

Clinical Course and Risk Factors for Liver Injury of Severe and Critical Patients With COVID-19: A Single-centered, Retrospective, Observational Study

Jingyuan Liu

Capital Medical University Affiliated Beijing Ditan Hospital

Chunjing Du

Capital Medical University Affiliated Beijing Ditan Hospital

Siyuan Yang

Capital Medical University Affiliated Beijing Ditan Hospital

Lin Pu

Capital Medical University Affiliated Beijing Ditan Hospital

Pan Xiang

Capital Medical University Affiliated Beijing Ditan Hospital

Ang Li (✉ liang@ccmu.edu.cn)

Department of Critical Care Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, P. R. China <https://orcid.org/0000-0002-1478-3072>

Research

Keywords: Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Abnormal liver tests, Liver injury, Pneumonia

Posted Date: September 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-66769/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

1 **Clinical course and risk factors for liver injury of severe and critical**
2 **patients with COVID-19: a single-centered, retrospective,**
3 **observational study**

4 Jingyuan Liu^{1*}, Chunjing Du^{1*}, Siyuan Yang^{2*}, Lin Pu¹, Pan Xiang¹, Ang Li^{1#}

5

6 ¹ Department of Critical Care Medicine, Beijing Ditan Hospital, Capital Medical
7 University, Beijing, P. R. China

8 ² Laboratory of Infectious Diseases Center, Beijing Ditan Hospital, Capital Medical
9 University, Beijing, P. R. China

10

11 *** These authors contributed equally to this work.**

12 **#Corresponding author:**

13 **Prof. Ang Li**

14 Department of Critical Care Medicine, Beijing Ditan Hospital, Capital Medical
15 University.

16 Postal address: Beijing Ditan Hospital, No. 8 Jingshundang Street, Chaoyang District,
17 Beijing 100015, China.

18 E-mail: liang@ccmu.edu.cn

19 Tel.: 00861084320001

20 Fax: 00861084322606

21

22

23 **Abstract**

24 **Background:** The information regarding the clinical course of COVID-19 patients
25 with liver injury is very limited, especially in severe and critical patients. The
26 objective of this study was to describe the characteristics and clinical course of
27 patients admitted with severe and/or critical SARS-CoV-2 infection in liver function,
28 as well as explore the risk factors that affect liver function in the enrolled COVID-19
29 patients.

30 **Methods:** Information on clinical characteristics of 63 severe and critical patients
31 with confirmed COVID-19 were collected and analyzed.

32 **Results:** The incidence of abnormal aspartate aminotransferase, alanine
33 aminotransferase, and total bilirubin in the critical group was obviously higher than in
34 the severe group (81.48%, 81.49%, 62.67%, and 45.71%, 63.88%, 22.86%,
35 respectively, $p < 0.05$). The time for liver parameters to reach their peak or trough was
36 approximately 2-3 weeks. No significant difference was observed in cycle threshold
37 values of open reading frame 1ab and nucleocapsid protein gene on admission or at
38 the peak among liver injury group, abnormal group and normal group ($p > 0.05$).

39 Patients with invasive ventilator, decreased percentage of neutrophil, lymphocyte and
40 monocyte, and SOFA score ≥ 2 ($p < 0.05$) were the independent factors associated
41 with liver injury.

42 **Conclusions:** Abnormal liver tests are commonly observed in severe and critical
43 patients with COVID-19. The time of 2-3 weeks after admission should be paid
44 attention to patients with critical COVID-19 in case of the occurrence of liver injury.
45 As independent risk factors for the occurrence of liver injury, regarding decreased
46 ratio of neutrophils, lymphocytes and monocytes, the requirement of invasive
47 ventilator, and SOFA score ≥ 2 , patients with these abnormal parameters should be of

48 particular concerned during hospitalization.

49 **Keywords:** Coronavirus disease 2019 (COVID-19) · Severe acute respiratory

50 syndrome coronavirus 2 (SARS-CoV-2) · Abnormal liver tests · Liver

51 injury · Pneumonia

52

53 **Background**

54 The pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute

55 respiratory syndrome coronavirus 2 (SARS-CoV-2), poses an unprecedented threat to

56 public health[1-3]. Patients with COVID-19 are frequently associated with pulmonary

57 lesions, however, increasing data revealed that COVID-19 has systemic

58 manifestations affecting multiorgan system including liver injury, myocarditis,

59 thrombosis, and coagulation[4-7]. While the impact of COVID-19 on the liver

60 remains unclear, a considerable proportion of patients with elevated liver enzyme

61 have been reported [7-12]. Some studies found a mild [1-2 times the upper limit of

62 normal (ULN)] increase in transaminases, while severe liver injury also has been

63 reported[6,13].

64

65 However, the information regarding the clinical course of COVID-19 patients with

66 liver injury is very limited, especially in severe and critical patients. Knowledge of the

67 clinical characteristics of liver injury in this disease is vital to answering questions

68 about the therapy and management for patients infected with SARS-CoV-2. Thus, we

69 present a detailed characteristics and clinical course of patients admitted with severe

70 and/or critical SARS-CoV-2 infection in liver function and further to explore the

71 independent risk factors that affect liver function in enrolled patients.

72

73 **Methods**

74 **Study design**

75 This retrospective study included 63 severe and critical patients with confirmed
76 COVID-19 hospitalized in Beijing Ditan Hospital from January 20th ,2020 to April
77 06th ,2020. The diagnosis and severity assessment of COVID-19 were defined in
78 accordance with Chinese management guideline for COVID-19 (version 7) released
79 by National Health Commission of China. Patients meeting any one of the following
80 should be considered as severe cases: oxygen saturation at rest $\leq 93\%$ on room air;
81 respiratory distress, or respiratory rate ≥ 30 breaths/min. Patients who occurred acute
82 respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 300$, $30 >$ breaths/min), shock, or any organ failure that
83 required mechanical ventilation or intensive care management should be considered
84 as critical cases. Acute respiratory distress syndrome (ARDS) was defined according
85 to Berlin definition[14]. Cases were excluded for patients who were younger than 18
86 years, as well as mild and moderate ill patients. This study was approved by the
87 Institutional Review Board of Capital Medical University affiliated Beijing Ditan
88 Hospital and patient-level informed consent was waived owing to its retrospective
89 nature.

