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EXAMINING HEPATORENAL ALTERATIONS IN COVID-19 PATIENTS: IMPLICATIONS FOR SEVERITY AND MORTALITY

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ABSTRACT

***Background*:** COVID-19 severity varies widely among individuals - from asymptomatic to acute respiratory distress cases (who require ventilation). The virus causes multi-organ damage, leading to significant variations in parameters controlled by these organs. We designed this study to check the effect of the COVID-19 virus on the hepatorenal health of patients.

***Methods*:** Blood samples were collected from 240 COVID-19 patients (divided into Moderate=186 and Severe=54) and 89 healthy individuals, serving as controls. After a post-COVID-19 follow-up of two months, all the patients were categorized into survivors (212) and non-survivors (28). Hepatic (ALT, AST, ALP, Total Bilirubin and AST/ALT) and renal (Creatinine, Uric acid and Albumin) parameters were assessed using biochemistry analyzer. Statistical analysis was conducted using the student "t" test and One-Way ANOVA through GraphPad Prism software.

***Results*:** Serum level of AST, ALT, ALP, and Total Bilirubin were considerably elevated in moderate and severe patient groups compared to the control group. Among the renal profiles, the serum creatinine level was also considerably higher (P=0.015). In contrast, Uric acid and albumin levels showed significant decrease in moderate and severe patient groups compared to the control group (P< 0.001). However, the comparison between survivors and non-survivors showed that serum AST, ALT, ALP, total bilirubin, and creatinine levels were significantly high for non-survivors. At the same time, uric acid and albumin levels were significantly low in non-survivors.

***Conclusion*:** The hepatic and renal profiles exhibited alterations linked with COVID-19 severity and mortality. It is recommended to monitor these organs during hospitalization to prevent the risk of multiple organ damage, acute medical complications and death even after recovery from coronavirus disease.

INTRODUCTION

In December 2019, a new coronavirus was discovered in Wuhan, China, following a series of mysterious pneumonia cases. On March 12, 2020, the WHO (World Health Organization) declared this virus a pandemic (Yang et al. 2020). Unfortunately, numerous people worldwide have lost their lives since the reporting of the first case.

Most patients admitted to the hospital exhibit symptoms of cough, high fever, dyspnea, anosmia, and tiredness, which are primary indicators of coronavirus disease 2019, also called COVID-19. Respiratory failure, an important contributor to death, occurs in approximately 2–3% of cases (Chen et al. 2020). Despite the primary clinical indications being associated with lung damage, there is evidence of the virus affecting other organs, such as the liver, pancreas, kidneys, and heart, as

indicated by pathological clinical results. This multi-organ impact is likely attributed to various organs' chief receptor for viral entry, the ACE2 receptor (Angiotensin-converting enzyme two receptor) (Specific 2020; Zhang et al. 2020). Hepatocytes and bile duct cells may be affected by the distribution of these receptors throughout the body, leading to reported malfunctioning of the liver in affected patients (Zhang et al. 2015).

Various mechanisms contribute to damaging the liver in COVID-19 patients. A biopsy of the liver reveals moderate lobular and portal activity and moderate microvesicular steatosis, consistent with either drug-induced liver injury or direct viral infection. However, viral inclusions within hepatocytes were not identified (Xu 2020). Liver function tests show anomalies in around 14–53% of severe COVID-19 cases, with the abnormalities most commonly presenting in a hepatocellular pattern (Shi et al. 2020; Yang et al. 2020).

Creatinine is a nitrogenous substance (non-protein) that belongs to the group of guanidine compounds. It strongly indicates normal renal metabolism (Kumara et al., 2017). Fluctuations in serum creatinine levels point out pathophysiological anomalies of the renal system.

The diverse range of biochemicals in intra and intercellular environments efficiently maintain normal human metabolism. With advancements in the post-genomic period, systemically analyzing biochemical makers present in human serum has become interesting for prognosis of organ damage.

MATERIALS AND METHODS

In this case-control study, a total of 329 subjects were involved. Among them, 240 RT-PCR positive COVID-19 patients were categorized into different groups (Moderate=186 and Severe=54) based on WHO criteria, recruited from Mayo Hospital and Ittefaq Hospital in Lahore. All these patients were followed up for two months, after discharge from hospital, and categorized into survivors and non-survivors. Among them 28 were non-survivors and 212 were survivors. Additionally, 89 healthy individuals of a matching age group were selected as controls from the University of the Punjab, Lahore. The study received approval from the ethical review committee of the University of the Punjab, Lahore.

Before enrollment, all subjects were provided with information about the study, and we obtained written informed consent. Subjects with co-morbidities like diabetes, cancer, cardiovascular diseases, etc., and smokers were excluded from the study. A comprehensive questionnaire was developed to gather information on subjects' clinical symptoms and socio-demographic data.

