**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 56665

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Clinical characteristics and risk factors of** **liver injury in COVID-19 patients in Wuhan**

Zhang H *et al.* COVID-19 in Wuhan

Hu Zhang, Yu-Sheng Liao, Jing Gong, Jing Liu, Heng Zhang

**Hu Zhang, Yu-Sheng Liao, Jing Gong, Jing Liu, Heng Zhang,**Department of Gastroenterology, the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430014, Hubei Province, China

**Author contributions:** Zhang H designed this study and critically revised the manuscript; Zhang H, Gong J and Liu J were responsible for data acquisition and extracting the data; Zhang H and Zhang H drafted the manuscript, analyzed the data and interpreted the results; Gong J and Liao YS were involved in editing the manuscript; all authors read and approved the final manuscript to be published.

**Supported by** the Health and Family Planning Commission of Wuhan, No. WX18Y04.

**Corresponding author: Heng Zhang, MA, MD, Chief Doctor,** Department of Gastroenterology, the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, No. 26 Shengli Street, Jiang’an District, Wuhan 430014, Hubei Province, China. 497697662@qq.com

**Received:** May 9, 2020

**Revised:** June 20, 2020

**Accepted:** July 30, 2020

**Published online:**

**Abstract**

BACKGROUND

Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic. We investigated the clinical characteristics and risk factors of liver injury in Wuhan region COVID-19 patients. We retrospectively analyzed the epidemiological, clinical and laboratory data for 218 COVID-19 patients and investigated liver injury risk factors with multivariate analysis.

AIM

To investigated the clinical characteristics and risk factors of liver injury in Wuhan region COVID-19 patients.

METHODS

The 218 patients included 94 males (43.1%), aged 22 to 94 (50.1 ± 18.4) years, notransferase (ALT) were present in 42 (53.2%) and 36 (45.6%) cases, and 79 patients (36.2%) had abnormally elevated transaminase levels at admission. Patients with liver injury were older than those with normal liver function by a median of 12 years, with a significantly higher frequency of males (68.4% *vs* 28.8%, *P* < 0.001) and more coexisting illnesses (48.1% *vs* 27.3%, *P* = 0.002). Significantly more patients had fever and shortness of breath (87.3% *vs* 69.8%, 29.1% *vs* 14.4%, respectively) in the liver injury group. Elevated aspartate aminotransferase (AST) and alanine amirespectively, while only 12 (15.2%) had elevated total bilirubin. ALT and AST levels were mildly elevated [1-3 × upper limit of normal (ULN)] in 86.1% and 92.9%, respectively. Only two patients (2.5%) had ALT or AST levels > 5 × ULN. Elevated γ-glutamyl-transpeptidase was present in 45 (57.0%), and 86.7% of these were < 135 U/L (3 × ULN). Serum [alkaline](javascript:;) [phosphatase](javascript:;) levels were almost normal in all patients. Patients with severe liver injury had a significantly higher frequency of abnormal transaminase than non-severe patients, but only one case had a very high level of aminotransferase.

RESULTS

Multivariate analysis revealed that male sex, high D-dimer levels, and high neutrophil percentages were linked to higher risk of liver injury. The early stage of COVID-19 may be associated with mildly elevated aminotransferase levels in Wuhan region patients. Male sex and high D-dimer levels and neutrophil percentages may be important predictors of liver injury in patients with COVID-19.

CONCLUSION

We believed male sex and high D-dimer levels and neutrophil percentages may be important predictors of liver injury in patients with COVID-19.

**Key words:** COVID-19; Liver injury; Clinical characteristics; Risk factors

Zhang H, Liao YS, Gong J, Liu J, Zhang H.Clinical characteristics and risk factors of liver injury in COVID-19 patients in Wuhan. *World J Gastroenterol* 2020;In press

**Core tip:** Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic. The study analyzed the clinical characteristics and risk factors of liver injury in Wuhan region COVID-19 patients. The early stage of COVID-19 may be associated with mildly elevated aminotransferase levels. We believed male sex and high D-dimer levels and neutrophil percentages may be important predictors of liver injury in patients with COVID-19.

