

Implications of Liver Injury in Risk-Stratification and Management of Patients with COVID-19

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Research Article

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Abstract

Background

Infection with SARS-CoV-2 has been associated with liver dysfunction, aggravation of liver burden, and liver injury. This study aimed to assess the effects of liver injuries on the clinical outcomes of patients with COVID-19.

Methods

A total of 1,564 patients with severe or critical COVID-19 from Huoshenshan Hospital, Wuhan, were enrolled. Chronic liver disease (CLD) was confirmed by consensus diagnostic criteria. Laboratory test results were compared between different groups. scRNA-seq data and bulk gene expression profiles were used to identify cell types associated with liver injury.

Results

A total of 10.98% of patients with severe or critical COVID-19 developed liver injury after admission that was associated with significantly higher rates of mortality (21.74%, $p<0.001$) and intensive care unit admission (26.71%, $p<0.001$). A pre-existing CLD was not associated with a higher risk. However, fatty liver disease and cirrhosis were associated with higher risks, supported by evidences from single cell and bulk transcriptome analysis that showed more TMPRSS2⁺ cells in these tissues. By generating a model, we were able to predict the risk and severity of liver injury during hospitalization.

Conclusion

We demonstrate that liver injury occurring during therapy in patients with COVID-19 is significantly associated with the severity of disease and mortality, but the presence of CLD is not associated. We provide a risk-score model that can predict whether patients with COVID-19 will develop liver injury or proceed to higher risk stages during subsequent hospitalizations. These findings may prove beneficial for the clinical management of patients infected with SARS-CoV-2.

Introduction

A novel coronavirus named SARS-CoV-2 began to rapidly spread across the world in December 2019 and was declared a global pandemic by the World Health Organization. Several recent studies have shown that more than 50% of patients with COVID-19 develop liver abnormalities, of whom 20% have liver injury (1-4). Two reports showed that SARS-CoV-2 might bind to cholangiocytes that are angiotensin-converting enzyme 2 (ACE2) positive and directly disrupt the barrier and bile acid transporting functions of these cells, which could further contribute to liver injury (5, 6). Furthermore, a pathological study based on patients who had died from severe COVID-19 showed that their liver tissue had moderate microvesicular

steatosis and mild lobular and portal activity indicating that SARS-CoV-2 might cause liver injury (7). Previous research has also examined the association between markers of liver injury and mortality rates in patients with COVID-19, and has reported that aspartate transaminase (AST) levels display the highest correlation with mortality compared to other indicators of liver injury (8).

Chronic liver disease (CLD), such as chronic viral hepatitis, metabolic dysfunction-associated fatty liver disease (MAFLD) that was previously termed non-alcoholic fatty liver disease, and alcohol-related liver disease, affects approximately 1.5 billion people throughout the world and causes 2 million deaths each year (9). Previous studies have shown that 2%-11% of patients with COVID-19 have a pre-existing CLD (1, 3, 10). Recent studies have found that obese patients with MAFLD have higher risks of severe COVID-19 symptoms (11), and patients with hepatitis B virus (HBV) infection have a higher mortality rate (12). However, research on early risk-stratification and management is limited. Thus, the purpose of this study was to explore the implication of liver injury and CLD in patients with COVID-19.

Methods

Study design and data collection

We collected electronic health records, including medical history and all laboratory results, from February 4 to April 10 for 1,564 patients diagnosed with severe or critical COVID-19 and admitted to Huoshenshan hospital from February 4 to March 30, 2020. We excluded patients with autoimmune hepatitis and hepatic hemangioma, and obtained 1,466 patients who performed liver function tests. The study design was approved by institutional ethics boards. Written informed consent was waived due to the urgency of the COVID-19 pandemic. The diagnosis and severity of COVID-19 were based on practice guidelines issued by The Chinese National Health Commission.

We used a six-category scale score to describe the clinical status of COVID-19: 1) discharged; 2) hospitalized, not requiring oxygen therapy; 3) hospitalized, requiring low-flow oxygen therapy; 4) hospitalized, requiring high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5) hospitalized, requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both; 6) death. Higher scores indicated higher risks.

Liver injury definition and chronic liver disease classification

The upper limit unit of normal of liver function tests was as follows: alanine aminotransferase (ALT), 40 IU/L; AST, 40 IU/L; total bilirubin, 17.1 μ mol/L; total bile acid, 10 μ mol/L; gamma-glutamyl transferase (GGT), 50 IU/L; and alkaline phosphatase (ALP), 125 IU/L. Patients whose ALT and/or AST, ALP, and/or GGT levels were higher than twice the upper limit unit of normal were considered as having hepatic injury (2). The patients with liver injury were further divided into groups based on the hepatic injury criterion together with a categorization of when the abnormal liver function value occurred for the first-time relative to hospitalization time: A pre-admission injured group that had patients who had already

presented with liver injury on admission, and post-admission injured group that had patients who developed liver injury during hospitalization.

Pre-existing CLDs, including chronic hepatitis B (CHB), chronic hepatitis C (CHC), and fatty liver disease (FLD), were diagnosed by consensus diagnostic criteria.

