High Child-Pugh and CRUB65 scores predict mortality of decompensated cirrhosis patients with COVID-19: A 23-center, retrospective study

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ABSTRACT

Background: COVID-19 has rapidly become a major health emergency worldwide. The characteristic, outcome, and risk factor of COVID-19 in patients with decompensated cirrhosis remain unclear.

Methods: Medical records were collected from 23 Chinese hospitals. Patients with decompensated cirrhosis and age- and sex-matched non-liver disease patients were enrolled with 1:4 ratio using stratified sampling.

Results: There were more comorbidities with higher Chalson Complication Index (p < 0.001), higher proportion of patients having gastrointestinal bleeding, jaundice, ascites, and diarrhea among those patients (p < 0.05) and in decompensated cirrhosis patients. Mortality (p < 0.05) and the proportion of severe ill (p < 0.001) were significantly high among those patients. Patients in severe ill subgroup had higher mortality (p < 0.001), MELD, and CRUB65 score but lower lymphocytes count. Besides, this subgroup had larger proportion of patients with abnormal (PT), activated partial thromboplastin time (APTT), D-Dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL) and Creatinine (Cr) (p < 0.05). Multivariate logistic regression for severity showed that MELD and CRUB65 score reached significance. Higher Child-Pugh and CRUB65 scores were found among non-survival cases and multivariate logistic regression further inferred risk factors for adverse outcome. Receiver Operating Characteristic (ROC) curves also provided remarkable demonstrations for the predictive ability of Child-Pugh and CRUB65 scores.

Conclusions: COVID-19 patients with cirrhosis had larger proportion of more severely disease and higher mortality. MELD and CRUB65 score at hospital admission may predict COVID-19 severity while Child-Pugh and CRUB65 score were highly associated with non-survival among those patients.

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Introduction

 Decompensated cirrhosis is end-stage of chronic liver disease with microbial infection acting as its major complication and cause of the death [1,2]. Boivin Z et al. suggested that physicians should monitor cirrhotic patients carefully to prevent 90-day mortality caused by pneumonia [3]. A recent Coronavirus Disease 2019 (COVID-19) study with 21 cirrhosis patients (compensated vs. decompensated: 17 vs. 4) shown that lymphocyte, platelets count, and bilirubin level were associated with their high mortality (23.8%) [4]. However, there have been few studies focusing on clinical features and risk factors of adverse outcome in COVID-19 patients with decompensated cirrhosis. This study aimed to describe characteristics, as well as to identify risk factors associated with severity and adverse outcomes of those patients.

Method

Study design and participants

Among 15,732 COVID-19 patients from 23 medical centers in central China between January and March 2020, 66 decompensated cirrhotic patients were identified (Supplemental Table 1). We enrolled age and sex-matched 264 patients without liver diseases at the ratio 1:4 from corresponding hospitals to reduce statistical linkage on bias by stratified sampling.

Data collection

Electronic medical records were collected, which included: demographic characteristics, disease comorbidities, clinical manifestations (COVID-19 related symptoms: fever, cough, expectoration, myalgia, headache, dyspnea, etc.; cirrhosis related symptoms: black stool, hematemesis, abdominal distention, hydrothorax, etc.), laboratory examination (complete blood counts: white blood cells, lymphocytes, red blood cell, hemoglobin and platelets (PLT); serum biochemistry test: alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB) and creatinine (Cr); coagulation profile), therapy (antiviral, antimicrobial, corticosteroid, respiratory support, immunoglobulin, plasma products, etc.) and treatment outcomes (discharge, hospitalization or death). Three researchers reviewed data independently. For patients whose epidemiological or symptom data could not be obtained from records, themselves or their family members will be contacted.

Definition

The diagnosis criteria of COVID-19 and the disease severity classification were based on the Chinese management guideline for COVID-19 (version 6.0) established by the National Health Commission of the People’s Republic of China [5]. Patients who met any of the following criteria were assigned into “Severe” subgroup: 1) shortness of breath, respiratory rate ≥30 breath per minute (bpm); 2) oxygen saturation ≤93%; 3) Arterial oxygen partial pressure (PaO2)/fraction of inspired oxygen (FiO2) ≤ 300 mmHg; 4) lung imaging shows a substantial progression of lesions (greater than 50%) within 24–48 h. The diagnosis criteria of decompensated cirrhosis were based on the European Association for the Study of the Liver (EASL) clinical practice guidelines for the management of patients with decompensated cirrhosis and Chinese guidelines on the management of liver cirrhosis [6,7].

Ethics

Approval for this study was obtained from the Ethics Committee of Renmin Hospital of Wuhan University (reference number: WDRY2020-K171). A waiver for informed consent was also approved due to the retrospective nature of this study and analysis was carried out anonymously.