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19), an emerging infectious respiratory disease, has become a worldwide pandemic. The clinical features of COVID-19 are complicated and varied. In addition to lung injury, liver injury has been reported to occur during the course of the disease[1-3]. Similarly, previous studies have shown that patients infected by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus may develop different degrees of liver injury. Nevertheless，the specific mechanism of liver injury is not clear. It has been confirmed that SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) as the receptor for cell entry[4]. Chai *et al*[5] found that both liver cells and bile duct epithelial cells express ACE2. Whether the liver injury may be associated with the significant expression of ACE2 in liver or bile duct epithelial cells requires further research. The Central Hospital of Wuhan, China, is a major tertiary teaching hospital assigned to the treatment of COVID-19. We retrospectively investigated the clinical characteristics and risk factors for liver injury in COVID-19 patients in Wuhan.

**MATERIALS AND METHODS**

***Patients***

Clinical data was extracted and analyzed retrospectively from electronic medical records of COVID-19 patients at the Central Hospital of Wuhan from January 14, 2020 to March 3, 2020. All patients were diagnosed according to the 7th version of the National Health Commission of China coronavirus guide[6]. A confirmed case was defined as nucleic acid-positive for 2019-nCoV. This study was approved by the institutional ethics board of the Central Hospital of Wuhan affiliated to Tongji medical college, Huazhong University of Science and Technology. Informed consent was not required due to the retrospective design of the trial.

***Data collection***

The enrolled patients were divided into liver injury and normal liver function groups. Liver injury was defined as one or more of the following: Alanine transaminase (ALT) > 40 U/L, aspartic acid transaminase (AST) > 35 U/L, total bilirubin (TBil) > 20.4 μmol/L, alkaline phosphatase > 150 U/L, or γ-glutamyl-transferase (GGT) > 45 U/L. Patients without [these](javascript:;) criteria were classified as the normal liver function group. The liver injury group was further classified as severe (severe and critical subgroups) or non-severe (mild and moderate subgroups).

The clinical data collection included sex, age, coexisting illness, maximum temperature before admission, complete blood count, C-reactive protein (CRP), procalcitonin, D-dimer, liver function tests, and [coagulation](javascript:;) [function](javascript:;) tests. The coexisting illnesses included chronic lung diseases, hypertension, cardiovascular diseases, diabetes, chronic kidney diseases, chronic liver diseases, cerebrovascular diseases, and malignancies.

***Statistical analysis***

The analyses were performed by SPSS version 25.0 (International Business Machine Corp., Armonk, New York, United States). Continuous variables with normal distribution were expressed as *X* ± S and compared with a Student *T* test. Continuous variables with non-normal distribution were compared with the Mann-Whitney *U* test. Categorical variables were expressed as frequency and compared using the*X2* test. A logistic regression model was used to analyze the independent risk factors of the severe cases. *P* < 0.05 was considered statistically significant.

**RESULTS**

***Epidemiologic features***

Data was extracted and analyzed for 505 COVID-19 patients, and 287 cases were excluded due to unavailable or negative 2019-nCoV results. Finally, 218 cases were included in the study, with 79 (36.2%) patients in the liver injury group and 139 (63.8%) in the normal liver function group (Table 1). The mean age for all patients was 50.1 (range 22-91) years old. The mean age in the liver injury group was significantly higher than in the normal liver function group (57.94 ± 16.57 *vs* 45.66 ± 17.82, *P* < 0.001). There was a significantly higher frequency of patients older than 60 years in the liver injury group. There were 94 (43.1%) male patients, with significantly more males in the liver injury group than in the normal group [54 (68.4%) *vs* 40(28.8%), *P* < 0.001].

There were 79 patients with at least one coexisting illness, including 52 (23.9%) with hypertension, 22 (10.1%) with diabetes, 21 (9.6%) with coronary diseases, 16 (7.3%) with chronic lung diseases, 12 (5.5%) with cerebrovascular diseases, 7 (3.2%) with [malignanc](javascript:;)ies, 5 (2.3%) with chronic renal diseases, and 3 (1.4%) with chronic liver diseases. Patients with liver injury were more likely to have at least one coexisting illness than those with normal liver function (48.1% *vs* 27.3%, *P* = 0.002). As shown in Table 1, the proportion of patients with coexisting illnesses such as hypertension, coronary diseases, and chronic lung diseases, was significantly higher in the liver injury group than in the normal liver function group. In addition, a higher frequency of coexisting illness was observed in the severe liver disease group compared to the non-severe disease group.

