version 23.0; IBM Corp., Chicago, IL, USA) were used for statistical analyses. Quantitative variables were expressed as mean±standard deviation or median with interquartile range according to normal or non-normal distribution and compared using Student's t-test or Mann-Whitney U test,

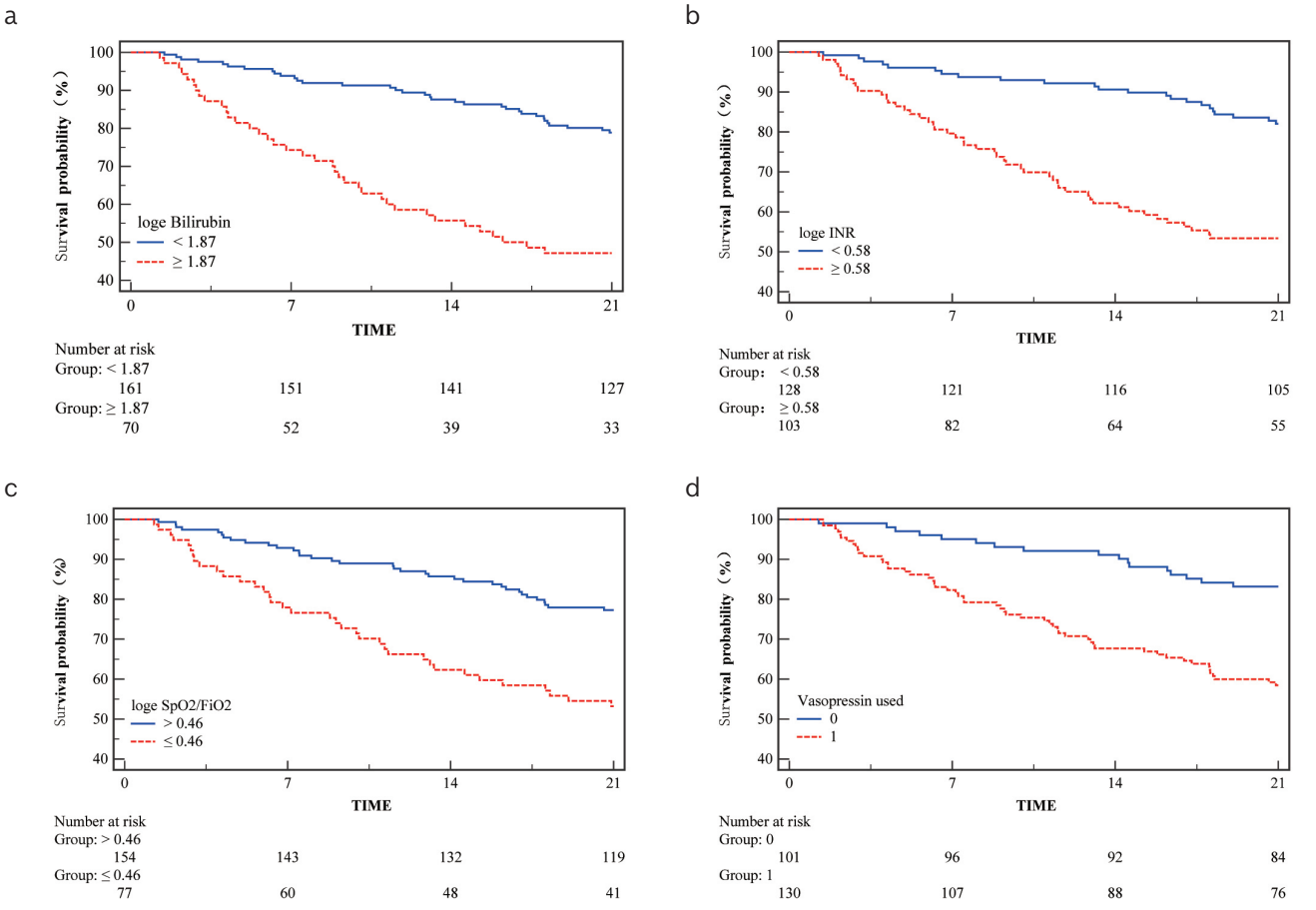


**Figure 1. a-d.** Kaplan-Meier curves stratified by bilirubin (A), INR (B), $SpO_2/FiO_2$ (C), and vasopressors used (D), respectively (all p<0.05).

respectively. Qualitative variables were expressed as number (%) and compared using chi-square test or Fisher's exact test. To diminish the influence of extreme parameters, variables were transformed to their natural logarithms. Univariate Cox proportional hazards regression was conducted to determine the unadjusted association of parameters with the mortality risk. In addition, multivariate Cox proportional hazards regression was used to identify independent predictors for the prognosis. The results were presented as hazard ratio (HR) with 95% confidence interval (CI). Prognostic models were developed using Cox proportional hazards in a derivation dataset and tested in the validation dataset. The Kaplan-Meier method was used to generate survival curves, and the log-rank test was used to compare. Area under the receiver operating characteristic (AUROC) curves of each scoring system were used to compare the prognostic utility. All tests were two sided. A p-value <0.05 was considered statistically significant.