Statistical analysis

The statistical analyses in this study were performed using R (version 3.6.0). Fisher's exact test was applied for categorical variables. We utilized the Mann-Whitney U test or Kruskal-Wallis H test for continuous variables, and the results were presented as the median (25%-75% interquartile range, IQR). A *P-value* < 0.05 was considered statistically significant.

Liver scRNA-seq data processing and estimation of the abundance of liver cell type

The healthy liver and cirrhotic liver 10X scRNA-seq matrices were downloaded from GSE136103 (13), and the HBV liver 10X scRNA-seq matrix was obtained from Ido Amit Lab (14). The unsupervised clustering and visualization were performed in the Seurat R package v3.1.1 (15). The cells expressing ACE2 and TMPRSS2 were counted, and Fisher's exact test was then conducted.

The bulk gene expression profiles for HBV-infected, HCV-infected, MAFLD, cirrhotic, and healthy livers were downloaded from GSE83148, GSE149601, GSE130970, GSE112221, and GSE83148, respectively. CIBERSORTx (16) was used to estimate the abundance of cell types in livers, with custom signature matrices from scRNA-seq labeled by progenitor markers including ALB, AFP, KRT8, KRT19, THY1, and KIT (17, 18) and mixture files from bulk RNA-seq.

Construction of risk score

*The significance of each variable was assessed between the non-injury and post-admission injured groups by univariate logistic regression. Indicators with an odds ratio (OR) > 1 and *P-value* < 0.001 were used for the final model to investigate whether the patient would develop liver injury. We also selected significant indicators between patients who stayed at 2-4 scales and who developed into 5-6 scales to predict the highest six-category scale score. The performance of the scoring model was assessed by using receiver operating characteristic (ROC) curves created from 5-fold cross validation. The average area under ROC (AUROC) was calculated by the cvAUC R package (version 1.1.0).*

Results

Liver injury is associated with a poor prognosis in patients with COVID-19

We identified 263 (17.9%) patients with liver injury (**Table S1**) to explore the impact of liver injury on severe or critical cases of COVID-19. Amongst these patients, 102 (38.78%) had presented with liver injury on admission (pre-admission injured group) and 161 (61.22%) patients developed liver injury during their

hospitalization (post-admission injured group). As shown in **Fig. 1A**, hypertension was more commonly seen in the post-admission injured group (45.68%, $p=0.025$). The median time from symptom onset to admission was significantly shorter in the post-admission injured group than that in the pre-admission injured and non-injured groups (**Fig. 1C**, median:15 vs. 25 or 26 days, $p<0.001$), suggesting that disease progression was faster in the post-admission injured patients. The length of hospital stay was significantly longer in the post-admission injured group (**Fig. 1C**, median 21 days) than that in the other two groups (median 14 days for each). Furthermore, the six-category scale scores for the post-admission injured group were significantly enriched in the 3 to 6 range (**Fig. 1D**), indicating a higher risk. Conversely, over 50% of patients without liver injury remained at levels 2 and 3. The post-admission injured group also had significantly higher mortality rates than the pre-admission injured and non-injured groups during hospitalization (**Fig. 1F**, 21.74% vs. 6.86% or 1.25%, $p<0.001$), as well as increased intensive care unit (ICU) admission rates (**Fig. 1E**, 26.71% vs. 12.75% or 3.99%, $p<0.001$).

CLD is not significantly associated with a poor prognosis in patients with COVID-19

We compared the differences between severe or critical COVID-19 patients with and without CLD to evaluate the influence of SARS-CoV-2 on patients with pre-existing CLD. As shown in **Table S2**, 127 (8.35%) of the 1,520 patients with severe or critical cases of COVID-19 had CLD, including 64 patients with CHB, 20 with CHC, 37 with FLD, and 6 with liver cirrhosis but without documented etiological factors. Among all the comorbidities tested in this study, hypertension was the only one that showed a significant difference between the groups (27.56% with CLD vs. 37.19% without CLD, $p=0.034$).

Laboratory test results were also compared between the two groups. The median platelet count was significantly lower in the patients with CLD than that in those without CLD ($206.00 \times 10^9/L$ vs. $220.00 \times 10^9/L$, $p=0.008$). Interferon gamma was significantly decreased in patients with pre-existing CLD than that in those without pre-existing CLD (median: 2.68 vs. 5.32 pg/mL, $p=0.032$). A similar trend was also observed for interleukin-2 and CD3+/CD4+ T-helper cell fractions, but these changes were not statistically significant.

No significant evidence of CLD being a risk factor for the severity or mortality of COVID-19 was found. This result may be due to the consistent and targeted delivery of liver protection treatments in patients with CLD. In addition, this result implies that liver injury occurring during the course of COVID-19 is associated with a poorer prognosis but pre-existing CLD is not.

Patients with FLD are at a higher risk of liver injury compared to patients with viral hepatitis

We conducted a comprehensive analysis of 121 patients with both COVID-19 and chronic liver comorbidities. Of these 121 patients, 64 (52.89%) had CHB, 20 (16.53%) had CHC, and 37 (30.58%) had FLD (**Table S3**). The clinical outcomes were not significantly different among the different types of CLD ($p=0.535$). However, all 5 recorded deaths occurred in patients with viral hepatitis. Patients with FLD had higher levels of ALT (median: 36.70 IU/L, $p=0.038$) and GGT (median: 54.15 IU/L, $p<0.001$) than those

with CHB or CHC. Furthermore, over 50% of patients with FLD had abnormal levels of ALT ($p=0.391$) and GGT ($p=0.006$).