A registered laboratory technician collected blood samples from the participants using sterilized Becton and Dickson syringes. Five ml of blood was collected from each subject. The collected blood was transferred to labelled red serum tubes containing a clot activator and transported to the physiology laboratory. The vials were placed at room temperature for half an hour in the laboratory to allow clot formation. Subsequently, the tubes were centrifuged at 4000rpm for 15 minutes. After centrifugation, the serum was separated, transferred to labelled Eppendorf tubes and stored at -80◦C in the freezer for further analysis.

Serum hepatic profile (ALT, AST, ALP, Total Bilirubin and AST/ALT) and renal profile analysis (Creatinine, Uric acid, and Albumin levels) were assessed with commercially available kits of “Monlab” Spain.

Biochemistry analyzer Robert Riele photometer 5010 V5+ of Germany was used for the biochemical analysis.

Statistical Analysis:

A statistical investigation of the data obtained was done using a student t-test and one-way ANOVA to match the results in comparable groups. P value <0.05 statistically significant. Outcomes obtained were presented as Mean ± SEM in tabular and graphical form.

RESULTS

An intergroup comparison of hepatic and renal profiles using One-Way ANOVA revealed significant elevations in ALT, AST, ALP, and Total Bilirubin (P<0.001) in both moderate and severe patient

groups compared to the control group. Notably, AST/ALT ratio displayed a significant variation only when comparing patients in the severe group (P=0.02). At the same time, no considerable difference was observed between the control group and moderate patients (Table 1, Fig. 1-5).
Similarly, among the renal parameters, the serum creatinine levels in patients were significantly higher (P=0.01) compared to the control group (Fig. 6). However, both uric acid and albumin levels exhibited a significant decline in both the moderate and severe patient groups in comparison to the control group (P<0.001) (Fig. 7 and 8). Nevertheless, renal profile parameters did not significantly vary when compared between moderate and severe patient groups. However, the result of the comparison between survivors and non-survivors showed that Serum AST, ALT, ALP, Total Bilirubin and Creatinine were significantly high in non-survivors, While Uric acid and albumin were significantly low in non-survivors (Table 2).

Table 1: A comparative presentation of renal and hepatic profile among control and patients with moderate and severe COVID-19.

Parameter	**Mean ± SEM**			***P-V*alue**
	Control (n=89)	**Moderate** (n=186)	**Severe** (n=54)	
ALT (IU/L)	37.60±1.81	58.61±2.80	74.24±6.54	< 0.001
AST (IU/L)	31.93±1.10	57.46± 2.75	67.19 ±7 .09	< 0.001
ALP (IU/L)	97.99± 2.72	167.50±5.74	201.20±11.90	< 0.001
T. Bilirubin (mg/dL)	0.62±0.02	1.00±0.02	1.20±0.04	< 0.001
AST/ALT	0.96±0.04	1.17±0.05	1.33±0.18	0.02
Creatinine (mg/dL)	1.00±0.03	1.44±0.11	1.59±0.21	0.01
Uric Acid (mg/dL)	5.98±0.13	4.61±0.25	4.53±0.43	0.001
Albumin (ng/mL)	4.56±0.11	2.62±0.08	2.53±0.16	< 0.001

Group comparison showing Mean ± SEM **ALT:** Alanine aminotransferase; **AST**: Aspartate aminotransferase; **ALP**: Alkaline phosphatase; **T.Bilirubin**: Total Bilirubin

Table 2: Intergroup comparison of Mean ± SEM Hepatic and Renal Parameters of survivors and non-survivors.

Parameter	**Mean ± SEM**		**P-*V*alue**
	Survivors (n=212)	**Non-survivors (n=28)**	
ALT (IU/L)	57.54 ± 2.65	96.89 ± 8.11	< 0.001
AST (IU/L)	58.79 ± 2.84	80.86 ± 7.85	0.008
ALP (IU/L)	171.10 ± 5.50	204.70 ± 16.52	0.04
T. Bilirubin (mg/dL)	1.03± 0.02	1.09 ± 0.06	0.3
Creatinine (mg/dL)	1.48 ± 0.10	1.50 ± 0.24	0.9
Uric Acid (mg/dL)	4.72 ± 0.23	3.38 ± 0.40	0.04
Albumin (ng/mL)	2.67 ± 0.08	2.15 ± 0.16	0.03

Group comparison showing Mean ± SEM **ALT:** Alanine aminotransferase; **AST**: Aspartate aminotransferase; **ALP**: Alkaline phosphatase; **T.Bilirubin**: Total Bilirubin