The only three patients with chronic liver disease had a history of chronic hepatitis B, with no active virus at present. No other cases had a history of chronic liver disease, such as viral hepatitis, non-alcoholic fatty liver disease, alcohol related liver disease, [autoimmune](javascript:;) [liver](javascript:;) [disease](javascript:;), or hereditary liver disease. The incidence of liver injury showed a positive correlation with the clinical classification of COVID-19. A significantly higher frequency of liver injury was observed in the severe patients when compared to the non-severe patients (*P* = 0.007).

***Clinical manifestations***

The most common symptom was fever (166 patients), including 63 (38.0%) with low-grade fever, 76 (45.7%) with mild-grade fever, and 27 (16.3%) with hyperthermia at admission. There were 92 cases (42.2%) with dry coughing, 77 (35.3%) with fatigue, 73 (33.5%) with a sense of heaviness in the chest, 59 (27.1%) with expectoration, 43 (19.7%) with shortness of breath, and 42 (19.3%) with myalgia. Atypical symptoms included diarrhea (33 cases, 15.1%), [poor](javascript:;) [appetite](javascript:;) (32 cases, 14.7%), dizziness (20 cases, 9.2%), headache (19 cases, 8.7%), pharyngalgia (13 cases, 6.0%), nausea (10 cases, 4.6%), abdominal pain (6 cases, 2.8%), nasal discharge (6 cases, 2.8%), and vomiting (3 cases, 1.4%). Among all the symptoms, fever (87.3% *vs* 69.8%, *P* = 0.003) and shortness of breath (29.1% *vs* 5.0%, *P* = 0.009) were significantly higher in the liver injury group.

***Laboratory parameters***

**Liver function tests:** There were 79 cases (36.2%) with elevated ALT, AST, GGT, or TBil at admission. Elevated GGT was present in 45 (57.0%), and 86.7% of these had GGT < 135U/L [3 times the upper limit of normal (ULN)]. Elevated AST and ALT were seen in 42 (53.2%) and 36 (45.6%) cases, respectively. Serum level of AST was significantly higher in patients with severe COVID-19. An elevated AST level was observed in 13.9% of patients with non-severe disease and 44.7% of patients with severe disease, while an elevated ALT level was observed in 16.1% of patients with non-severe disease and 18.4% of patients with severe disease. These data suggest that liver injury is more prevalent in severe cases than in mild cases of COVID-19. However, the ALT and AST levels were only mildly elevated (1-3 ULN） in 86.1% and 92.9% of the cases, respectively. Only two patients (2.5%) had ALT or AST levels greater than five times the ULN. Elevated TBil was seen in only 12 patients (15.2%), and 83.3% of these were mildly elevated (1-1.5 times the ULN). Of 100 patients with test results available, only one patient had elevated [alkaline](javascript:;) [phosphatase](javascript:;).

There were 23 cases (29.1%) of simultaneous elevation of both ALT and AST and 15 cases (19.0%) of simultaneous elevation of ALT, AST and GGT. Only 2 cases (2.5%) had simultaneous increases in TBil, ALT, AST and GGT. More than 85% of abnormal transaminase levels were mildly elevated, and only one case had a very high level of aminotransferases.

The level of serum albumin was decreased in 108 (50%) of 216 patients. The incidence of decreased serum albumin level was significantly higher in severe COVID-19 patients than that in non-severe patients (76.3% *vs* 44.4%, *P* < 0.001). There were 55 patients with decreased serum albumin level who had ALT, AST, TBil, and GGT in the normal range.

**Hematology and coagulation:**Leukocytes were normal in most of patients (74.8%), with 19.2% decreased and 6.0% increased. Lymphopenia was found in 62.0% of patients with liver injury. Other laboratory findings in the liver injury group included high CRP (79.5%), neutrophil percentage (48.1%), D-dimer (47.2%), serum procalcitonin (32.9%), fibrinogen (11.8%), and white blood cell count (10.1%).