C-reactive protein (CRP) (median: 54.15 mg/L, $p<0.001$) and the absolute lymphocyte count (lymphocyte#; median: 1.86, $p=0.003$) were higher in the FLD patients. Prothrombin time was also significantly prolonged (median: 96.90 s, $p=0.003$) and the international normalized ratio was significantly lower in patients with FLD (median: 0.38, $p=0.042$), suggesting that coagulation disorders and dysfunction of the liver occurred concurrently in patients with pre-existing FLD. These results imply that patients with FLD suffer more severe liver damage.

Patients with both COVID-19 and cirrhosis are at a higher risk of disease progression

Cirrhosis is a complication of many liver diseases. Therefore, we analyzed the clinical characteristics and laboratory features of patients with CLD and with and without cirrhosis. As shown in **Table S4**, 13 (10.24%) patients had CLD with cirrhosis, of which 4 had CHB, 2 had CHC, 1 had MAFLD, and 6 had cryptogenic cirrhosis. No significant differences in terms of hospital stays ($p=0.774$) or ICU admission rates ($p=0.231$) were observed. However, the highest six-category scale scores for patients with both CLD and cirrhosis were significantly enriched at 3 and 4, while for those without cirrhosis were mainly at 2 and 3 ($p=0.045$). This result indicated that patients with both CLD and cirrhosis are at a higher risk of disease progression.

We confirmed by examining laboratory results that most liver enzymes were significantly higher in patients with cirrhosis, except ALT, AST, and GGT. Moreover, the levels of D-dimer and two well-known proinflammatory biomarkers (interleukin-6 and CRP) were found to be higher in patients with cirrhosis. All evidence mentioned above showed that patients with both COVID-19 and cirrhosis were at an elevated risk of disease progression compared with the patients who had CLD without cirrhosis.

Cirrhotic and fatty livers generate more TMPRSS2-expressing cells

We studied the liver scRNA-seq data in recent publications to investigate why patients with cirrhosis are more affected by SARS-CoV-2 (13, 14). Consistent with many recent reports, the level of the SARS-CoV-2 entry-receptor ACE2 was low in liver tissue. However, a small population of TROP2⁺ liver epithelial progenitors expressed ACE2 and the SARS-CoV-2 entry-associated protease TMPRSS2 (**Fig. 2**). Of the 11,106 cells detected in healthy livers, only 2 cells expressed ACE2 and 108 expressed TMPRSS2 (**Fig. 2A**). Of the 6,620 cells analyzed from cirrhotic livers, 7 cells expressed ACE2 and 143 expressed TMPRSS2 (**Fig. 2B**). This result represents a significant increase in the number of TMPRSS2-expressing cells in the cirrhotic livers ($p<0.001$, Fisher's exact test). Of 7,244 cells analyzed from untreated HBV livers, only 1 cell expressed ACE2 and 35 expressed TMPRSS2 (**Fig. 2C**). The TMPRSS2-expressing cells were significantly fewer in HBV liver than those in both healthy and cirrhotic livers ($p<0.001$, Fisher's exact test) (**Fig. 2D**).

We estimated the abundance of TMPRSS2⁺ progenitor cells for other liver bulk expression profiles with CIBERSORTx using the signatures built from the same healthy liver scRNA-seq dataset. To obtain a better reference signature, we limited TMPRSS2⁺ progenitor cells to a subset of the cell population in “cluster 4” marked by markers ALB, KRT8, and KRT19 (**Fig. S2**). Compared to HBV and HCV infected livers, MAFLD livers had much higher TMPRSS2⁺ progenitor cells (**Fig. 2E**) indicating that MAFLD livers might be more susceptible to the SARS-CoV-2 virus. Similarly, the cirrhotic livers also had higher TMPRSS2⁺ progenitor cells than healthy livers, which is comparable to the scRNA-seq results.

Hypertension may increase the risk of liver injury for patients without pre-existing CLD

A logistical regression model was used to identify the clinical characteristics, comorbidities, and symptoms that could increase the risk of liver injury among patients without pre-existing CLD. As shown in **Fig. 3**, male sex was highly associated with the risk of liver injury suggesting that male patients are more likely to develop liver injury (see **Table S5** for details). Furthermore, the association of hypertension and liver injury was significant for patients without pre-existing CLD but not for patients with pre-existing CLD (**Table S6**).