## *RESULTS*

### *Baseline characteristics of included patients*

After the exclusion criteria were applied, a total of 231 consecutive patients were included in our study. Patients were randomly assigned to training cohort (n=161, 70%) and validation cohort (n=70, 30%). The mean age of the patients was 55 years. The study included 145 (63%) male patients. The most common etiology of cirrhosis was alcoholic cirrhosis (57%). Seventy-five patients had pneumonia caused by inhalation of food or vomitus, and 15 patients had ventilator-associated pneumonia. After 21 days of follow-up, 71 (31%) patients died. Depending on whether they survived after 21 days of follow-up, patients were divided into two groups as survivors and non-survivors. Detailed baseline characteristics among two groups are shown in Table 1. Table 2 presents the details of pneumonia pathogens.

**Table 1.** Characteristics of the study population on the first day of admission, stratified by survival

| Variable | Survivor (n=160) | Non-survivor (n=71) | p |
|---|---|---|---|
| Demographic parameters | | | |
| Age, year | 54.2±10.8 | 57.6±16.6 | 0.132 |
| Sex male no, % | 96 (60.0%) | 49 (69.0%) | 0.191 |
| Weight, kg | 87.0±24.3 | 86.3±21.8 | 0.947 |
| Height, cm | 171.7±10.7 | 172.2±9.7 | 0.64 |
| Ethnicity | | | |
| White no, % | 114 (71.2%) | 54 (76.1%) | 0.018 |
| African-Black no, % | 14 (8.8%) | 0 (0.0%) | |
| Other no, % | 32 (20.0%) | 17 (23.9%) | |
| Etiologies of cirrhosis | | | |
| Alcoholic no, % | 95 (59.4%) | 37 (52.1%) | 0.253 |
| Biliary no, % | 2 (1.2%) | 4 (5.6%) | |
| Hepatitis B virus no, % | 8 (5.0%) | 4 (5.6%) | |
| Hepatitis C virus no, % | 26 (16.3%) | 14 (19.7%) | |
| Autoimmune, % | 5 (3.1%) | 1 (1.4%) | |
| Unspecified, % | 24 (15.0%) | 11 (15.5%) | |
| Causes of pneumonia | | | |
| Community acquired, % | 70 (43.8%) | 22 (31.0%) | 0.298 |
| Hospital acquired, % | 31 (18.4%) | 18 (25.4%) | |
| Inhalation of food or vomitus, % | 50 (31.2%) | 25 (35.2%) | |
| Ventilator related, % | 9 (5.6%) | 6 (8.5%) | |
| Clinical parameters | | | |
| Heart rate | 91.6±16.2 | 93.7±16.8 | 0.368 |
| Respiratory rate | 19.7±5.0 | 21.3±4.3 | 0.007 |
| Temperature, °C | 36.9±0.7 | 36.7±0.9 | 0.045 |
| SBP, mm Hg | 114.3±15.4 | 109.6±15.0 | 0.006 |
| DBP, mm Hg | 60.5±9.9 | 56.0±8.3 | <0.001 |
| MAP, mm Hg | 76.9±10.4 | 71.6±9.3 | <0.001 |
| Vasopressors used, no (%) | 76 (47.5%) | 54 (76.1%) | <0.001 |
| Ventilator | 145 (90.6%) | 62 (87.3%) | 0.486 |
| Laboratory parameters | | | |
| Anion gap, mmol/L | 14.9±4.2 | 17.1±4.8 | <0.001 |
| Albumin, mg/dL | 2.8±0.5 | 3.0±0.8 | 0.18 |
| Bilirubin, mg/dL | 4.9±5.9 | 10.8±11.1 | <0.001 |
| Creatinine, mg/dL | 1.6±1.4 | 2.1±1.5 | 0.017 |
| Glucose, mg/dL | 135.3±44.0 | 139.0±48.6 | 0.469 |
| Hematocrit, % | 29.5±4.5 | 28.7±3.7 | 0.149 |
| Hemoglobin, mg/dL | 10.0±1.6 | 9.6±1.3 | 0.095 |
| Lactate, mg/dL | 2.9±1.9 | 3.7±2.5 | 0.013 |
| INR | 1.8±0.6 | 2.2±0.8 | <0.001 |