90

91 **Data collection**

92 The medical records of 63 patients were collected by the research team. Data on
93 patients' demographics, comorbidities, vital signs, laboratory characteristics and
94 treatment were acquired by the hospitalization management system.

95

96 **Laboratory examination and Liver test parameters**

97 On admission, laboratory parameters including peripheral leukocyte count,
98 neutrophils, lymphocytes, monocytes, platelets, haemoglobin, hematocrit, C-reactive
99 protein (CRP), International Normalized Ratio (INR), D-dimer, creatine kinase,
100 aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin (TBIL),
101 serum albumin, and A/G (albumin/ globulin) ratio were collected. Since COVID-19 is
102 an emerging infectious disease, consensus or guidance on the classifications of liver
103 injury are lacking, we classified the pattern of liver test into three groups: normal liver
104 test, abnormal liver test, and liver injury. Abnormal liver test was defined as the
105 elevation of serum liver enzymes exceeding the upper limit of normal (ULN), that is,
106 $AST > 40 \text{ U/L}$, $ALT > 40 \text{ U/L}$, and $TBIL > 17.1 \text{ umol/L}$. Liver injury was defined
107 when ALT and/or AST over $3 \times \text{ULN}$, and/or TBIL over $3 \times \text{UL}$. Furthermore, the
108 dynamic changes of liver enzymes, serum albumin, INR, and A/G ratio were also
109 recorded.

110

111 **SARS-CoV-2 RNA Detection**

112 COVID-19 was diagnosed according to the cycle threshold (Ct) values of open
113 reading frame 1ab (ORF1ab) and nucleocapsid protein (N) gene by RT-PCR assay.
114 The assay was performed by the National Center for Disease Control or the Clinical
115 Laboratory of Beijing Ditan hospital using a commercial kit (Daan, Guangzhou,
116 China). The SARS-CoV-2 viral loads were measured by the copy number of the N
117 gene from sputum samples or throat swabs of the COVID-19 cases. Ct values were
118 negatively correlated with viral RNA copy numbers[15]. According to the instruction
119 of RT-PCR kit, patients with Ct value less than 40 was considered as positive.

120

121 **Statistical analysis**

122 All statistical analyses were performed with SPSS 19.0 for Windows (IBM, USA).
123 Continuous variables were described as mean and SD or median and IQR, and
124 categorical variables as frequency and percentages. Normally distributed variables
125 were analyzed using independent group t-test or one-way ANOVA, whereas the
126 Mann-Whitney nonparametric were used for non-normally distributed variables.
127 Categorical variables were conducted using the chi-square (χ^2) or Fisher's exact tests.
128 Pearson's correlation coefficient was performed to assess the correlation between the
129 severity of liver injury and laboratory results. Ordinal logistic regression analysis was
130 conducted to evaluate the association of baseline characteristics with the severity of
131 liver injury. Two-sided P values of less than 0.05 were considered statistically
132 significant.

133

134 **Results**

135 **Baseline characteristics of enrolled patients with COVID-19**

136 The clinical characteristics of enrolled patients with COVID-19 are shown in Table 1.
137 A total of 63 patients were enrolled in the study. The average age of 63 patients was
138 56.75 years and 41 patients (65.08%) were male. According to the severity of the
139 disease, subjects were classified as severe group (36, 57.14%) and critical group (27,
140 42.86%). There was significant difference between two groups in oxygen therapy and
141 drug use except the requirement of high flow oxygen or non-invasive ventilator. In
142 terms of laboratory results, blood indices, including peripheral white cell count,
143 neutrophil, C-reactive protein (CRP), BUN, and LDH (lactate dehydrogenase), in
144 critical patients were significantly higher than in severe patients ($p < 0.05$).
145 Contrastingly, lymphocyte, percentage of monocyte, haemoglobin, and hematocrit in
146 critical patients were significantly lower than in severe patients ($p < 0.05$).

147

148 **Clinical features of enrolled patients with COVID-19 and liver function tests**
149 **during hospitalization**

150 The serum liver enzyme parameters of enrolled patients were further analyzed.
151 Results showed that there was no difference between both groups in AST, ALT,
152 TBIL, INR, albumin, and A/G ratio on admission (Supplemental Table), whereas the
153 peak values (or trough values) of these parameters have significant differences except
154 ALT (Table 2, Figure 1a,b). The incidence of abnormal AST, ALT, and TBIL in the
155 critical group was obviously higher than in the severe group (81.48%, 81.49%,
156 62.67%, and 45.71%, 63.88%, 22.86%, respectively, $p < 0.05$) during hospitalization.
157 Based on the test of liver function, subjects were further classified as normal liver test
158 (11, 17.46%), abnormal liver test (32, 50.79%), and liver injury group (20, 31.75%)
159 (Table 3). Patients in the three groups were not significantly different in sex ratio and
160 age. The CRP, percentage of neutrophil, BUN, and LDH in liver injury group were
161 significantly higher than in non-liver group, while the percentage of lymphocyte and
162 monocyte were on the contrary ($p < 0.05$). Additionally, the oxygenation index of
163 liver injury group was significantly lower than that of the other groups ($p = 0.015$),
164 while the CURB-65 score, SOFA score, the incidence of ARDS, and the requirement
165 of invasive ventilator were significantly higher in the liver injury group than in the
166 non-liver group ($p < 0.05$) (Table 3, Figure 1c-f).