Risk scoring model for assessing liver injury and clinical outcomes for COVID-19 patients

We built a risk scoring system based on 22 routine laboratory tests performed within 3 days after admission, such as liver function and routine blood tests. This system was used to evaluate the risk of liver injury in patients with COVID-19 as early as possible and provide guidance for the management of these patients. The univariate logistic regression model was applied to select potential laboratory parameters, and only those with an OR >1 and *p*-value <0.001 were retained for final modeling. We selected 3 indicators at admission, including ALT (OR 1.07, 95% CI 1.02-1.12), CRP (OR 1.02, 95% CI 1.01-1.04), and LDH (OR 1.29, 95% CI 1.20-1.39). **Fig. 4A** shows the distribution of tested values for selected indicators. To determine the robustness of this model, a 5-fold cross-validation method was employed. The average AUC of 5-fold cross-validation was 85% (**Fig. 4C**). Similarly, we selected 6 indicators (**Fig. 4B**) to predict whether patients would proceed to six-category scale scores of 5 or 6. The average AUC reached 92% (**Fig. 4D**). An R-package provides all operations required for the clinical outcome prediction of new patients (<https://github.com/liangyuan-njmu/PredictModel>).

Discussion

Liver dysfunction has frequently been observed in patients with COVID-19 (19) and often requires intensive care (20). We found that patients who developed liver injuries during hospitalization had higher mortality and ICU admission rates than those without liver injury and with liver injury upon admission. In addition, the patients with post-admission liver damage had significantly prolonged hospital stays.

No significant differences in mortality or ICU admission rates between patients with and without CLD were observed, suggesting that liver injury but not CLD is associated with disease severity and clinical outcomes in patients with COVID-19. 30.58% of patients with FLD developed liver injury, which was higher

than the overall percentage of liver injury in this COVID-19 cohort (17.9%); this result suggests that patients with FLD may be at a higher risk of liver injury. Obesity is known to be associated with a spectrum of liver abnormalities in MAFLD, and one recent study showed that COVID-19 more severely affected younger adults with obesity (21). Given the known association between obesity and MAFLD (22), our observation of higher risks for patients with FLD and the higher abundance of TMPRSS2⁺ progenitor cells in MAFLD livers may provide a possible explanation for why obese patients suffer more from COVID-19.

Patients with advanced liver disease and those after liver transplantation were considered vulnerable populations at an increased risk of severe COVID-19. In this study, patients with cirrhosis had higher levels of interleukin-6 and CRP. Interleukin-6 is a pro-inflammatory factor that plays an important role in cytokine release syndrome (23), which highlights the importance of monitoring cytokine levels in patients with COVID-19 and pre-existing cirrhosis. Compared to CLD at a pre-cirrhotic stage, the quantity of neutrophils and lymphocytes in our study were significantly lower in patients with cirrhosis; in addition, the six-category scale scores for patients with cirrhosis were higher. Together, these findings suggest that patients with cirrhosis have worse clinical outcomes.

Fan et al. and Lin et al. revealed that SARS-CoV-2 could directly bind to ACE2-positive cholangiocytes and damage bile duct tissue, suggesting a possible mechanism for SARS-CoV-2-induced liver injury (5, 6). A more recent study found that SARS-CoV-2 entry receptor ACE2 and the entry associated protease TMPRSS2 are expressed in TROP2⁺ liver progenitor cells highlighting another potential cause of liver damage (24). ACE2 has also been shown to be up-regulated in cirrhotic livers (25) indicating that patients with pre-existing cirrhosis may suffer from severe liver injury and faster disease progression. By analyzing public scRNA-seq data, we revealed that the cirrhotic livers generated more ACE2 and TMPRSS2 expressing cells than healthy livers, and HBV infected livers had the fewest ACE2 and TMPRSS2 expressing cells among the 3 liver types. This may explain why patients with COVID-19 and cirrhosis had worse clinical outcomes than those with viral hepatitis.

Patient risk must be classified upon admission. Inspired by the MELD score, which is an existing scoring system used to prioritize liver transplantation and predict overall and postoperative outcomes in patients with hepatic and renal dysfunction (26-28), we constructed a similar scoring system to evaluate the liver impairment of patients with severe or critical COVID-19. The levels of ALT, lactate dehydrogenase, and CRP upon admission were used to build a linear regression equation to predict liver injury in subsequent hospital stays that could be used by clinicians to determine whether early liver protection management is required. Our other model can be used to predict those patients with COVID-19 who may have the highest severity of symptoms. However, these models require further validation to understand their full clinical potential.

In conclusion, we comprehensively evaluated the clinical characteristics and laboratory parameters of patients with severe or critical COVID-19 symptoms. Patients who developed liver injuries during hospitalization had worse clinical outcomes and longer hospital stays. Our study suggests that

performing liver protection treatments within one week of admission is beneficial for these patients. In particular, careful attention should be paid to patients with pre-existing CLD, cirrhosis, or FLD because of their worse liver function. Similarly, the liver function of patients with hypertension but without pre-existing CLD should be monitored. Further, we built a risk scoring system to predict liver injury upon admission. To conclude, we assessed the implication of liver injury and CLD for risk-stratification and management of patients with COVID-19, and we believe that our findings will help to improve clinical outcomes for these patients.

Abbreviations

ACE2, angiotensin-converting enzyme 2; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CLD, chronic liver disease; CRP, C-reactive protein; FLD, fatty liver disease; GGT, γ -glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; CI, confidence interval;

Declarations

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Disclosures:

We declare that we have no conflicts of interest.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, et al. COVID-19: Abnormal liver function tests. J Hepatol 2020.
3. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428-430.