**Table 1.** Characteristics of the study population on the first day of admission, stratified by survival (Continue)

| Variable | Survivor (n=160) | Non-survivor (n=71) | p |
|---|---|---|---|
| Platelet, 109/L | 128.0±88.3 | 99.7±60.5 | 0.011 |
| Potassium, mEq/L | 4.1±0.6 | 4.2±0.6 | 0.493 |
| Sodium, mEq/L | 139.3±5.1 | 138.8±5.9 | 0.379 |
| WBC, 109/L | 11.7±6.9 | 14.5±9.9 | 0.063 |
| A-aDO2 | 256.2±138.5 | 310.4±139.6 | 0.005 |
| PaO2/FiO2, mm Hg | 234.0±108.5 | 190.0±104.6 | <0.001 |
| SpO2/FiO2 | 1.9±0.5 | 1.7±0.5 | 0.001 |
| PH | 7.4±0.1 | 7.4±0.1 | 0.107 |
| Urine output, mL/kg/h | 0.7±0.6 | 0.6±0.7 | 0.039 |
| Hepatorenal syndrome | 27 (16.9%) | 24 (33.8%) | 0.004 |
| Clinical scores | | | |
| MELD | 18.6±9.4 | 25.9±10.9 | <0.001 |
| MELD-Na | 19.5±10.1 | 27.2±11.3 | <0.001 |
| MELD-P | 10.0±7.8 | 18.6±9.0 | <0.001 |
| PSI | 119.5±29.4 | 139.9±30.2 | <0.001 |
| CURB65 | 2.0±1.0 | 2.5±0.9 | <0.001 |

A-aDO2, alveolar-arterial oxygen difference; CURB65, score comprising confusion, blood urea nitrogen, respiratory rate, blood pressure, and age > 65 years; DBP, diastolic blood pressure; FiO2, fraction of inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease; MELD-Na, Model for End-stage Liver Disease with incorporation of serum sodium; MELD-P, Model for End-stage Liver Disease and Pneumonia; PaO2, partial pressure of arterial oxygen; PH, potential of hydrogen; SBP, systolic blood pressure; PSI, pneumonia severity index; SpO2, pulse oxygen saturation; WBC, white blood cell.

**Table 2.** Pathogen of pneumonia based on blood culture or sputum culture, stratified by survival.

| Pathogen | Survivors (n=160) | Non-survivor (n=71) | p |
|---|---|---|---|
| Methicillin-susceptible *Staphylococcus aureus* | 23 (14.4%) | 7 (9.9%) | 0.376 |
| Methicillin-resistant *Staphylococcus aureus* | 1 (0.6%) | 0 (0.0%) | |
| *Streptococcus pneumoniae* | 3 (1.9%) | 2 (2.8%) | |
| *Escherichia coli* | 2 (1.2%) | 3 (4.2%) | |
| *Klebsiella pneumoniae* | 4 (2.5%) | 1 (1.4%) | |
| *Pseudomonas* | 1 (0.6%) | 0 (0.0%) | |
| Other Gram-negative bacteria | 5 (3.1%) | 0 (0.0%) | |
| Candidiasis of the lung | 4 (2.5%) | 0 (0.0%) | |
| Pneumonia, organism unspecified | 124 (77.5%) | 59 (83.1%) | |

***Rebuild model for end-stage liver disease in training cohort***

Univariate and multivariate Cox proportional hazards regression was used to estimate the relationship between variables and risk of 21-day all-cause mortality. Finally, loge bilirubin (HR 1.29, 95% CI 1.01-1.73), loge INR (HR 3.57, 95% CI 1.30-9.78), loge pulse oxygen saturation ($SpO_2$)/fraction of inspired oxygen ($FiO_2$) (HR 0.38, 95% CI 0.14-0.99), and vasopressors used (HR 3.72, 95% CI 1.85-7.49) were considered as independent prognostic values for 21-day mortality (Table 3). Figure 1 displays the survival curves of these four indicators generated by the Kaplan-Meier method and compared by log-rank