167

168 **Dynamic profile of liver function indicators and viral clearance**

169 To determine the dynamic changes of enrolled patients in liver function parameters
170 and virus clearance, data of liver enzymes and Ct values were recorded during
171 hospitalization. Results showed that the level of AST, TBIL, and INR was significant

172 higher in the critical group than in the severe group and the time for these indicators
173 to reach their peak was approximately 2-3 weeks (Figure 2a-b, e). Compared with
174 AST, the duration of TBIL was longer, which reached its peak at about 4 weeks, then
175 gradually decreased. Conversely, the level of ALT, albumin and A/G ratio, was
176 significant lower in the critical group than in the severe group, the time for these
177 parameters to reach their trough was approximately 2-3 weeks as well (Figure 2b-c,
178 f). As shown in Supplemental Figure 1 a-f, the liver injury group has similar
179 characteristics. Despite the level of Ct values in the critical group was higher than in
180 the severe group (Figure 3a), there was no significant difference on admission or at
181 the peak between severe group and critical group, as well as among liver injury group,
182 abnormal group and normal group (Supplemental Figure 2a-d). The Ct values of
183 patients with different groups decreased gradually during hospitalization and the time
184 of virus clearance was approximately 2-3 weeks after admission (Figure 3a-b).

185

186 **Independent factors associated with severity of liver function**

187 We further to assess the correlation between the severity of liver injury and laboratory
188 results, as well as the independent factors associated with liver tests of abnormality or
189 injury. As shown in Figure 4a-f, the severity of liver function were positively
190 correlated with percentage of neutrophil, CRP, CURB-65 score and SOFA score, and
191 negatively correlated with percentage of lymphocyte, percentage of monocyte (data
192 were not shown), and oxygenation index. Variables with p-values of <0.05 in
193 univariable analysis were included in the ordinal logistic analysis to identify the
194 significant indicators affecting liver function in enrolled COVID-19 patients (Table
195 4). Results revealed that SOFA score ≥ 2 [OR=165.41, 95% confidence interval (CI)=
196 (1.57, 8.64); p=0.005] were factors positively associated with abnormality or injury

197 as indicated by liver tests. After adjustment for age, sex, and comorbidities, patients
198 with invasive ventilator, the decreased percentage of neutrophil, lymphocyte and
199 monocyte, and SOFA score ≥ 2 were the independent factors associated with liver
200 tests of abnormality or injury.

201

202 **Discussion**

203 In this cohort with 63 cases, we demonstrate that abnormal liver tests are common in
204 patients with severe and critical COVID-19. Patients with critical COVID-19 should
205 be aware of the occurrence of liver injury in 2-3 weeks after admission. Particular
206 attention should be paid to patients with decreased ratios of neutrophils, lymphocytes
207 and monocytes, the requirement of invasive ventilator, and SOFA score ≥ 2 during
208 hospitalization, as these are independent risk factors for the occurrence of liver injury.

209

210 The occurrence of liver enzyme elevation observed here is ranged from 22.86% to
211 81.49% in severe and critical patients during hospitalization, which is higher than
212 previous studies ranged from 14% to 53 % in patients including mildly and moderate
213 COVID-19[16], mainly manifested by the elevated levels of ALT AST and TBIL
214 accompanied by the slightly decreased albumin levels. Indeed, the increased liver
215 enzymes were observed more commonly in the critical group than in the severe group.
216 Interestingly, we observed that the levels of AST and TBIL were more higher in
217 critical group than in severe group, while no difference were observed between both
218 groups in ALT. Considering the elevated AST could be from muscle damage rather
219 than directly reflecting liver injury and the levels of INR were primarily within the
220 range of 1.5 in this study, the discovery that SARS-CoV-2 virus bind to angiotensin-

221 converting enzyme 2 (ACE2) on hepatocytes, especially on biliary epithelial cells,
222 then cause liver injury[17] may partially explain the results in our patients. In other
223 words, patients with liver injury in COVID-19 were more likely to cholestatic type
224 rather than hepatocellular type.

225

226 Currently, the underlying mechanisms of COVID-19 related liver injury remain
227 unclear. In fact, it may be multifactorial and individualized. First, a hyper-
228 inflammatory response to COVID-19 may contribute to liver injury[11,18,19].
229 Evidence is that the severity of liver function were positively correlated with the
230 percentage of neutrophil and CRP, as well as negatively correlated with percentage of
231 lymphocyte and monocyte, meanwhile, the decreased ratios of neutrophils,
232 lymphocytes and monocytes are independent risk factors for the occurrence of liver
233 injury. Hepatic inflammation involving activation of innate immune system
234 accompanied by the cytokine storm is a well-established driver of liver injury[20].
235 Notably, lymphopenia was commonly observed in COVID-19 studies and patients
236 with lower counts of lymphocyte are more susceptible to fatal outcomes[21]. Second,
237 whether SARS-CoV-2 can directly infect hepatocytes remain undetermined[19,22]. In
238 present study, no significant difference was observed in Ct values on admission or at
239 the peak among liver injury group, abnormal group and normal group. However, it is
240 impossible to demonstrated whether the virus has an impact on liver cytopathy owing
241 to the lack of liver biopsy and Ct values of the liver in situ. ACE2 is abundantly
242 expressed in the hepatocytes, especially in biliary epithelial cells, and the liver may be
243 a potential target for direct infection [17], that was however not yet demonstrated.
244 Thus, the influence of SARS-CoV-2 on liver begs for further investigation. Third,
245 hypoxia induced by COVID-19-related complications (i.e., acute respiratory distress

246 syndrome and multiple organ failure) may also induce hepatic ischemia and hypoxia-
247 reperfusion dysfunction[23,24]. Evidence is that the severity of liver function were
248 positively correlated with CURB-65 score and SOFA score, and negatively correlated
249 with oxygenation index, meanwhile, the requirement of invasive ventilator and SOFA
250 score ≥ 2 are independent risk factors for the occurrence of liver injury. Lastly, drug-
251 elicited liver injury may also account for laboratory test abnormalities[25,26].
252 However, there was no significant difference in drug use among liver injury group,
253 abnormal group and normal group in this study, except the vasoactive drug. Besides,
254 the vasoactive drug wasn't independent risk factor for the occurrence of liver injury in
255 the logistic analysis. Thus, the enrolled drugs in this study may not directly induce
256 liver injury.