***Risk factors for liver injury***

We compared patients in the two groups to identify possible risk factors of liver injury in patients with COVID-19. Univariate analysis of epidemiological, clinical, and [laboratorial](javascript:;) variables identified age ≥ 60, male sex, severe disease, coexisting illness, fever, shortness of breath, albumin, globulin, white blood cell count, neutrophils, leukomonocyte, CRP, prothrombin time, prothrombin active, fibrinogen and D-dimer as significant risk factors of liver injury in patients with COVID-19 (Tables 1 and 2). Multivariate logistic regression analysis further revealed that male sex, high D-dimer level, and neutrophil percentage were significantly associated with the incidence of liver injury (Table 3).

**DISCUSSION**

A high level of serum aminotransferase is believed to be a major biochemical manifestation of liver injury. A recent study on COVID-19 has shown that the incidence of liver injury ranges from 14.8% to 53%[7]. In this study, liver injury occurred in 36.2% (79/218) of COVID-19 patients, and most abnormal transaminase levels were mildly elevated, similar to previous reports[1,8]. We found that 86.1% of the abnormal ALT levels and 92.9% of the abnormal AST levels were mildly elevated (1−3 times the ULN). Serum ALT and AST levels in severe COVID-19 patients were significantly higher than those in the non-severe patients. These data suggest that more than 85% of abnormal transaminase levels were mildly elevated at admission.

Multivariate regression analysis showed that male sex, high D-dimer level, and high neutrophil percentage were predictive risk factors of liver injury in patients with COVID-19. Li *et al*[9] found that male sex was associated with the severity of disease in COVID-19, and men are likely to have more severe disease than women. Sex differences in clinical findings among severe patients may be due to estrogen effects. The higher estrogen level in females may help to protect these patients from liver injury[10,11]. Our data showed similar findings to the above study, suggesting that male sex may be closely related to severe COVID-19. In our study, 28.2% (57/202) of COVID-19 patients presented with increased D-dimer. Serum levels of D-dimer in severe COVID-19 patients were significantly higher than those in the non-severe patients. Further, the proportion of patients with elevated D-dimer level was significantly higher in severe patients than in non-severe patients, which is also similar to previous reports[2,12]. In severe patients, D-dimer increases were considered to be related to advanced age, long-term bedridden status, and comorbid cardiovascular and cerebrovascular diseases. Furthermore, it is noteworthy that the older patients often with comorbidities, such as chronic obstructive pulmonary disease, may also result in the liver injury. With aging degenerative changes, the older patients, especially with underlying diseases, were more susceptible to the attack of SARS-CoV-2. It may be related to the low immunity of the body. Yu *et al*[13] studied the age-related rhesus macaque models of COVID-19 and found that viral replication of nasopharyngeal swabs, anal swabs and lung was more active in old monkeys after infection, and SARS-CoV-2 caused more severe pneumonia in old monkeys.

It is particularly worth noting that we found higher GGT levels in 45 (57.0%) of 79 patients, and 86.7% of them had GGT < 135U/L (3 × ULN). As the patients’ clinical status deteriorated, the serum GGT levels progressively elevated. However, serum alkaline phosphatase level was at normal range in both mild and severe COVID-19 cases.

Currently, the specific mechanism of liver injury caused by SARS-CoV-2 is still unclear. Firstly, it has been shown that SARS-CoV2, like SARS-CoV, uses ACE2 as its entry receptor[14]. Chai *et al*[5] found that ACE2 expression is much higher in bile duct epithelial cells than in liver cells. Bile duct epithelial cells are known to play important roles in immune response and liver regeneration[15]. These results suggest that liver injury could be caused by SARS-CoV-2 as a result of the damage to bile duct epithelial cells in COVID-19.

Secondly, liver injury may be related to the cytokine storm syndrome. In our study, lymphocytes were decreased in patients with COVID-19. As the clinical status deteriorated, the lymphocytes progressively decreased. Previous studies have shown that over-activated lymphocytes secrete a large number of cytokines, resulting in systemic inflammatory response syndrome, which causes inflammation and damage of the liver[16].

At the same time, patients with hypoxic saturation have extensive pulmonary inflammation, which leads to tissue ischemia and hypoxia, resulting in the internal environment disorder and multiple organ dysfunction[17], including liver dysfunction. One study reported that serum IL-1, IL-6, and IL-10 levels in patients with liver injury were higher than those in patients with normal liver function[18]. In this study, the serum CRP levels and neutrophil percentage were increased significantly in patients with liver injury, while the leukomonocyte count was decreased. These data suggest a possible correlation between liver injury and the inflammatory responses induced by SARS-CoV-2 infection.