Statistical analysis

Categorical variables were described as frequency and percentage, while continuous variables were illustrated by average, median, and quartile spacing (IQR). Student’s t-test would be applied to compare the mean of continuous variables if normally distributed; otherwise, Mann–Whitney U test would be utilized. Categorical variables were analyzed by chi-square tests or Fisher’s exact test. Univariate and multivariate logistic regression was used to explore risk factors that could predict the severity and outcomes. As we enrolled 38 patients in the severe subgroup and 11 non-survival cases, only 5 factors for severity and 2 factors for survival were tested in multivariate logistic regression in case of overfitting. We considered a P value less than 0.05 as statistically significant. Discrimination abilities of scores were assessed with Receiver Operating Characteristic (ROC) curves. The Area Under the Curve (AUC) was calculated and the maximum Youden’s Index (J = sensitivity + specificity − 1) was employed to define an optimal cutoff point. Statistical analyses were performed in SPSS software version 16.0 for Windows (SPSS, Inc.) and Medcalc software version 19.7.
Results

Patient characteristics

Decompensated cirrhosis group included 43 men and 23 women with an average age of 61.5 ± 13.6 years, while the non-liver disease group enrolled 150 men and 114 women with an average age of 60.5 ± 14.4 (Figure 1).

COVID-19 patients with decompensated cirrhosis vs. patients without liver disease

The most common COVID-19 symptoms in decompensated cirrhosis group are shortness of breath (56.1%), fever (43.9%), and cough (40.9%), while fever (83.7%), cough (75%), and fatigue (43.9) were more common in patients without liver disease. Among patients who had a fever, decompensated cirrhosis group had a higher proportion of high fever (p < 0.05). And those patients had more gastrointestinal (GI) symptoms at hospital admission, such as GI bleeding, ascites, jaundice, and diarrhea (p < 0.05). Besides, more comorbidities, including hypertension (28.8% vs 14.4%, p = 0.006), diabetes (15.2% vs 6.4%, p = 0.02), and respiratory system diseases (COPD, tuberculosis et al, 13.6% vs 5.3%, p = 0.04) and CCI (0.83 ± 1.26 vs 0.08 ± 0.47, p < 0.001) were found in those patients, but there was no difference in cardiovascular disease, urinary system disease, and neoplasia (Table 1).

Complete blood count showed COVID-19 patients with decompensated cirrhosis had lower RBC and platelets count (p < 0.001), less hemoglobin (p < 0.001) but a higher proportion of patients with abnormal WBC (<4*10⁹/L, >10*10⁹/L) and lymphocytes (<1*10⁹/L) count. Prolonged prothrombin time (PT), activated partial thromboplastin time (APTT), and evaluated D-Dimer, as well as a higher proportion of patients having abnormal D-Dimer (>1 mg/ml) were found in

Figure 1. Age and gender distribution of patients.
Table 1. Characteristics of COVID-19 patients.