257

258 Our results showed the time for liver parameters to reach their peak or trough was
259 approximately 2-3 weeks, which is critical for clinical implication in management for
260 patients infected with SARS-CoV-2. Thus, regular monitoring of liver function tests
261 should be performed, particularly in patients with severe and critical COVID-19.

262

263 This study has some limitations. First, not all laboratory tests were collected in
264 enrolled patients, including alkaline phosphatase, and gamma-glutamyl transferase
265 owing to the retrospective design. Additionally, it is impossible to demonstrated
266 whether the virus has an impact on liver cytopathy owing to the lack of liver biopsy
267 and viral loads results of the liver in situ. Further studies should corroborate the
268 pathogenic mechanism. Meanwhile, the relatively small sample size also a limitation
269 of this study. Future studies are needed to enroll a larger sample sizes to strengthen
270 the accuracy of the results.

271

272 **Conclusion**

273 In summary, abnormal liver tests are commonly observed in severe and critical
274 patients with COVID-19. The time of 2-3 weeks after admission should be paid
275 attention to patients with critical COVID-19 in case of the occurrence of liver injury.
276 As independent risk factors for the occurrence of liver damage, regarding decreased
277 ratio of neutrophils, lymphocytes and monocytes, the requirement of invasive
278 ventilator, and SOFA score ≥ 2 , patients with these abnormal parameters should be of
279 particular concern during hospitalization.

280

281 **Abbreviations**

282 COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory
283 syndrome coronavirus 2; ALT, alanine aminotransferase; AST, aspartate
284 aminotransferase; TBIL = total bilirubin; ARDS, acute respiratory distress syndrome;
285 ECMO = extracorporeal membrane oxygenation; SOFA = Sequential Organ Failure
286 Assessment; NLR = neutrophil to lymphocyte ratio; CRP = C-reactive protein; BUN
287 = blood urea nitrogen; A/G = albumin/ globulin; INR = international normalized ratio;
288 LDH = lactate dehydrogenase; Ct = cycle threshold

289

290 **Acknowledgments**

291 The authors gratefully acknowledge Gang Wan Ph.D. and Junnan Li Ph.D. for their
292 assistance with data analysis. Thanks to all the front-line medical staff of Beijing Ditan

293 hospital for their bravery and efforts in SARS-CoV-2 prevention and control.

294 Jingyuan Liu^{1*}, Chunjing Du^{1*}, Siyuan Yang^{2*}, Lin Pu¹, Pan Xiang¹, Ang Li^{1#}

295

296 **Authors' contributions**

297 Jingyuan Liu, Chunjing Du and Siyuan Yang collected the clinical data. Lin Pu, Pan

298 Xiang and Ang Li interpreted the data. Chunjing Du and wrote the manuscript.

299 Jingyuan Liu proofread the manuscript. Ang Li calculated the statistics and proofread

300 the manuscript. All authors read and approved the final manuscript.

301

302 **Funding:** This work was supported by Beijing Municipal Science and technology

303 commission, China [Grant No: Z201100005420012].

304

305 **Availability of data and materials**

306 The datasets used and/or analyzed during the current study are available from the

307 corresponding author on reasonable request.

308

309 **Ethics approval and consent to participate**

310 This study was approved by the Institutional Review Board of Capital Medical

311 University affiliated Beijing Ditan Hospital and patient-level informed consent was

312 waived owing to its retrospective nature. The study was performed in accordance with

313 the ethical standards laid down in the 1964 Declaration of Helsinki and its later

314 amendments.

315

316 **Consent for publication**

317 Not applicable

318

319 **Competing interests**

320 The authors declare that they have no competing interests.

321

322

References:

323 1 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia
324 J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z,
325 Jin Q, Wang J, Cao B: Clinical features of patients infected with 2019 novel coronavirus in Wuhan,
326 China. *The Lancet* 2020;395:497-506.

327 2 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP,
328 Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-
329 Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM,
330 Mogavero JN, Osorio GA, Qiu M, Zanos TP: Presenting characteristics, comorbidities, and outcomes
331 among 5700 patients hospitalized with COVID-19 in the new york city area. *JAMA* 2020

332 3 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A,
333 Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV,
334 Scandroglio AM, Storti E, Cecconi M, Pesenti A: Baseline characteristics and outcomes of 1591 patients
335 infected with SARS-CoV-2 admitted to ICUs of the lombardy region, italy. *JAMA* 2020;323:1574.

336 4 Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H: Clinical characteristics of non-ICU hospitalized
337 patients with coronavirus disease 2019 and liver injury: A retrospective study. *LIVER INT*
338 2020;40:1321-1326.

339 5 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H,
340 Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B: Clinical course and risk factors for mortality of adult
341 inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *LANCET* 2020;395:1054-
342 1062.

343 6 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li
344 Y, Wang X, Peng Z: Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-
345 Infected Pneumonia in Wuhan, China. *JAMA* 2020

346 7 Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang
347 X, Zhang L: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus
348 pneumonia in Wuhan, China: A descriptive study. *LANCET* 2020;395:507-513.