**Table 3.** Univariate and multivariate analyses of the association between mortality and clinical parameters in the training cohort.

| | Univariate analysis | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|
| Loge variables | HR | 95% CI | p | HR | 95% CI | p | β coefficient |
| Respiratory rate | 3.98 | (1.19-13.4) | 0.025 | | | | |
| Temperature, °C | 0.00 | (0.00-0.01) | 0.002 | | | | |
| MAP, mm Hg | 0.05 | (0.01-0.43) | 0.007 | | | | |
| Vasopressors used* | 3.22 | (1.68-6.17) | <0.001 | 3.72 | (1.85-7.49) | <0.001 | 1.314 |
| Bilirubin | 1.67 | (1.28-2.18) | <0.001 | 1.29 | (1.01-1.73) | 0.049 | 0.255 |
| Creatinine | 1.44 | (0.98-2.10) | 0.060 | | | | |
| Platelet | 0.70 | (0.41-1.18) | 0.176 | | | | |
| INR | 5.73 | (2.76-11.9) | <0.001 | 3.57 | (1.30-9.78) | 0.037 | 0.013 |
| $SpO_2/FiO_2$ | 0.22 | (0.09-0.54) | 0.001 | 0.38 | (0.14-0.99) | 0.046 | −0.970 |
| WBC | 1.80 | (1.03-3.15) | 0.039 | | | | |

$FiO_2$, fraction of inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; $SpO_2$, pulse oxygen saturation; WBC, white blood cell.

test (all p<0.05). Compared with the MELD scoring systems, the new model lacked creatinine, but kept bilirubin and INR. $SpO_2/FiO_2$ and vasopressors used as two new indexes were included in our remolding scoring model. Therefore, the improved prognostic model was named as MELD-P. The final model was represented as follows: R=2.6×loge (bilirubin (mg/dL))+12.7×(INR)−9.7×loge ($SpO_2/FiO_2$)+13.1x (vasopressors used: 1, yes; 0, no).

### *Performance of different scoring systems in training cohort and validation cohort*

The MELD-P had AUROC values of 0.78 (95% CI 0.71-0.84) in predicting in-hospital mortality, 0.78 (95% CI 0.70-0.84) at 21-day, 0.88 (95% CI 0.82-0.93) at 14-day, and 0.87 (95% CI 0.81-0.92) at 7-day. Compared with CURB65, PSI, MELD, and MELD-Na, MELD-P had predictive advantages at 21-day, 14-day, 7-day, and in-hospital mortality in our study. The performance of the different models is shown in Figure 2. A similar result was obtained in validation set. The AUROC values of MELD-P were 0.79 (95% CI 0.68-0.88) in predicting in-hospital mortality, 0.75 (95% CI 0.63-0.84) at 21-day, 0.76 (95% CI 0.65-0.86) at 14-day, and 0.71 (95% CI 0.60-0.81) at 7-day. The score of MELD-P also performed better than other scoring systems in validation cohort (Supplementary Table 1). The patients were grouped into three subgroups after sorting by mortality risk (score: ≤10 as grade A, 10-20 as grade B, >20 as grade C); each grade represented a different outcome according to Kaplan-Meier curves (Figure 3).

## *DISCUSSION*

According to published researches, in critically ill patients with cirrhosis, the morbidity in pneumonia is approximately 10.1%, and the mortality rate is 37%-41% (20,21). Our study demonstrated the high mortality rate of critically ill patients with cirrhosis and pneumonia. Patients with cirrhosis are predisposed to infectious diseases because of their potential immunodeficiency. They are usually accompanied with defects in pulmonary defenses that may explain why pneumonia contributes to the high mortality rate among patients with cirrhosis (22,23). On the contrary, immunological abnormalities in patients with cirrhosis hinder the control of lung pathogens; on the other hand, pulmonary infection is a major cause of septic shock and acute renal failure in patients with cirrhosis. Even if patients with pneumonia receive antibiotics, innate immunity is necessary for the clearance of pathogens in these patients (24,25). The combination of the two causes the progressive decompensation of the liver and the imbalance of the body's dynamic balance and eventually leads to multiple organ failure and death.