| Variable                  | Patients with decompensated cirrhosis (n = 66) | Patients without liver disease (n = 264) | P value |
|---------------------------|-------------------------------------------------|----------------------------------------|---------|
| Comorbidities             |                                                 |                                        |         |
| Hypertension              | 19 (28.8%)                                      | 38 (14.4%)                             | 0.006   |
| Cardiovascular disease    | 5 (7.6%)                                        | 14 (5.3%)                              | 0.68    |
| Diabetes                  | 10 (15.2%)                                      | 17 (6.4%)                              | 0.02    |
| Respiratory               | 9 (13.6%)                                       | 14 (5.3%)                              | 0.04    |
| Renal system              | 4 (6.1%)                                        | 10 (3.8%)                              | 0.63    |
| Malignancy                | 5 (7.6%)                                        | 5 (1.9%)                               | 0.031   |
| Charlson Comorbidity Index| 0.83 ± 1.26                                     | 0.08 ± 0.47                            | <0.001  |
| Chief complaints on admission |                                              |                                        |         |
| Hemorrhage                | 6 (9.1%)                                        | 2 (0.8%)                               | <0.001  |
| Ascites                   | 25 (38%)                                        | 0 (0%)                                 | <0.001  |
| icterus admission         | 16 (24.2%)                                      | 14 (5.3%)                              | <0.001  |
| Cough                     | 27 (40.9%)                                      | 198 (75%)                              | <0.001  |
| Myalgia or fatigue        | 28 (42.4%)                                      | 116 (43.9%)                            | 0.82    |
| Headache                  | 4 (6%)                                          | 20 (7.6%)                              | 0.796   |
| Hemoptysis                | 2 (3%)                                          | 4 (1.5%)                               | 0.345   |
| Diarrhea                  | 9 (13.6%)                                       | 15 (5.7%)                              | 0.05    |
| Polyneuropathy            | 37 (56.1%)                                      | 110 (41.7%)                            | 0.04    |
| Fever                     | 29 (43.9%)                                      | 221 (83.7%)                            | <0.001  |
| Highest temperature, °C   |                                                 |                                        |         |
| 37.3–38                   | 9 (31.0%)                                       | 111 (50.2%)                            | -       |
| 38–39                     | 8 (27.9%)                                       | 71 (32.1%)                             | -       |
| >39                       | 12 (41.4%)                                      | 38 (17.2%)                             |         |
| Blood Routine             |                                                 |                                        |         |
| White blood cell count, 10⁹/L | 5.89 ± 0.53                                    | 6.05 ± 0.18                            | 0.77    |
| <4                        | 25 (37.9%)                                      | 60 (22.7%)                             | 0.012   |
| 4–10                      | 29 (43.9%)                                      | 183 (69.3%)                            | <0.001  |
| >10                       | 12 (18.2%)                                      | 21 (8.0%)                              | 0.013   |
| Neutrophil count, 10⁹/L   | 4.59 ± 0.49                                     | 4.70 ± 0.38                            | 0.89    |
| Lymphocyte count, 10⁹/L   | 0.79 ± 0.07                                     | 1.10 ± 0.46                            | 0.003   |
| <1.0                      | 48 (72.7%)                                      | 129 (48.9%)                            | 0.001   |
| Red blood cell count, 10¹²/L | 3.66 ± 0.89                                    | 4.23 ± 0.6                             | <0.001  |
| Hemoglobin, g/L           | 110.1 ± 26.5                                    | 129.6 ± 17.9                           | <0.001  |
| PLT                       | 114.8 ± 11.5                                    | 201.5 ± 15.06                          | <0.001  |
| Coagulation function      |                                                 |                                        |         |
| Prothrombin time, sec     | 15.9 ± 5.6                                      | 13.7 ± 5.5                             | 0.005   |
| Activated partial thromboplastin, sec | 35.1 ± 10.1                                    | 31.7 ± 7.9                             | 0.02    |
| D-dimer, mg/L             | 5.28 ± 1.8                                      | 1.72 ± 0.32                            | 0.001   |
| ≥1                        | 33 (86.8%)                                      | 57 (21.6%)                             | <0.001  |
| Liver function            |                                                 |                                        |         |
| ALB, g/L                  | 31.4 ± 6.7                                      | 36.8 ± 5.4                             | <0.001  |
| <27                       | 17 (25.8%)                                      | 18 (6.8%)                              | <0.001  |
| 27–30                     | 13 (19.2%)                                      | 34 (12.9%)                             | 0.16    |
| ≥30                       | 36 (54.5%)                                      | 212 (80.3%)                            | <0.001  |
| ALT, U/L                  | 68.84 ± 18.01                                   | 35.16 ± 2.49                           | 0.069   |
| <40                       | 39 (59.1%)                                      | 196 (74.2%)                            | 0.015   |
| 40–100                    | 15 (22.7%)                                      | 54 (20.5%)                             | 0.69    |
| ≥100                      | 12 (18.2%)                                      | 14 (5.3%)                              | 0.001   |
| AST, U/L                  | 90.72 ± 22.57                                   | 37.92 ± 3.5                            | 0.024   |
| <40                       | 23 (34.8%)                                      | 217 (82.2%)                            | <0.001  |
| 40–100                    | 33 (50%)                                        | 37 (14%)                               | <0.001  |
| ≥100                      | 10 (15.2%)                                      | 10 (3.8%)                              | 0.001   |
| TBL, μmol/L               | 42.8 ± 8.72                                     | 12.65 ± 0.56                           | 0.001   |
| Kidney function           |                                                 |                                        |         |
| Creatinine, μmol/L        | 117.03 ± 15.89                                  | 114.96 ± 10.68                         | 0.93    |
| ≥133                      | 12 (18.2%)                                      | 38 (14.4%)                             | 0.44    |
| Treatments                |                                                 |                                        |         |
| Antibiotics               | 66 (100%)                                       | 264 (100%)                             | NA      |
| Antiviral treatment       | 66 (100%)                                       | 264 (100%)                             | NA      |
| Corticosteroids           | 19 (29%)                                        | 50 (18.9%)                             | 0.078   |
| Intravenous immunoglobin  | 18 (27.3%)                                      | 79 (29.9%)                             | 0.672   |
| High-flow nasal cannula   | 34 (51.5%)                                      | 187 (70.8%)                            | 0.003   |
| Noninvasive mechanical ventilation | 8 (12.1%)                              | 28 (10.6%)                             | 0.724   |
| Invasive mechanical ventilation/ECMO | 5 (7.6%)                               | 12 (4.5%)                              | 0.349   |