4. Fu Y, Zhu R, Bai T, Han P, He Q, Jing M, Xiong X, et al. Clinical Features of COVID-19-Infected Patients With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. *Hepatology* 2020.
5. Zhao B, Ni C, Gao R, Wang Y, Yang L, Wei J, Lv T, et al. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. *Protein Cell* 2020.
6. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, Zhou J, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. *bioRxiv* 2020;2020.2002.2003.931766.
7. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420-422.
8. Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, Zhang XJ, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology* 2020.
9. Moon AM, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. *Clin Gastroenterol Hepatol* 2019.
10. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, Li SB, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. *BMJ* 2020;368:m606.
11. Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020.
12. Chen X, Jiang Q, Ma Z, Ling J, Hu W, Cao Q, Mo P, et al. Clinical Characteristics of Hospitalized Patients with SARS-CoV-2 and Hepatitis B virus Co-infection. *medRxiv* 2020;2020.2003.2023.20040733.
13. Ramachandran P, Dobie R, Wilson-Kanamori JR, Dora EF, Henderson BE, Luu NT, Portman JR, et al. Resolving the fibrotic niche of human liver cirrhosis at single-cell level. *Nature* 2019;575:512-518.
14. Bost P, Giladi A, Liu Y, Bendjelal Y, Xu G, David E, Blecher-Gonen R, et al. Host-Viral Infection Maps Reveal Signatures of Severe COVID-19 Patients. *Cell* 2020;181:1475-1488 e1412.
15. Satija R, Farrell JA, Gennert D, Schier AF, Regev A. Spatial reconstruction of single-cell gene expression data. *Nat Biotechnol* 2015;33:495-502.
16. Newman AM, Steen CB, Liu CL, Gentles AJ, Chaudhuri AA, Scherer F, Khodadoust MS, et al. Determining cell type abundance and expression from bulk tissues with digital cytometry. *Nat Biotechnol* 2019;37:773-782.
17. Chen J, Chen L, Zern MA, Theise ND, Diehl AM, Liu P, Duan Y. The diversity and plasticity of adult hepatic progenitor cells and their niche. *Liver Int* 2017;37:1260-1271.
18. Miyajima A, Tanaka M, Itoh T. Stem/progenitor cells in liver development, homeostasis, regeneration, and reprogramming. *Cell Stem Cell* 2014;14:561-574.
19. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol* 2020.
20. Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep*

2020;2:100113.

21. David A Kass, Priya Duggal, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. *Lancet* 2020;395:1544-1545.
22. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism* 2019;92:82-97.
23. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents* 2020;105954.
24. Justine Jia Wen Seow, Rhea Pai, Archita Mishra, Edwin Shepherdson, Tony Kiat Hon Lim, Brian KP Goh, Jerry KY Chan, et al. scRNA-seq reveals ACE2 and TMPRSS2 expression in TROP2+ Liver Progenitor Cells: Implications in COVID-19 associated Liver Dysfunction. *bioRxiv* 2020;<https://doi.org/10.1101/2020.03.23.002832>.
25. Herath CB, Warner FJ, Lubel JS, Dean RG, Jia Z, Lew RA, Smith AI, et al. Upregulation of hepatic angiotensin-converting enzyme 2 (ACE2) and angiotensin-(1-7) levels in experimental biliary fibrosis. *J Hepatol* 2007;47:387-395.
26. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464-470.
27. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864-871.
28. Kamath PS, Kim WR, Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). *Hepatology* 2007;45:797-805.