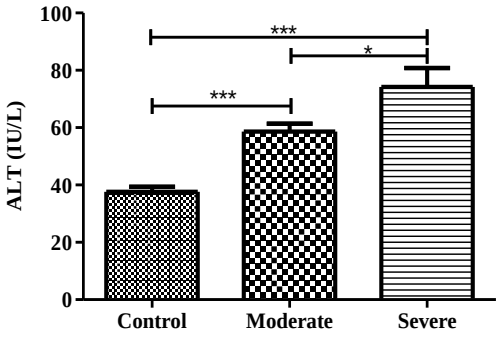

Figure1 Comparison of ALT in COVID-19 patients (moderate and severe) with the controls. * and * represent the significance level at P<0.05 and 0.001, respectively.**

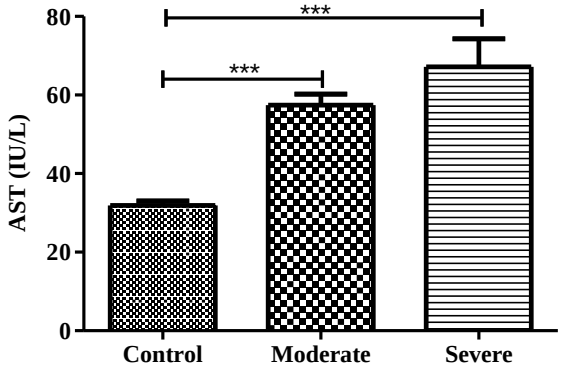

Figure 2: Comparison of AST in COVID-19 patients (moderate and severe) with the controls. * represents the significance level at *P*< 0.001, respectively.**

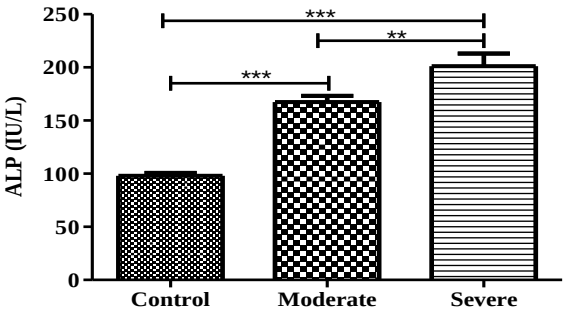

Figure 3: Comparison of ALP in COVID-19 patients (moderate and severe) with the controls. ** and * represents the significance level at *P*< 0.01, and 0.001, respectively.**

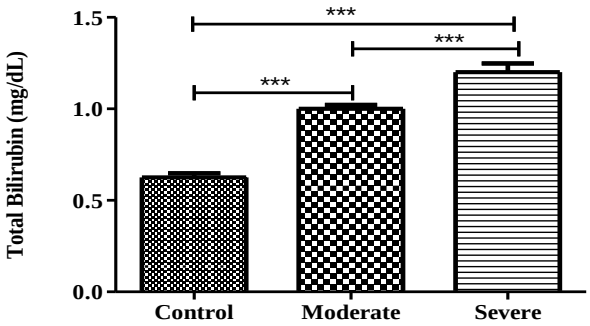

Figure 4: Comparison of Total Bilirubin in COVID-19 patients (moderate and severe) with the controls. * represents the significance level at *P*< 0.001.**

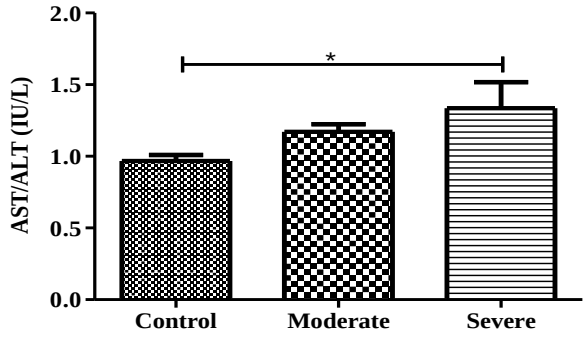

Figure 5: Comparison of AST/ALT in COVID-19 patients (moderate and severe) with the controls. * represents the significance level at *P*<0.05.

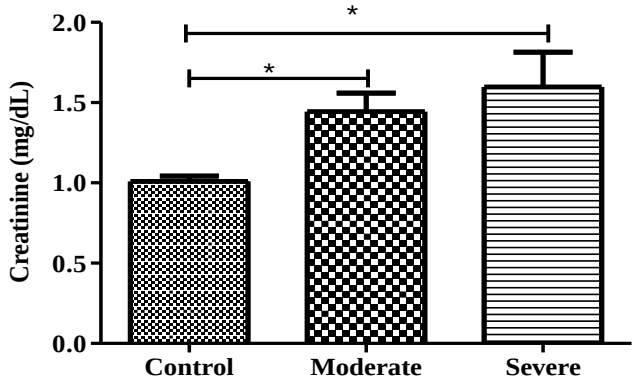

Figure 6: Comparison of Creatnine in COVID-19 patients (moderate and severe) with the controls. * represents the significance level at P<0.05.