Those patients’ coagulation profile (p < 0.05). What’s more, in serum biochemical tests (including renal and liver function), they showed elevated ALT, AST, and TBL, but reduced ALB. The proportion of patients with abnormal ALB (<27 g/L), ALT (>100 U/L) and AST (>100 U/L) were also significantly high in decompensated cirrhotic COVID-19 patients (p < 0.001), while Cr in serum shown no difference (Table 2). COVID-19 patients with decompensated cirrhosis had more severe/critically ill cases (57.5% vs 42%, p < 0.01) and higher mortality (17% vs 6%, p < 0.001)
### Table 2. Characteristics of decompensated cirrhosis patients with COVID-19.

| Variable                  | Severe (n = 38) | Nonsevere (n = 28) | P value |
|---------------------------|-----------------|--------------------|---------|
| Age (years, IQR)         | 60.2 ± 10.9     | 63.4 ± 16.9        | 0.39    |
| Male                      | 26 (68.4%)      | 14 (60.7%)         | 0.52    |
| **Etiology of cirrhosis** |                 |                    | 0.80    |
| Hepatitis                 | 25 (65.8%)      | 16 (57.1%)         | 0.47    |
| Alcohol                   | 2 (5.3%)        | 3 (10.7%)          | 0.64    |
| Schistosome               | 4 (10.5%)       | 4 (14.3%)          | 0.71    |
| Others                    | 7 (18.4%)       | 5 (17.9%)          | 0.95    |
| Spleenectomy              | 5 (13.2%)       | 1 (3.6%)           | 0.23    |
| **Child-Pugh Class**      |                 |                    | 0.001   |
| A                         | 12 (31.6%)      | 20 (71.4%)         | 0.01    |
| B                         | 13 (34.2%)      | 5 (17.9%)          | 0.14    |
| C                         | 13 (34.2%)      | 3 (10.7%)          | 0.03    |
| **MELD**                  | 19.1 ± 9.66     | 10.5 ± 3.6         | <0.001  |
| <10                       | 6 (15.8%)       | 14 (50%)           | 0.003   |
| ≥10 ~ 20                  | 15 (39.5%)      | 13 (46.4%)         | 0.57    |
| CURB-65 SCORE             | 2.82 ± 0.77     | 1.39 ± 0.5         | <0.001  |
| 0–1                       | 3 (7.9%)        | 15 (53.6%)         | <0.001  |
| 2                         | 12 (31.6%)      | 11 (39.3%)         | 0.52    |
| ≥3–5                      | 23 (60.5%)      | 2 (7.1%)           | <0.001  |
| **Comorbidities**         |                 |                    |         |
| No comorbidities          | 10 (26.3%)      | 5 (17.9%)          | 0.42    |
| Hypertension              | 12 (31.6%)      | 7 (25%)            | 0.56    |
| Cardiovascular disease    | 3 (7.9%)        | 2 (7.1%)           | 0.91    |
| Diabetes                  | 8 (21.1%)       | 2 (7.1%)           | 0.12    |
| Chronic pulmonary disease | 4 (10.5%)       | 5 (17.9%)          | 0.62    |
| Chronic renal insufficiency | 4 (10.5%)       | 0 (0%)             | 0.13    |
| Charlson Comorbidity Index| 1.03 ± 1.48     | 0.57 ± 0.82        | 0.153   |
| **Signs and symptoms**    |                 |                    |         |
| Hemorrhage                | 3 (7.9%)        | 3 (10.7%)          | 0.69    |
| Ascites                   | 21 (55.3%)      | 4 (14.3%)          | 0.001   |
| Icterus admission         | 13 (34.2%)      | 3 (10.7)           | 0.03    |
| Cough                     | 19 (50%)        | 8 (28.6%)          | 0.08    |
| Myalgia or fatigue        | 16 (42.1%)      | 12 (42.9%)         | 0.95    |
| Headache                  | 3 (7.9%)        | 1 (3.6%)           | 0.63    |
| Hemoptysis                | 1 (2.6%)        | 1 (3.6%)           | 0.83    |
| Diarrhea                  | 6 (15.8%)       | 3 (10.7%)          | 0.82    |
| Fever                     | 18 (47.4%)      | 11 (39.3%)         | 0.51    |
| **Highest temperature, °C** | 37.3–38         | 3 (7.9%)           | 0.22    |
| 38–39                     | 4 (10.5%)       | 4 (14.3%)          | 0.71    |
| >39                       | 11 (28.9%)      | 1 (3.6%)           | 0.008   |
| **Blood Routine**         |                 |                    |         |
| White blood cell count, 10⁶/L | 6.61 ± 4.85     | 5.01 ± 3.08        | 0.13    |
| <4                       | 12 (31.6%)      | 13 (46.4%)         | 0.22    |
| 4–10                     | 17 (44.7%)      | 12 (42.9%)         | 0.88    |
| >10                      | 9 (23.7%)       | 3 (10.7%)          | 0.18    |
| Neutrophil count, 10⁹/L   | 5.45 ± 4.52     | 3.5 ± 2.7          | 0.49    |
| Lymphocyte count, 10⁹/L   | 0.60 ± 0.4      | 1.04 ± 0.6         | 0.002   |
| <1.0                     | 33 (86.8%)      | 15 (53.6%)         | 0.003   |
| Red blood cell count, 10¹²/L | 5.46 ± 4.52    | 3.50 ± 2.73        | 0.49    |
| Hemoglobin, g/L           | 104.4 ± 25.5    | 117 ± 26.5         | 0.06    |
| PLT                       | 101 ± 17.0      | 132 ± 14.2         | 0.19    |
| **Coagulation function**  |                 |                    |         |
| Prothrombin time, sec     | 17.7 ± 6.7      | 13.6 ± 2.1         | 0.002   |
| Activated partial thromboplastin, sec | 36.9 ± 11   | 32.7 ± 8.6      | 0.013   |
| D-dimer, mg/L             | 6.2 ± 2.4       | 2.6 ± 1.2          | 0.38    |
| ≥30                       | 25 (65.8%)      | 8 (28.6%)          | 0.003   |
| **Liver function**        |                 |                    |         |
| ALB, g/L                  | 29.2 ± 6.1      | 34.2 ± 6.6         | 0.003   |
| <27                       | 13 (34.2%)      | 4 (14.3%)          | 0.09    |
| 27–30                     | 7 (18.4%)       | 6 (21.4%)          | 0.35    |
| ≥30                       | 18 (47.4%)      | 18 (64.3%)         | 0.17    |
| ALT, U/L                  | 91.73 ± 31.4    | 39.4 ± 5.5         | 0.11    |
| <40                       | 20 (52.6%)      | 19 (67.9%)         | 0.21    |
| 40–100                    | 8 (21.1%)       | 7 (25%)            | 0.71    |
| ≥100                      | 10 (26.3%)      | 2 (7.1%)           | 0.046   |
| AST, U/L                  | 125.2 ± 39.3    | 46.4 ± 14.6        | 0.054   |
| <40                       | 16 (42.1%)      | 7 (25%)            | 0.15    |
| 40–100                    | 13 (34.2%)      | 20 (71.4%)         | 0.003   |
| ≥100                      | 9 (23.7%)       | 1 (3.6%)           | 0.02    |
| TBL, µmol/L               | 62.5 ± 15.2     | 19.4 ± 10.1        | 0.008   |
| **Kidney function**       |                 |                    |         |
| Creatinine, µmol/L        | 130.7 ± 22.8    | 99.9 ± 21.6        | 0.34    |
| ≥133                      | 10 (26.3%)      | 2 (7.1%)           | 0.046   |
| Death                     | 11 (28.9%)      | 0 (0%)             | <0.001  |
(Figure 1). As for therapy, patients without the liver disease had high proportion of patients using high flow nasal cannula (p = 0.003), but there was no difference in antibiotics, antiviral, glucocorticoid, γ globulin, invasive/noninvasive ventilator and ECMO using (Table 1).