Figures

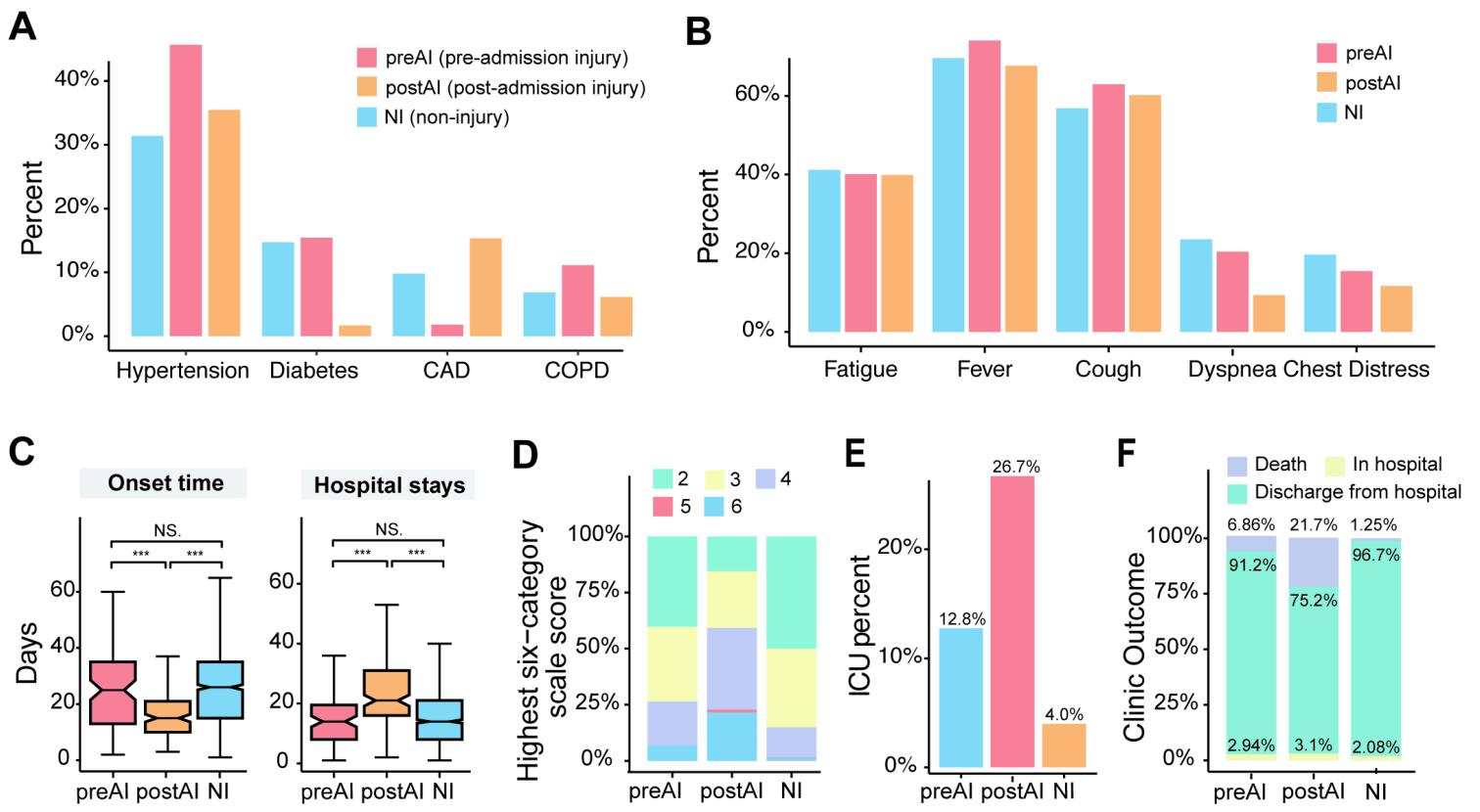


Figure 1

Characteristics of patients with or without liver injury during hospitalization. (A) Comorbidities (B) Symptoms (C) Onset time and hospital stays (D) Highest six-category scale scores (E) ICU admission (F) Clinic outcome for patients in the three groups. preAI: pre-admission injury; postAI: post-admission injury; NI: non-injury