Last, liver injury may be drug-induced. Although there is no effective antiviral therapy for SARS-CoV-2, Interferon-α, lopinavir/ritonavir, ribavirin and chloroquine phosphate are used for treatment of COVID-19[6]. These drugs may result in liver injury, yet whether this results in liver damage in patients remains to be investigated.

This study has several limitations. First, inflammatory and immune indicators such as interleukin-6, ferritin, blood sedimentation, immunoglobulin series and lymphocyte subgroup analysis are closely related to liver function. Due to the limited medical conditions surrounding the pandemic, these factors could not be adequately analyzed. Therefore, it is necessary to further analyze the relationship between these indicators and liver injury in COVID-19. Moreover, in view of possible drug-induced liver injury, patients’ pre-admission medication information should be noted in detail. In this study, it is impossible to exclude the influence of pre-admission medication on liver injury. Finally, the retrospective design of this study may decrease its credibility and there may have been bias due to the small number of samples.

In summary, liver injury is common in COVID-19, and most patients with abnormal transaminase had mildly elevated levels. Elevated D-dimer and neutrophil percentages and male sex may be important independent risk factors of liver injury. COVID-19 may be associated with a mild elevation of aminotransferase levels during the early stage of the disease in the Wuhan region. While further studies are needed to clarify these findings, they will provide reference for the management and treatment of liver injury in patients with COVID-19.

**ARTICLE HIGHLIGHTS**

Coronavirus disease 2019 (COVID-19), an emerging infectious respiratory disease, has become a worldwide pandemic. The clinical features of COVID-19 are complicated and varied. In addition to lung injury, liver injury has been reported to occur during the course of the disease[1-3]. Similarly, previous studies have shown that patients infected by severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus may develop different degrees of liver injury. Nevertheless，the specific mechanism of liver injury is not clear.

***Research background***

COVID-19 has become a worldwide pandemic. We investigated the clinical characteristics and risk factors of liver injury in Wuhan region COVID-19 patients. We retrospectively analyzed the epidemiological, clinical and laboratory data for 218 COVID-19 patients and investigated liver injury risk factors with multivariate analysis.

***Research motivation***

The investigated the clinical characteristics and risk factors of liver injury in Wuhan region COVID-19 patients and investigated liver injury risk factors with multivariate analysis.

.

***Research objectives***

To investigated the clinical characteristics and risk factors of liver injury in Wuhan region COVID-19 patients.

***Research methods***

The 218 patients included 94 males (43.1%), aged 22 to 94 (50.1 ± 18.4) years, notransferase were present in 42 (53.2%) and 36 (45.6%) cases, and 79 patients (36.2%) had abnormally elevated transaminase levels at admission. Patients with liver injury were older than those with normal liver function by a median of 12 years, with a significantly higher frequency of males (68.4% *vs* 28.8%, *P* < 0.001) and more coexisting illnesses (48.1% *vs* 27.3%, *P* = 0.002). Significantly more patients had fever and shortness of breath (87.3% *vs* 69.8%, 29.1% *vs* 14.4%, respectively) in the liver injury group.

***Research results***

The early stage of COVID-19 may be associated with mildly elevated aminotransferase levels in Wuhan region patients. Male sex and high D-dimer levels and neutrophil percentages may be important predictors of liver injury in patients with COVID-19.

***Research conclusions***

We believed male sex and high D-dimer levels and neutrophil percentages may be important predictors of liver injury in patients with COVID-19.

***Research perspectives***

While further studies are needed to clarify these findings, they will provide reference for the management and treatment of liver injury in patients with COVID-19.

**ACKNOWLEDGEMENTS**

We sincerely thank all the front-line medical staff of Wuhan Central Hospital North and South Hospital and Support Hospital and their families for fighting COVID-19.