**Comparison between severe and non-severe subgroup among COVID-19 patients with decompensated cirrhosis**

Death cases in COVID-19 patients with decompensated cirrhosis were all from severe ill subgroup (28.9% vs 0%). Significant difference was also found in patients percentage of Child-Pugh C (34.2% vs 10.7%, P = 0.03), high MELD score (≥20,44.7% vs 3.6%, P < 0.001), ascites (55.3% vs 14.3%, P = 0.001), jaundice (34.2% vs 10.7%, P = 0.03) and high fever (>39°C, 28.9% vs 3.6%, P = 0.008) between severe and non-severe subgroup (Table 3). However, there was no difference in age, gender, etiology of cirrhosis, underlying condition, history of splenectomy, GI bleeding, cough, hemoptysis, muscle pain, fatigue, and diarrhea.

In laboratory examination, significant prolonged PT (17.7 vs 13.6 sec, P = 0.013), lower ALB (29.2 vs 34.2 g/L, P = 0.003) but higher TBIL (62.5 VS 19.4 μmol/L, p = 0.008) as well as higher proportion of patients who had abnormal lymphocytes count (<1 × 10⁹/L, 86.8% vs 53.6%, P = 0.002), D-Dimer (≥1 mg/L, 65.8% vs 28.6%, P = 0.003), ALT (>100 U/L, 26.3% vs 7.1%, p = 0.046), AST (>100 U/L, 23.7% vs 3.6%, p = 0.02) and Cr (>>133 μmol/L, 26.3% vs 7.1%, P = 0.046) was found in severe ill subgroup.