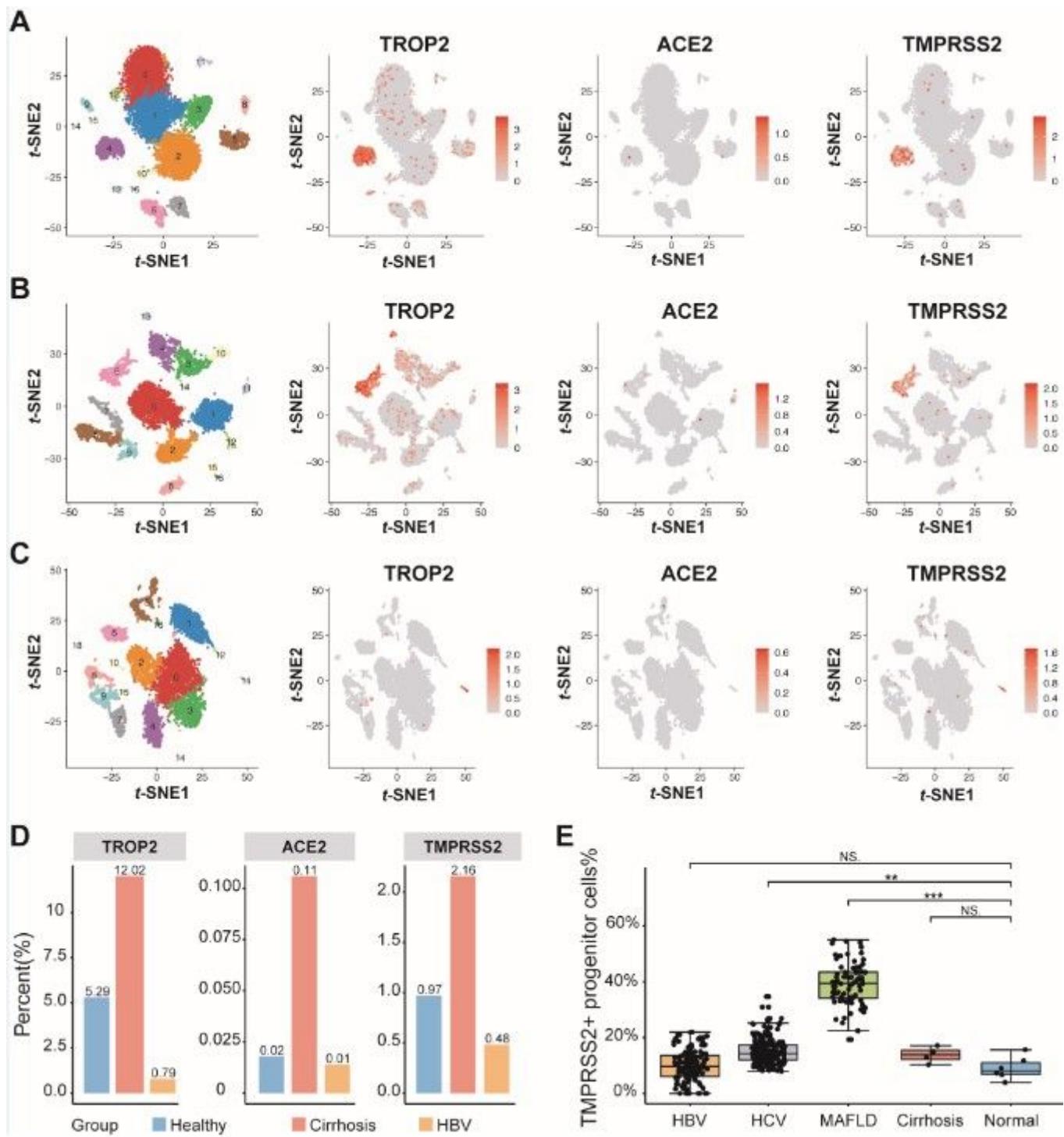


Figure 2

Overview of TMPRSS+ progenitor cells from healthy, cirrhosis and HBV liver tissues. tSNE of the scRNA-seq for (A) healthy liver (B) liver cirrhosis (C) HBV liver, and the expression of TROP2, ACE2 and TMPRSS2 genes for each cluster. (D) Fractions of cells with TROP2, ACE2 and TMPRSS2 expressed. (E) Distribution of the estimated TMPRSS+ progenitor cell fractions from HBV livers, HCV livers, MAFLD, cirrhotic livers and healthy livers.