349 8 Zhang C, Shi L, Wang FS: Liver injury in COVID-19: Management and challenges. *Lancet*
350 *Gastroenterol Hepatol* 2020;5:428-430.

351 9 Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen
352 J, Liu L, Xu L: COVID-19: Abnormal liver function tests. *J HEPATOL* 2020

353 10 Xu L, Liu J, Lu M, Yang D, Zheng X: Liver injury during highly pathogenic human coronavirus
354 infections. *LIVER INT* 2020;40:998-1004.

355 11 Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, Zhang XJ, Cai J, Lin L, Ouyang S, Wang X, Yang

356 C, Cheng X, Liu W, Li H, Xie J, Wu B, Luo H, Xiao F, Chen J, Tao L, Cheng G, She ZG, Zhou J, Wang
357 H, Lin J, Luo P, Fu S, Zhou J, Ye P, Xiao B, Mao W, Liu L, Yan Y, Liu L, Chen G, Li H, Huang X,
358 Zhang BH, Yuan Y: Longitudinal association between markers of liver injury and mortality in COVID-
359 19 in China. *HEPATOLOGY* 2020

360 12 Mantovani A, Beatrice G, Dalbeni A: Coronavirus disease 2019 and prevalence of chronic liver
361 disease: A meta-analysis. *LIVER INT* 2020;40:1316-1320.

362 13 Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J,
363 Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J,
364 Song Y: Risk factors associated with acute respiratory distress syndrome and death in patients with
365 coronavirus disease 2019 pneumonia in wuhan, china. *JAMA INTERN MED* 2020

366 14 Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L,
367 Slutsky AS: Acute respiratory distress syndrome: The Berlin Definition. *JAMA* 2012;307:2526-2533.

368 15 Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song
369 T, He J, Yen HL, Peiris M, Wu J: SARS-CoV-2 viral load in upper respiratory specimens of infected
370 patients. *N Engl J Med* 2020;382:1177-1179.

371 16 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui D, Du B, Li LJ,
372 Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng
373 YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ,
374 Zhu SY, Zhong NS: Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*
375 2020;382:1708-1720.

376 17 Zhao B, Ni C, Gao R, Wang Y, Yang L, Wei J, Lv T, Liang J, Zhang Q, Xu W, Xie Y, Wang X,
377 Yuan Z, Liang J, Zhang R, Lin X: Recapitulation of SARS-CoV-2 infection and cholangiocyte damage
378 with human liver ductal organoids. *PROTEIN CELL* 2020

379 18 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ: COVID-19: Consider
380 cytokine storm syndromes and immunosuppression. *LANCET* 2020;395:1033-1034.

381 19 Li Y, Xiao SY: Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical
382 implications. *J MED VIROL* 2020

383 20 McDonald B, Kubes P: Innate immune cell trafficking and function during sterile inflammation of
384 the liver. *GASTROENTEROLOGY* 2016;151:1087-1095.

385 21 Henry BM: COVID-19, ECMO, and lymphopenia: A word of caution. *Lancet Respir Med*
386 2020;8:e24.

387 22 Guan GW, Gao L, Wang JW, Wen XJ, Mao TH, Peng SW, Zhang T, Chen XM, Lu FM: [Exploring
388 the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia].
389 *Zhonghua Gan Zang Bing Za Zhi* 2020;28:100-106.

390 23 Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, Poucke SV, Liu WY, Zheng MH:
391 COVID-19 and liver dysfunction: Current insights and emergent therapeutic strategies. *J Clin Transl*
392 *Hepatol* 2020;8:18-24.

393 24 Zhang XJ, Cheng X, Yan ZZ, Fang J, Wang X, Wang W, Liu ZY, Shen LJ, Zhang P, Wang PX,
394 Liao R, Ji YX, Wang JY, Tian S, Zhu XY, Zhang Y, Tian RF, Wang L, Ma XL, Huang Z, She ZG, Li
395 H: An ALOX12-12-HETE-GPR31 signaling axis is a key mediator of hepatic ischemia-reperfusion
396 injury. *NAT MED* 2018;24:73-83.

397 25 Sun J, Aghemo A, Forner A, Valenti L: COVID-19 and liver disease. *LIVER INT* 2020;40:1278-
398 1281.

399 26 Hajifathalian K, Mahadev S, Schwartz RE, Shah S, Sampath K, Schnoll-Sussman F, Brown RJ,

400 Carr-Locke D, Cohen DE, Sharaiha RZ: SARS-COV-2 infection (coronavirus disease 2019) for the
401 gastrointestinal consultant. World J Gastroenterol 2020;26:1546-1553.

402

403 **Figure legends**

404 **Fig. 1** Caption: The liver function parameters and percentage of liver injury under
405 different groups.

406 Fig. a: Description text: The peak values of AST, ALT, TBIL, and albumin between
407 the severe group and the critical group.

408 Fig. b: Description text: The peak values of INR and the trough value of A/G ratio
409 between the severe group and the critical group.

410 Fig. c: Description text: The percentage of liver injury between CURB-65 score <2
411 and CURB-65 score ≥ 2 .

412 Fig. d: Description text: Tthe percentage of liver injury between SOFA score <2 and
413 SOFA score ≥ 2 .

414 Fig. e: Description text: The percentage of liver injury between without ARDS and
415 with ARDS.

416 Fig. f: Description text: The percentage of liver injury between without ventilator and
417 with ventilator.

418

419 **Fig. 2** Caption: Dynamic profile of liver function indicators between the severe group
420 and the critical group.