**Risk factors of COVID-19 severity among decompensated cirrhosis patients**

CCI, Child-Pugh, MELD and CURB65 score, abnormal lymphocytes count (<1 × 10⁹/L) and D-Dimer level were included in multivariate logistic regression for COVID-19 severity (Table 4), which showed that MELD (odds ratio 1.3, 95%CI 1.06–1.60, p = 0.011) and CURB65 (odds ratio 11.58, 95%CI 2.18–61.36, p = 0.004) score were associated with COVID-19 severity.

**Risk factors of COVID-19 adverse outcome among decompensated cirrhosis patients**

Differences in Child-Pugh, MELD and CURB65 score, DBIL and PT level, lymphocytes count, and patients proportion of abnormal D-Dimer (≥1 mg/L) reached significance between survival and non-survival cases, but not age, gender, PLT count, TBIL level, PT, Cr level, and MELD score. Multivariate logistic regression

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**Table 3. Risk factors for severe/critical COVID-19 in decompensated cirrhosis patients.**

| Variable               | Univariable OR (95%CI) | P value | Multivariable OR (95%CI) | P Value |
|------------------------|------------------------|---------|--------------------------|---------|
| Age                    | 1.01 (0.97–1.05)        | 0.62    |                          |         |
| Age (<40)              | 0.23 (0.02–2.29)        | 0.21    |                          |         |
| 40–50                  | 1.04 (0.29–3.69)        | 0.95    |                          |         |
| 50–60                  | 1.23 (0.35–4.25)        | 0.75    |                          |         |
| Age (>60)              | 1.33 (0.50–3.37)        | 0.57    |                          |         |
| Gender                 | 1.2 (0.45–3.21)         | 0.72    |                          |         |
| Charlson Comorbidity Index | 0.54 (0.20–1.52)    | 0.24    |                          |         |
| Child-Pugh SCORE       | 0.71 (0.44–1.16)        | 0.54    |                          |         |
| A                      | 1.40 (1.11–1.77)        | 0.005   | 1.18 (0.82–1.69)         | 0.380   |
| B                      | 0.14 (0.05–0.43)        | <0.001  | 1.00 (0.95–1.05)         |         |
| C                      | 3.04 (0.94–9.62)        | 0.07    |                          |         |
| D                      | 4.33 (1.1–17.90)        | 0.04    |                          |         |
| ALB                    | 0.87 (0.49–1.57)        | 0.04    |                          |         |
| TBIL                   | 1.04 (1–1.08)           | 0.04    |                          |         |
| PT                     | 1.42 (1.13–1.80)        | 0.003   |                          |         |
| MELD SCORE             | 1.25 (1.10–1.43)        | <0.001  | 1.30 (1.06–1.60)         | 0.011   |
| <10                    | 0.29 (0.09–0.92)        | 0.04    |                          |         |
| ≥20                    | 17.61 (2.16–143.69)     | 0.007   |                          |         |
| Creatine U/L           | 1.00 (0.99–1.01)        | 0.34    |                          |         |
| D-dimer, g/L           | 1.17 (0.97–1.41)        | 0.011   | 1.05 (0.93–1.19)         | 0.41    |
| <1                     | 0.56 (0.19–1.64)        | 0.29    |                          |         |
| ≥1                     | 1.79 (0.61–5.25)        | 0.29    |                          |         |
| Lymphocyte count, 10⁹/L| 0.16 (0.05–0.533)       | 0.003   | 0.93 (0.19–4.48)         | 0.93    |
| <10                    | 5.7 (1.73–18.96)        | 0.004   |                          |         |
| ≥1                     | 0.18 (0.05–0.58)        | 0.004   |                          |         |
| CURB65 SCORE           | 11.47 (3.59–36.6)       | <0.001  | 11.58 (2.18–61.36)       | 0.004   |
| 0–1                    | 0.02 (0.003–0.195)      | 0.001   |                          |         |
| 2                      | 0.71 (0.26–1.98)        | 0.52    |                          |         |
| 3–5                    | 25 (5.12–122.19)        | <0.001  |                          |         |
showed that Child-Pugh (OR 5.71, 95%CI 1.85–17.72, p = 0.003) and CRUB65 (OR 5.88, 95%CI 1.96–17.68, p = 0.002) were highly associated non-survival (Table 4). In a ROC analysis for the mortality and survival, the area under ROC for CRUB65 was 0.787 (95% CI: 0.669–0.878), for Child-Pugh 0.748 (95% CI: 0.626–0.847), respectively (Figure 2). The optimum cutoff point for predicting mortality was 2 for the CRUB65 score (CRUB65 ≤ 2 for survival and CRUB65 ≥ 3 for mortality). At this value, the sensitivity was 67.27%, the specificity 81.82%, the positive predictive value 94.9% and the negative predictive value 33.3%. The optimum cutoff point for predicting mortality was 1 for the Child-Pugh score (Child-Pugh class A for survival and class B/C for mortality). At this value, the sensitivity was 49.09%, the specificity 90.91%, the positive predictive value 96.4% and the negative predictive value 26.3% (Table 5).