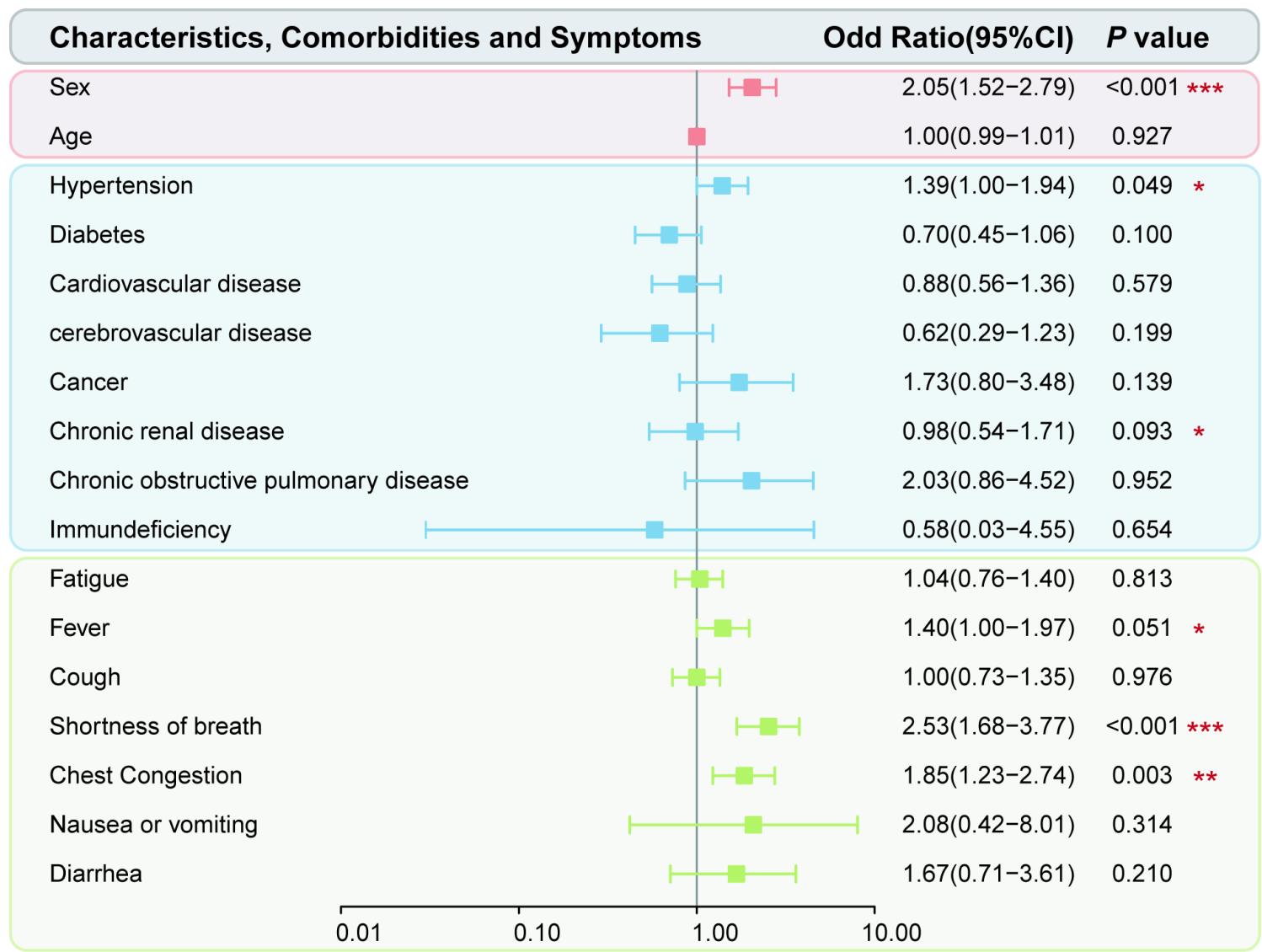


Figure 3

The association of clinical characteristics, comorbidities and symptoms with COVID-19 patients without chronic liver disease. Distribution of the odd ratios and p values estimated by univariate logistic regression model for COVID-19 patients without pre-existing CLD.

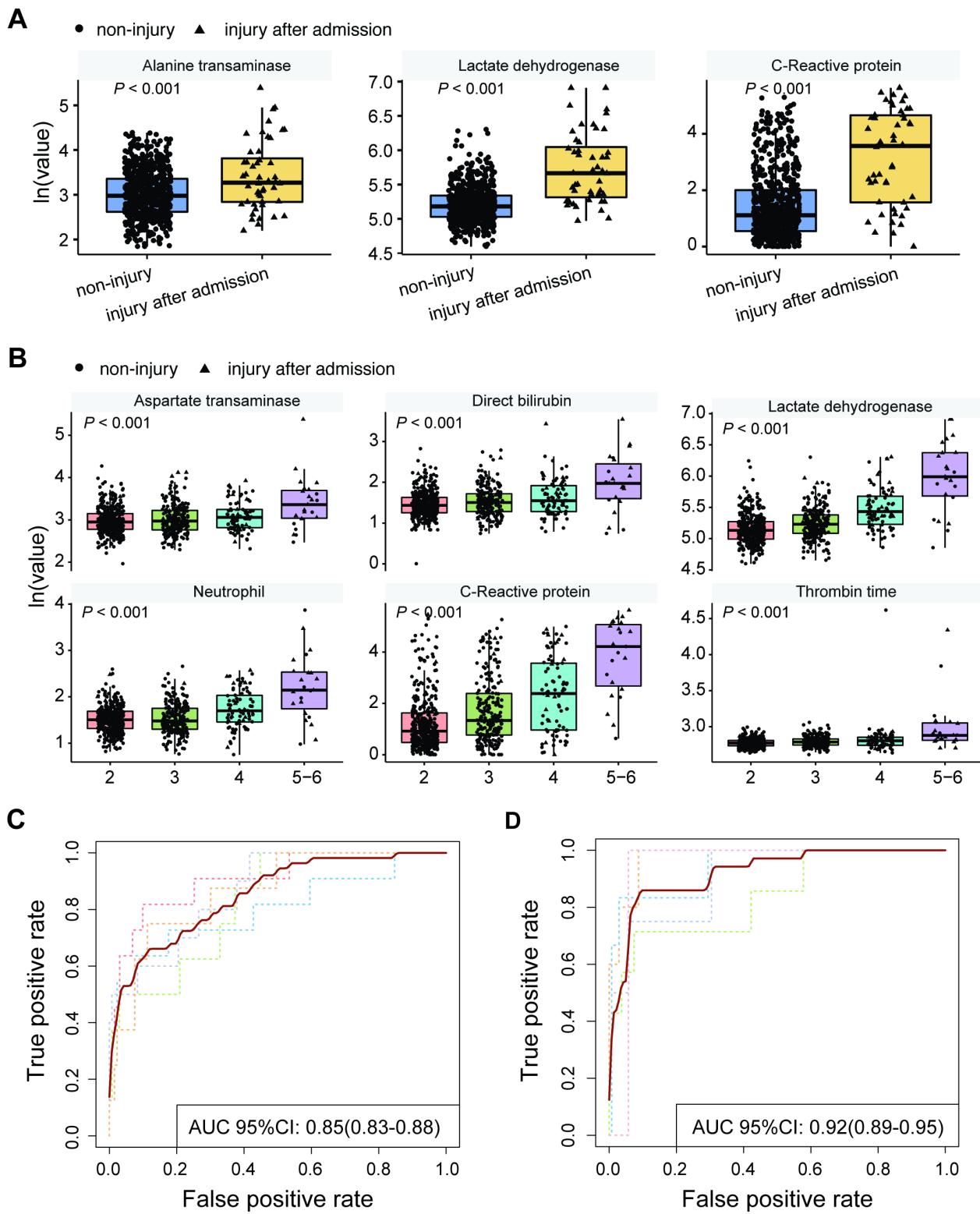


Figure 4

Accuracy of the risk scoring model. (A) Boxplot for blood tests used in liver injury prediction model. The P-values were from Wilcoxon test. (B) Boxplot for blood tests used in prognosis prediction model. The P-values were from Kruskal-Wallis test. (C) The ROC curves of 5-fold cross validation for predicting liver injury during hospitalization. (D) The ROC curves of 5-fold cross validation for predicting prognosis.

Supplementary Files

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