Timely and accurately estimating the prognosis of patients with cirrhosis and pneumonia is crucial for their treatments in clinical practice. To the best of our knowl-

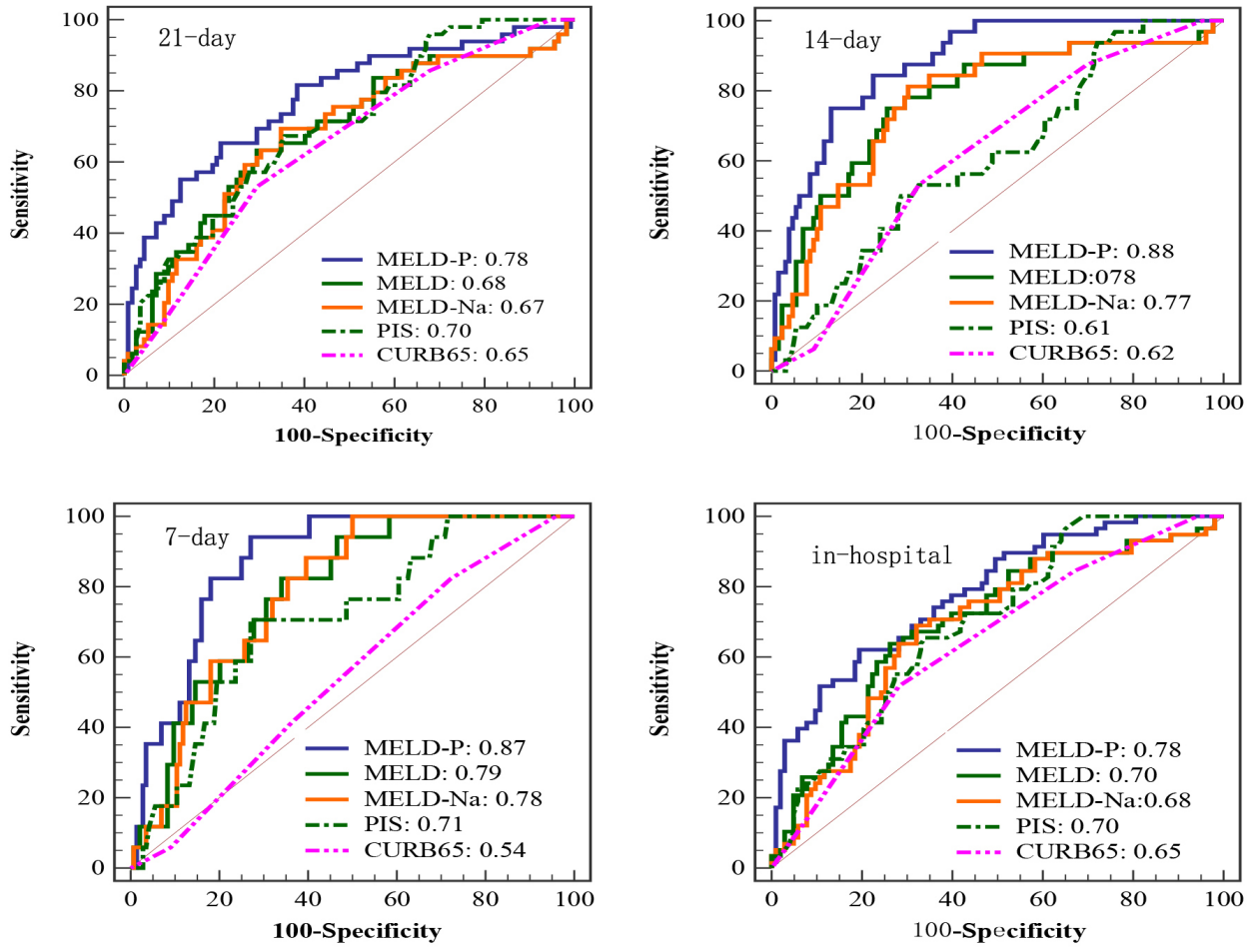


**Figure 2.** Receiver operating characteristic curve of the predictive ability of MELD-P and other scoring models to predict 21-day, 14-day, 7-day, and in-hospital mortality of patients with cirrhosis with pneumonia in training cohort.