**REFERENCES**

1 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng 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, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

2 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

3 **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 X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

4 **Li W**, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**: 450-454 [PMID: 14647384 DOI: 10.1038/nature02145]

5 **Chai XQ,** Hu LF, Zhang Y, Han WY, Lu Z, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Fan J, Lan F. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Preprint, 2020. [DOI: 10.1101/2020.02.03.931766]

6 **National Health Committee of the People's Republic of China.** Diagnosis and treatment plan for pneumonitis caused by new coronavirus (trial version 7). [2020-03-03]. Available from: <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf>

7 **Xu L**, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020; **40**: 998-1004 [PMID: 32170806 DOI: 10.1111/liv.14435]

8 **Fang D,** Ma JD, Guan JL, Wang MR, Song Y, Tian DA, Li PY. Manifestations of digestive system in hospitalized patients with novel coronavirus pneumoniain Wuhan, China: a single-center, descriptive study. *Chin J Dig* 2020; **40**. [doi: 10.3760/cma.j.issn.0254-1432.2020.0005]

9 **Li J,** Zhang Y, Wang F, Liu B, Li H, Tang G, Chang Z, Liu A, Fu C, Gao J, Li J. Sex differences in clinical findings among patients with coronavirus disease 2019 (COVID-19) and severe condition. [DOI: 10.1101/2020.02.27.20027524]

10 **Karlberg J**, Chong DS, Lai WY. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? *Am J Epidemiol* 2004; **159**: 229-231 [PMID: 14742282 DOI: 10.1093/aje/kwh056]

11 **Klein SL**, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016; **16**: 626-638 [PMID: 27546235 DOI: 10.1038/nri.2016.90]

12 **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 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, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

13 **Yu P**, Qi F, Xu Y, Li F, Liu P, Liu J, Bao L, Deng W, Gao H, Xiang Z, Xiao C, Lv Q, Gong S, Liu J, Song Z, Qu Y, Xue J, Wei Q, Liu M, Wang G, Wang S, Yu H, Liu X, Huang B, Wang W, Zhao L, Wang H, Ye F, Zhou W, Zhen W, Han J, Wu G, Jin Q, Wang J, Tan W, Qin C. Age-related rhesus macaque models of COVID-19. *Animal Model Exp Med* 2020; **3**: 93-97 [PMID: 32318665 DOI: 10.1002/ame2.12108]

14 **Hoffmann M,** Kleine-Weber H, Krüger N, Marcel M, Christian D, Stefan P. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. [DOI: 10.1101/2020.01.31.929042]

15 **Banales JM**, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 269-281 [PMID: 30850822 DOI: 10.1038/s41575-019-0125-y]

16 **Tisoncik JR**, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012; **76**: 16-32 [PMID: 22390970 DOI: 10.1128/MMBR.05015-11]

17 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

18 **Duan Z,** Chen Y, Zhang J, Zhao J, Lang Z, Meng F, Bao X. Clinical characteristics and mechanism of liver injury in patients with severe acute respiratory syndrome. *Chin J Hepatol* 2003; **11**: 493-496 [DOI: 10.3760/j.issn:1007-3418.2003.08.014]

**Footnotes**

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of the Central Hospital of Wuhan.

**Informed consent statement: T**he Ethics Committee of the Central Hospital of Wuhanwaived the informed consent statement.

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** May 9, 2020

**First decision:** June 13, 2020

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Boscá L, Cerwenka H, Corrales FJ, Ozen H **S-Editor:** Zhang L **L-Editor:** **E-Editor:**

**Table 1 Comparison of clinical data between the two groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Normal liver function group** | **Abnormal liver function group** | ***P* values** |
| Total cases | 139 | 79 | - |
| Average age (yr) | 45.66 ± 17.82 | 57.94 ± 16.57 | < 0.001 |
| Aged ≥ 60 yr (%) | 42 (30.2) | 39 (49.4) | 0.005 |
| Males (%) | 40 (28.8) | 54 (68.4) | < 0.001 |
| Severe disease1 (%) | 17 (12.2) | 21 (26.6) | 0.007 |
| Coexisting illness *n* (%) | 38 (27.3) | 38 (48.1) | 0.002 |
| Hypertension | 26 (18.7) | 26 (32.9) | 0.018 |
| Diabetes | 11 (7.9) | 11 (13.9) | 0.157 |
| Coronary heart disease | 9 (6.5) | 12 (15.2) | 0.036 |
| Chronic lung disease | 6 (4.3) | 10 (12.7) | 0.023 |
| Cerebrovascular disease | 4 (2.9) | 8 (10.1) | 0.0522 |
| Chronic kidney disease | 3 (2.2) | 2 (2.5) | 0.7692 |
| Chronic liver disease | 1 (0.7) | 2 (2.5) | 0.6182 |
| [Malignancy](javascript:;) | 4 (2.9) | 3 (3.8) | 0.9772 |

1Severe disease includes severe and critical pneumonia. 2Continuous correction chi square test used.