### Table 4. Risk factors for death in decompensated cirrhosis patients with COVID-19.

| Variable                     | Survived (n = 55) | Died (n = 11) | P value | OR (95%CI) for death | P Value |
|------------------------------|-------------------|---------------|---------|-----------------------|---------|
| Age                          | 66.63 ± 10.49     | 60.49 ± 14.16 | 0.18    |                       |         |
| Gender (male)                | 8 (72.7%)         | 35 (63.6%)    | 0.57    |                       |         |
| Charlson Comorbidity Index   | 1.36 ± 1.67       | 0.73 ± 1.14   | 0.15    |                       |         |
| PLT                          | 111.36 ± 10.8     | 136.09 ± 40.4 | 0.41    |                       |         |
| Child-Pugh SCORE             | -                 | -             | 0.012   | 5.71 (1.85–17.72)     | 0.003   |
| A                            | 1 (0.1%)          | 31 (56.4%)    | -       |                       |         |
| B                            | 5 (45.5%)         | 13 (23.6%)    | -       |                       |         |
| C                            | 5 (45.5%)         | 11 (20%)      | -       |                       |         |
| ALB                          | 32.02 ± 6.78      | 27.43 ± 5.24  | 0.04    |                       |         |
| TBIL                         | 36.54 ± 7.78      | 84.37 ± 39.84 | 0.008   |                       |         |
| DBIL                         | 20.4 ± 5.25       | 64.57 ± 29.25 | 0.04    |                       |         |
| PT                           | 14.98 ± 3.73      | 21.22 ± 3.42  | 0.008   |                       |         |
| MELD SCORE                   | 14.35 ± 8.5       | 20.18 ± 9.7   | 0.06    |                       |         |
| <10                          | 19 (28.8%)        | 1 (9.1%)      | 0.16    |                       |         |
| 10 – 20                      | 22 (40%)          | 6 (54.5%)     | -       |                       |         |
| ≥20                          | 14 (27.3%)        | 4 (36.4%)     | -       |                       |         |
| Creatine U/L                 | 105.33 ± 15.68    | 166.78 ± 49.48 | 0.06   |                       |         |
| ≥1                           | 24 (43.6%)        | 9 (18.8%)     | 0.033   |                       |         |
| <1.0                         | 37 (56.1%)        | 11 (100%)     | 0.99    |                       |         |
| Lymphocyte count, 10⁹/L      | 0.85 ± 0.08       | 0.44 ± 0.08   | 0.035   |                       |         |
| ≥1                           | 24 (43.6%)        | 9 (18.8%)     | -       |                       |         |
| CURB65 SCORE                 | 21.1 ± 0.12       | 3.09 ± 0.21   | 0.005   | 5.88 (1.96–17.68)     | 0.002   |
| 0–1                          | 18 (27.3%)        | 0 (0%)        | 0.007   |                       |         |
| 2                            | 21 (38.2%)        | 2 (18.2%)     | -       |                       |         |
| ≥3                           | 16 (29.1%)        | 9 (18.1%)     | -       |                       |         |

![Figure 2](image_url). Receiver Operating Characteristic (ROC) curves analysis for CRUB65 and Child-Pugh scores including the area under the curve (AUC) and P-value.

### Table 5. Calculation of sensitivity, specificity, PPV and NPV at cutoffs for CRUB65 and Child-Pugh scores.

| Score     | Cutoff       | Sensitivity (95%) | Specificity (95%) | Positive predictive value (95%) | Negative predictive value (95%) |
|-----------|--------------|-------------------|-------------------|-------------------------------|--------------------------------|
| CRUB65    | ≤2           | 67.27% (53.3–79.3) | 81.82% (48.2–97.7) | 94.9% (83.9–98.5) | 33.3% (23.8–44.5) |
| Child-Pugh| ≤1           | 49.09% (35.4–62.9) | 90.91% (58.7–99.8) | 96.4% (80.3–99.4) | 26.3% (20.6–33.0) |
**Discussion**

Our previous study suggested that the incidence of COVID-19 in decompensated cirrhotic patients from January 1 to February 4, 2020, in Wuhan, China was around 17% [8], and most of them were severely ill case. The purpose of this multi-center study was to further investigate the clinical characteristic and risk factors of adverse outcomes in decompensated cirrhotic patients with SARS-CoV-2 infection. Our results revealed that the proportion of severely ill and mortality in COVID-19 patients with decompensated cirrhotic was significantly higher than patients without liver disease. Besides, high MLED and CRUB65 score at hospital admission were associated with COVID-19 severity, while Child-Pugh and CURB65 score was associated with survival.