421 Fig. a: Description text: Dynamic changes of AST between the severe group and the
422 critical group.

423 Fig. b: Description text: Dynamic changes of TBIL between the severe group and the
424 critical group.

425 Fig. c: Description text: Dynamic changes of ALT between the severe group and the
426 critical group.

427 Fig. d: Description text: Dynamic changes of albumin between the severe group and
428 the critical group.

429 Fig. e: Description text: Dynamic changes of INR between the severe group and the
430 critical group.

431 Fig. f: Description text: Dynamic changes of A/G ratio between the severe group and
432 the critical group.

433

434 **Fig. 3** Caption: Dynamic changes of Ct values among differ groups.

435 Fig. a: Description text: Dynamic changes of Ct values between the severe group and
436 the critical group.

437 Fig. b: Description text: Dynamic changes of Ct values among the normal group, the
438 abnormal group, and the liver injury group.

439

440 **Fig. 4** Caption: the correlation between the severity of liver injury and laboratory results.

441 Fig. a: Description text: the correlation between the severity of liver injury and the
442 percentage of neutrophil.

443 Fig. b: Description text: the correlation between the severity of liver injury and CRP.

444 Fig. c: Description text: the correlation between the severity of liver injury and CURB-

445 65 score.

446 Fig. d: Description text: the correlation between the severity of liver injury and SOFA
447 score.

448 Fig. e: Description text: the correlation between the severity of liver injury and the
449 percentage of lymphocyte.

450 Fig. f: Description text: the correlation between the severity of liver injury and
451 oxygenation index.

452

453 **Supplemental Figure 1** Caption: Dynamic profile of liver function indicators among
454 different groups.

455 Fig. a: Description text: Dynamic changes of ALT among the normal group, the
456 abnormal group, and the liver injury group.

457 Fig. b: Description text: Dynamic changes of AST among the normal group, the
458 abnormal group, and the liver injury group.

459 Fig. c: Description text: Dynamic changes of TBIL among the normal group, the
460 abnormal group, and the liver injury group.

461 Fig. d: Description text: Dynamic changes of albumin among the normal group, the
462 abnormal group, and the liver injury group.

463 Fig. e: Description text: Dynamic changes of INR among the normal group, the
464 abnormal group, and the liver injury group.

465 Fig. f: Description text: Dynamic changes of A/G ratio among the normal group, the
466 abnormal group, and the liver injury group.

467

468 **Supplemental Figure 2** Caption: the Ct values under different groups.

469 Fig. a: Description text: the Ct values on admission between the severe group and the
470 critical group.

471 Fig. b: Description text: the peak values of Ct values between the severe group and the
472 critical group.

473 Fig. c: Description text: the Ct values on admission among the normal group, the
474 abnormal group, and the liver injury group.

475 Fig. d: Description text: the peak values of Ct values among the normal group, the
476 abnormal group, and the liver injury group.