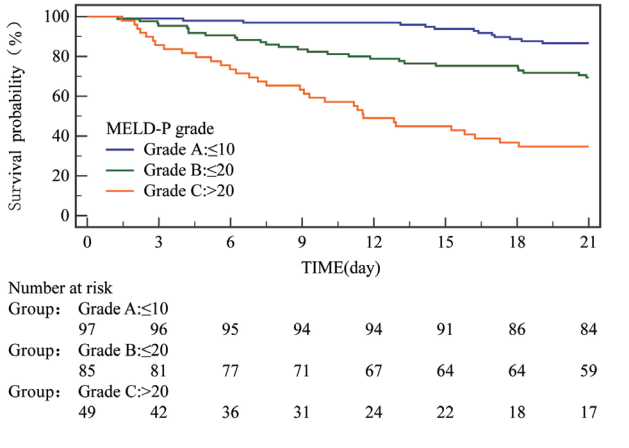


**Figure 3.** Kaplan-Meier curves stratified by different grades of CLIF-S-SOFA (grades A to C, all p<0.05).

edge, our research is the first and largest study to generate a clinical risk prognostic model for critically ill patients with cirrhosis with pneumonia. A previous study of 90 patients established a risk prediction model that is named MELD-CAP (10). The model was built for patients with hospitalized adults with cirrhosis and community-acquired pneumonia. However, our new model was specifically designed to evaluate the risk of mortality in critically ill patients with cirrhosis and pneumonia in the ICUs. Our study population had significantly higher mortality (31% (71/231) at 21-day mortality vs. 14% (13/90) at 30-day mortality).

There were four prediction models used to compare with each other in our study. Among these classic prediction models, CURB65 did not perform as well as other prog-

nostic models in predicting short-term mortality, which might be explained by the model initially built to predict death from community-acquired pneumonia, instead our study population was selected from the ICUs. Overall, the MELD scoring systems appeared to perform more accurately than PSI and CURB65 in predicting short-term mortality. This might reveal that in critically ill patients with cirrhosis and pneumonia, ultimately causing liver failure was their leading cause of death.

The new score only contains four variables and can be easily understood by all levels of medical staffs. The level of INR and the concentration of bilirubin are associated with liver function. On the contrary, cirrhosis plays an important role in the occurrence and worsening of pneumonia; on the other hand, severe infection can develop into liver failure with high mortality (26). Transcutaneous $SpO_2/FiO_2$ ratio is an easily available and non-invasive index (27-29). Low $SpO_2/FiO_2$ would correspond to a severe hypoxemic respiratory failure, which is common in patients with severe pneumonia. Vasopressor used is a key stress hormone to treat hypotension, and it is widely used in severe pneumonia with septic shock (30,31). The new score reflected dysfunction or damage to the liver, the lung, and the circulatory and, ultimately, a higher mortality rate.

Compared with other scoring systems, MELD-P had the best performance in our research. This might be explained by the fact that on the other hand, the model was derived from our database and validated in the same data; on the contrary, the model might really reflect the short-term mortality risk factors in critically ill patients with cirrhosis and pneumonia. Thus, more large scale prospective multicenter studies are needed to further verify its validity.

There are certain inadequacies in our study. First, the research we conducted is a single-center retrospective study. Second, we did not perform a stratified analysis according to the causes of pneumonia. Third, we were unable to extract indicators that were related to infections directly, such as C-reactive protein and procalcitonin. Finally, there was no adequate information in the dataset to distinguish the cause of mortality; therefore, the mortality in our study would be considered all-cause mortality.

In conclusion, to the best of our knowledge, this is the first study to build a prognostic scoring system for critically ill patients with cirrhosis with pneumonia. The MELD-P scoring system has the well discriminatory power for predicting in-hospital and short-term mortality in study cohorts and may be an optimal scoring system for critically ill patients with cirrhosis with pneumonia.

***Ethics Committee Approval:*** N/A.

***Informed Consent:*** N/A.

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**Supplementary Table 1.** Diagnostic accuracy of MELD-P, MELD, MELD-Na, PSI, and CURB65 in predicting 21-day, 14-day, 7-day, and in-hospital mortality in validation cohort.

| Model | 21-day | 14-day | 7-day | In-hospital |
|---|---|---|---|---|
| MELD-P | 0.78 (0.66-0.87) | 0.78 (0.66-0.87) | 0.71 (0.59-0.81) | 0.79 (0.68-0.88) |
| MELD | 0.76 (0.64-0.85) | 0.76 (0.65-0.86) | 0.67 (0.55-0.78) | 0.77 (0.65-0.86) |
| MELD-Na | 0.75 (0.63-0.84) | 0.76 (0.64-0.85) | 0.65 (0.53-0.76) | 0.77 (0.65-0.86) |
| PSI | 0.64 (0.52-0.76) | 0.67 (0.55-0.78) | 0.68 (0.56-0.79) | 0.64 (0.52-0.75) |
| CURB65 | 0.60 (0.47-0.71) | 0.58 (0.45-0.69) | 0.54 (0.42-0.66) | 0.64 (0.52-0.75) |