Previous studies have shown that 14–53% of COVID-19 patients had elevated ALT and AST which was associated with disease severity [9,10]. Fan et al. demonstrated that patients with abnormal liver function had more cough cases but no difference in comorbidities (hypertension, diabetes, and respiratory system disease, etc.) [10]. But in our studies, we found COVID-19 patients with decompensated cirrhosis had more hypertension and diabetes as well as GI symptoms, including GI bleeding, ascites, jaundice, and diarrhea. This may be explained by that decompensated cirrhosis patients were relatively old and had impaired liver-gut axis [11,12].

Interestingly, a national study has found that patients with any comorbidity yielded poorer clinical outcomes than those without [13]. Our results showed that although the CCI was also significantly higher in decompensated COVID-19 patients than in the control group, there was no difference between severe patients and nonsevere patients. Meanwhile, regression analysis showed no significant causal relationship with the severity and clinical outcome of COVID-19. Multiple comorbidities are a clinical feature of patients with cirrhosis [14], but they may not be the primary cause of disease outcomes.

Several studies have shown that severely ill cases in COVID-19 were characterized as elderly, reduced lymphocyte count, evaluated D-Dimer, venous thromboembolism formation, and having multiple comorbidities [15–17]. In our study, we found that decompensated cirrhotic infected with SARS-CoV-2 had decreased lymphocytes and RBC count, lower hemoglobin, and ALB level, prolonged PT, and APTT as well as evaluated ALT, AST, and TBIL compared with COVID-19 patients without liver disease.

In our study, 57.5% of COVID-19 patients with decompensated cirrhotic were severely ill with high mortality (28.9%), which was much higher than patients without liver disease. Angiotensin-converting enzyme 2 (ACE2) is the target of SARS-CoV-2 [18], which is also expressed on hepatic cell [9,19,20]. A recent autopsy also confirmed that SARS-CoV-2 injured hepatic cells directly [10]. Except for direct effects, global stress and inflammation induced by SARS-CoV-2, liver ischemia-reperfusion injury, previous liver disease aggravation, and medical treatment all could cause liver injury [9,21]. Decompensated cirrhotic patients also had impaired immune response to infection [2,22]. Portal hypertension leads to the imbalance of intestinal flora and intestinal barrier dysfunction [23], cytokine storm, and disorders of portal hemodynamics, all of which could accelerate acute liver function failure [22]. All those mentioned factors contributed to a higher proportion of severely illness and mortality in those patients.

Previous studies suggested that age and D-Dimer were associated with the severity and outcome of COVID-19. However, in this study, we did not repeat that correlation among COVID-19 patients with decompensated cirrhosis, which may because they were elderly and had abnormal D-Dimer. Child-Pugh and MELD score are models to predict the prognosis of cirrhotic [24,25]. In patients admitted to ICU, MELD score had higher sensitivity than Child–Pugh score, but for chronic liver failure patients Child–Pugh score had higher sensitivity but lower specificity than MELD score [25]. A newly study enrolled 152 patients with liver disease (decompensated cirrhosis patients: 36.7%) shown that Child–Pugh and new hepatic decompensation events during COVID-19 were associated with survival [26]. Our results demonstrated that MELD score at hospital admission could be used for predicting COVID-19 severity, while Child–Pugh had it advantage to predict survival. CURB65 is a severity-predicting model for community-acquired pneumonia [27]. We proved that it could be used to predict not only severity but also survival of COVID-19 patients with decompensated cirrhosis.

Still, our study had several limitations. Firstly, no portal hemodynamic-related readouts (hepatic venous pressure gradient, a ratio of portal/splenic vein diameter, and thrombus formation) were analyzed, which may influence patients’ prognosis. Secondly, long-term outcomes of SARS-CoV-2 infection were not explored in those patients. Thirdly, there may be systematic bias due to the retrospective study method. Additional larger sample size RCT study are still in great need.
To our knowledge, this is the first study exploring the characteristics and risk factors of severity and survival for COVID-19 patients with decompensated cirrhosis. Briefly, we found that those patients had a high proportion of severe/critically ill and mortality. MLED and CRU65 score at hospital admission was associated with COVID-19 severity, while Child-Pugh and CURB65 could be used to predict patients’ survival.

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