**Table 2 Comparison of laboratory parameters between the two groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Test** | | **Normal liver function group** | **Abnormal liver function group** | **Normal ranges** | ***P* values** |
|  | Biochemical parameters | | | | |
| TBil | | 8.78 ± 3.73 | 12.66 ± 6.89 | 2-20.4 µmol/L | < 0.001 |
| ALT | | 17.42 ± 8.05 | 69.74 ± 178.37 | 7-40 U/L | 0.011 |
| AST | | 18.96 ± 5.58 | 72.29 ± 269.68 | 13-35 U/L | 0.083 |
| GGT | | 17.51 ± 8.3 | 83.25 ± 93.48 | 7-45 U/L | < 0.001 |
| ALP | | 49.96 ± 17.85 | 57.52 ± 42.16 | 40-150 U/L | 0.330 |
| Total Protein | | 67.87 ± 7.39 | 67.31 ± 7.42 | 65-85 g/L | 0.594 |
| Albumin | | 40.70 ± 4.82 | 37.85 ± 4.95 | 40-55 g/L | < 0.001 |
| Globulin | | 27.17 ± 5.92 | 29.46 ± 6.12 | 20-40 g/L | 0.008 |
|  | Hematological parameters | | | | |
| WBC | | 5.11 ± 2.15 | 6.04 ± 2.78 | 3.5-9.5 × 109/L | 0.011 |
| Neutrophils | | 63.23 ± 13.23 | 71.45 ± 12.92 | 40-75% | < 0.001 |
| Hemoglobin | | 128.31 ± 15.98 | 129.00 ± 18.93 | 12-160 g/L (male); 110-150 g/L (female) | 0.785 |
| Leukomonocytes | | 1.32 ± 0.62 | 1.06 ± 0.55 | 1.1-3.2 × 109/L | 0.002 |
| Platelets | | 197.63 ± 77.69 | 203.92 ± 92.59 | 125-350 × 109/L | 0.611 |
| CRP | | 1.79 ± 2.87 | 4.34 ± 4.41 | 0-0.6 mg/dL | < 0.001 |
| Procalcitonin | | 0.05 ± 0.05 | 1.50 ± 6.77 | < 0.1 ng/mL | 0.078 |
|  | Coagulation parameters | | | | |
| PT | | 11.51 ± 1.55 | 11.94 ± 1.41 | 9-13 s | 0.043 |
| INR | | 1.00 ± 0.15 | 1.03 ± 0.13 | 0.7-1.3 | 0.132 |
| PTA | | 102.41 ± 22.35 | 95.42 ± 21.74 | 70%-130% | 0.029 |
| Fibrinogen | | 2.72 ± 0.71 | 3.02 ± 0.76 | 2-4 g/L | 0.006 |
| Thrombin time | | 16.82 ± 3.26 | 17.99 ± 12.59 | 14-21 s | 0.429 |
| APTT | | 29.12 ± 5.66 | 29.11 ± 5.54 | 20-40 s | 0.990 |
| D-dimer | | 0.76 ± 1.16 | 2.45 ± 3.80 | 0-1 µg/mL | < 0.001 |

TBil: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl-transpeptidase; ALP: Alkaline phosphatase; WBC: White blood cell count; CRP: C-reactive protein; PT: Prothrombin time; INR: International normalized ratio of prothrombin time; PTA: Prothrombin activity; APTT: Activated partial thromboplastin time.

**Table 3 Logistic regression analysis of liver injury in patients with coronavirus disease 2019**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **B value** | **Standard error** | **Wald** | ***P* values** | **OR** | **95%CI** |
| Sex1 | 1.825 | 0.339 | 28.981 | < 0.001 | 6.203 | 3.192-12.056 |
| NE | 0.039 | 0.013 | 8.986 | 0.003 | 1.004 | 1.014-1.067 |
| D-dimer | 0.396 | 0.112 | 12.515 | < 0.001 | 1.486 | 1.193-1.850 |

1Sex: male = 1, female = 0. NE: Neutrophil percentage; SE: Standard error; OR: Odds ratio; CI: Confidence interval.