Figures

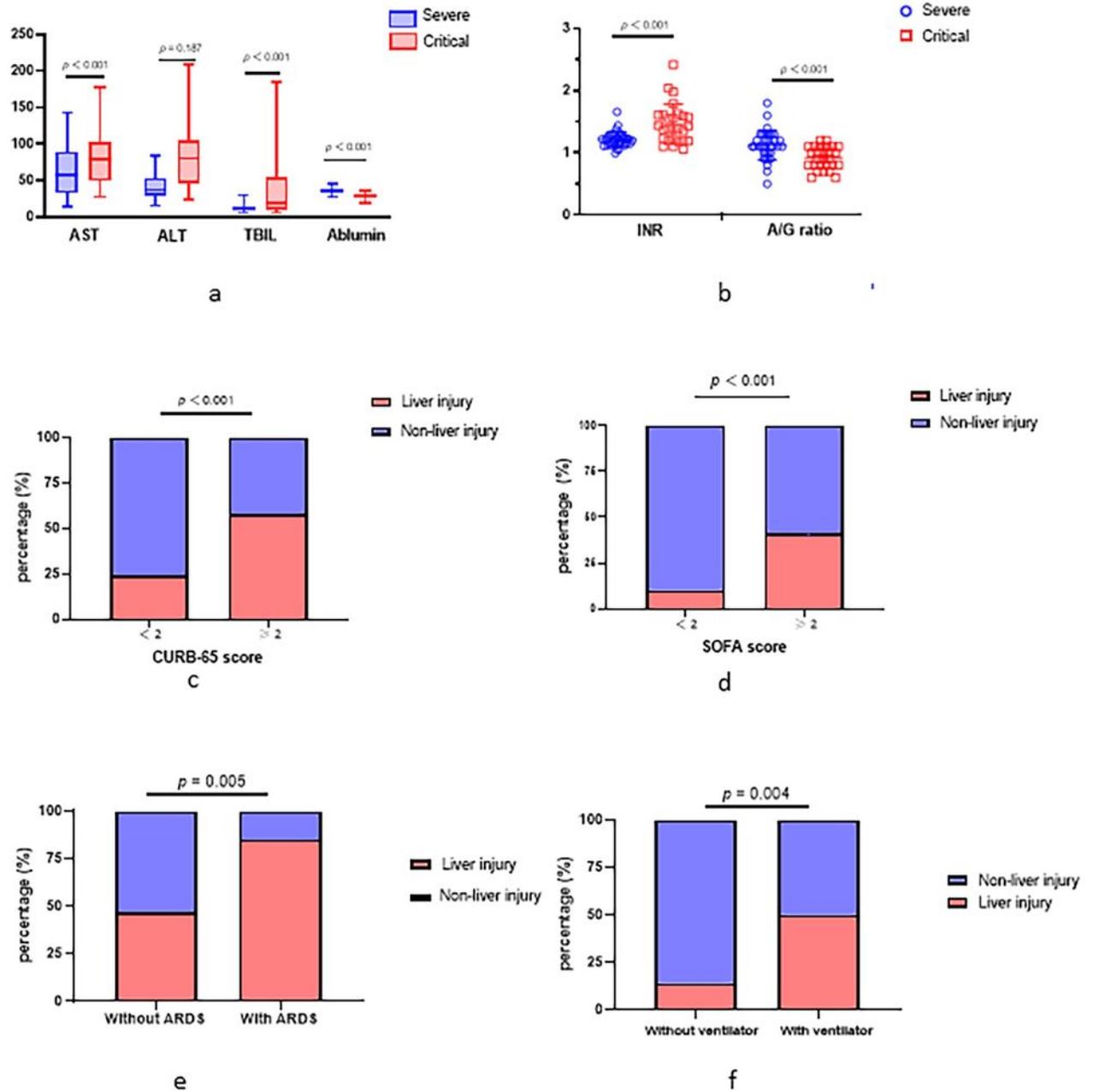


Figure 1

Caption: The liver function parameters and percentage of liver injury under different groups. Fig. a: Description text: The peak values of AST, ALT, TBIL, and albumin between the severe group and the critical group. Fig. b: Description text: The peak values of INR and the trough value of A/G ratio between

the severe group and the critical group. Fig. c: Description text: The percentage of liver injury between CURB-65 score ≥ 2 and CURB-65 score ≥ 2 . Fig. d: Description text: The percentage of liver injury between SOFA score ≥ 2 and SOFA score ≥ 2 . Fig. e: Description text: The percentage of liver injury between without ARDS and with ARDS. Fig. f: Description text: The percentage of liver injury between without ventilator and with ventilator.

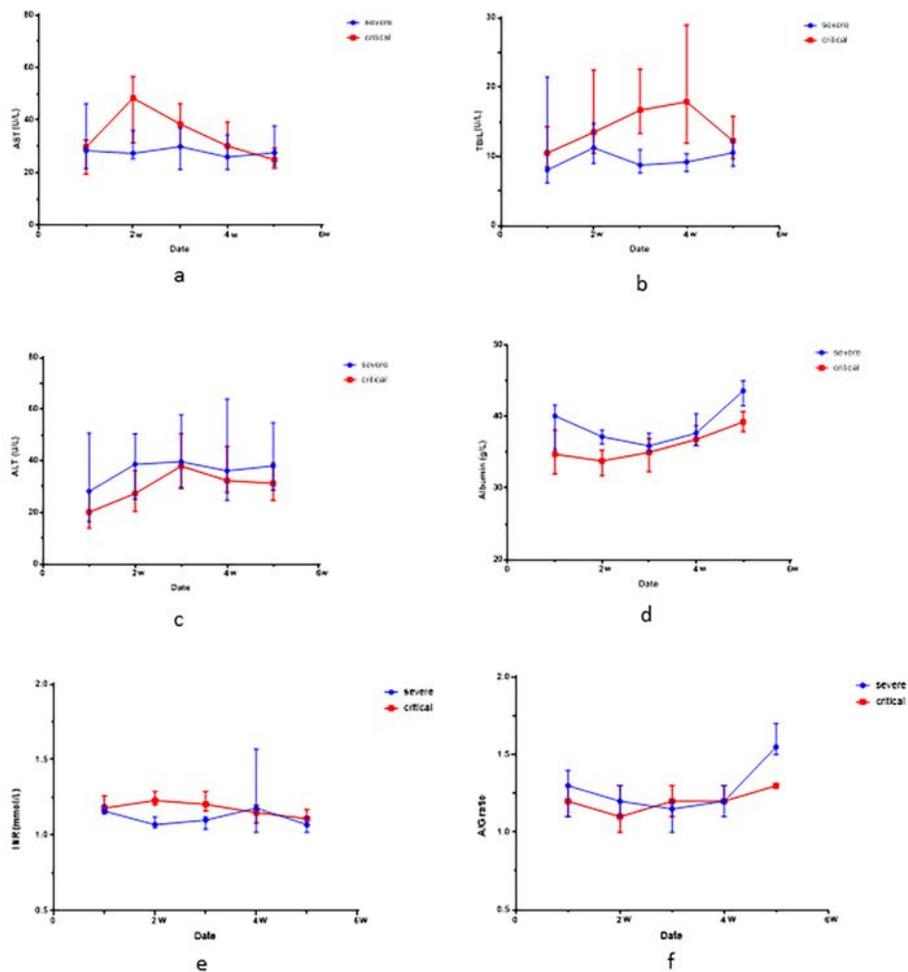


Figure 2

Caption: Dynamic profile of liver function indicators between the severe group and the critical group. Fig. a: Description text: Dynamic changes of AST between the severe group and the critical group. Fig. b: Description text: Dynamic changes of TBIL between the severe group and the critical group. Fig. c: Description text: Dynamic changes of ALT between the severe group and the critical group. Fig. d: Description text: Dynamic changes of albumin between the severe group and the critical group. Fig. e: Description text: Dynamic changes of INR between the severe group and the critical group. Fig. f: Description text: Dynamic changes of A/G ratio between the severe group and the critical group.

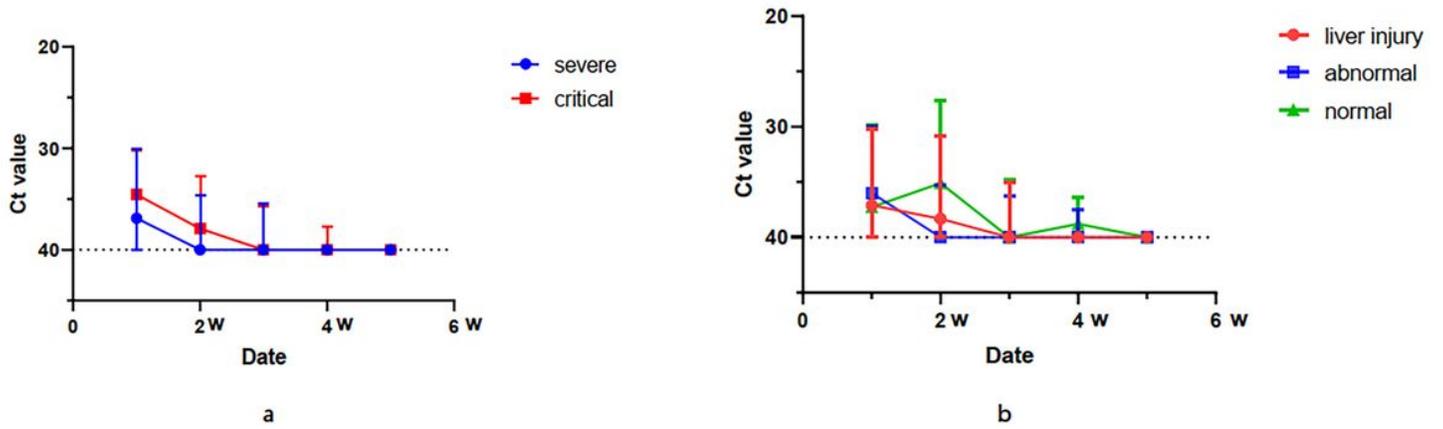


Figure 3

Caption: Dynamic changes of Ct values among differ groups. Fig. a: Description text: Dynamic changes of Ct values between the severe group and the critical group. Fig. b: Description text: Dynamic changes of Ct values among the normal group, the abnormal group, and the liver injury group.

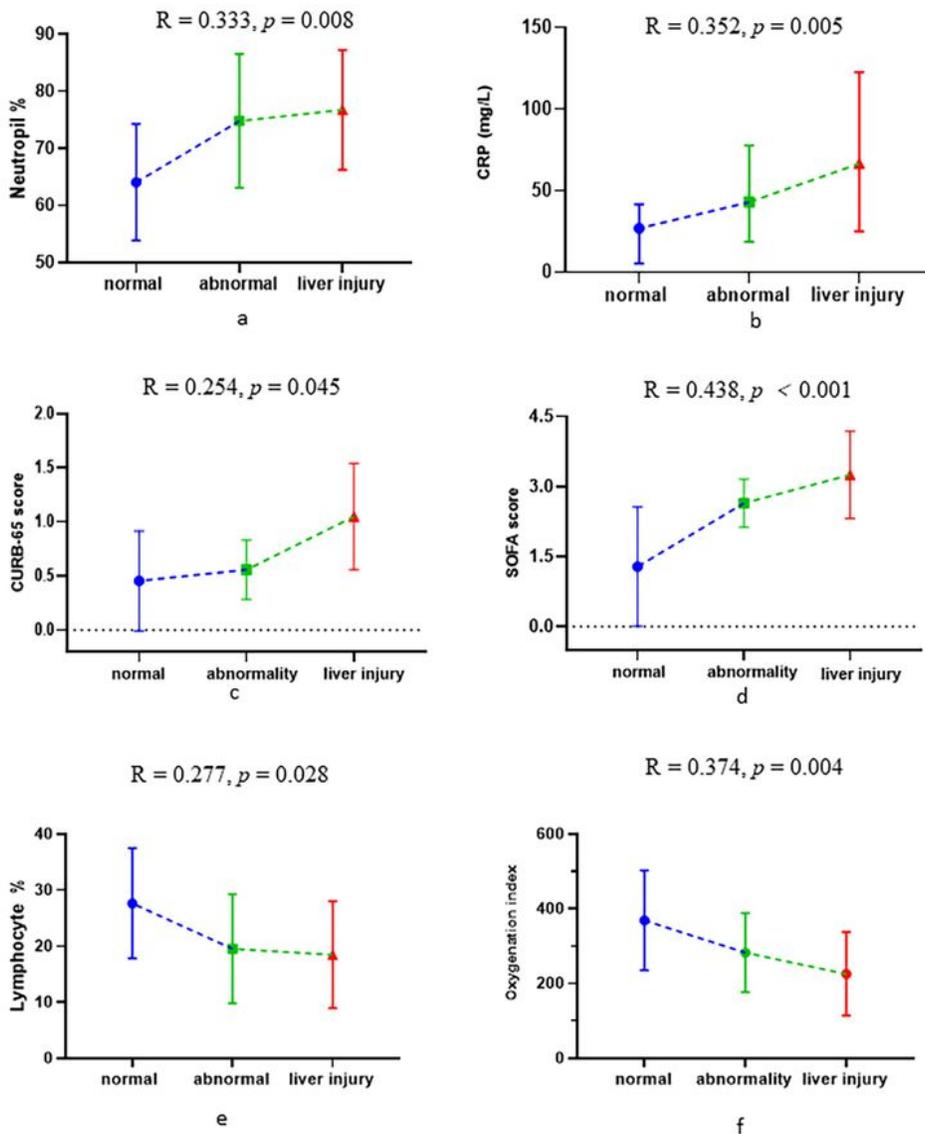


Figure 4

Caption: the correlation between the severity of liver injury and laboratory results. Fig. a: Description text: the correlation between the severity of liver injury and the percentage of neutrophil. Fig. b: Description text: the correlation between the severity of liver injury and CRP. Fig. c: Description text: the correlation between the severity of liver injury and CURB-65 score. Fig. d: Description text: the correlation between the severity of liver injury and SOFA score. Fig. e: Description text: the correlation between the severity of liver

injury and the percentage of lymphocyte. Fig. f: Description text: the correlation between the severity of liver injury and oxygenation index.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementalfigure11.tif](#)
- [supplementalfigure22.tif](#)