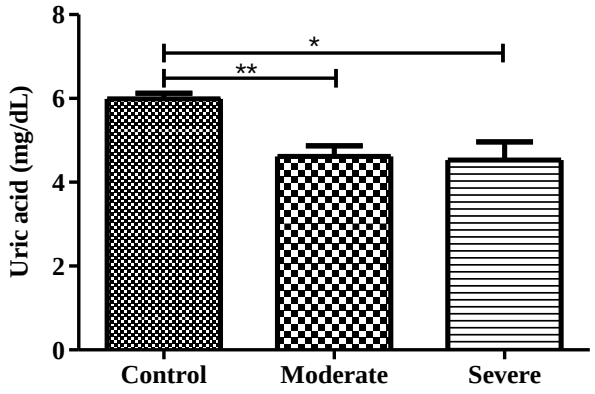

Figure7: Comparison of Uric Acid in COVID-19 patients (moderate and severe) with the controls. * and ** represents the significance level at P<0.05 and 0.01 respectively

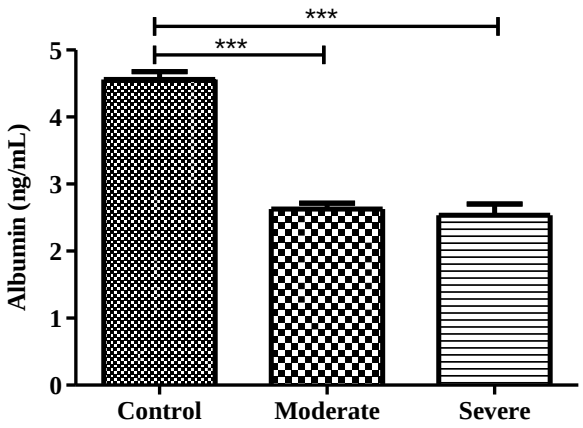

Figure 8: Comparison of Albumin in COVID-19 patients (moderate and severe) with the controls. * represents the significance level at P< 0.001.**

DISCUSSION

The relentless sharp syndrome of respiratory system coronavirus type 2, which was the basis of the pandemic of disease of coronavirus 2019, is associated with significant death and morbidity linked to pneumonia, which results in multi-organ collapse and sharp syndrome, which causes respiratory distress (Hundt et al. 2020). Individuals with an infection of the coronavirus commonly exhibit indications like issues of the respiratory system and fever pinpointing pneumonia (Bielecka-Dąbrowa et al. 2021; Wu and McGoogan 2020). SARS-CoV-2 is reported to be linked with several effects other than pulmonary complications (Wei et al. 2020), including gastrointestinal and hepatic manifestations (Agarwal et al. 2020).

The Corona virus type 2 is attached to a particular receptor, i.e., ACE2, articulated by different organs, including intrahepatic bile ducts and liver cells. Research has revealed that bile duct cells and liver cells together carry ACE2. Notably, cholangiocytes (bile duct cells) express the ACE2 significantly elevated compared to liver cells (Specific 2020).

This investigation intended to examine the effect of COVID-19 on liver and kidney medical results among patients hospitalized with confirmed infection in Lahore, Pakistan. While mainly ubiquitous indications recognized in infectious individuals are shortness of breath, cough, and fever, abnormal hepatic and renal outcomes are significant factors for extrapulmonary expression in COVID-19. This observation may probably associated with the liver function expressing the basic entry receptors of the virus (Sultan et al. 2020; Xu et al. 2020).

The results of this investigation concerning hepatic profiles revealed that Total Bilirubin, AST, ALP and ALT were significantly elevated in the experimental groups, i.e. severe and moderate patient groups, compared with the healthy control group. Notably, the AST/ALT ratio varied significantly compared to patients in the severe group. In contrast, when the moderate group patients and control group were linked, no noteworthy difference between them was reported.

The findings of another investigation align with previous interpretations, indicating that the trend of hepatic injury in infection of COVID-19 is primarily cells of the liver slightly more than cells of the gall bladder. However, this study proposes that an increase in total bilirubin (TBIL) along with alkaline phosphatase (ALP) possibly will be more prevalent than formerly stated (Hundt et al. 2020). In an investigation, we have detected increased biomarkers of ALT and AST, with increased cholestatic enzyme levels in 4% of patients. This finding has prompted us to investigate the association and assess if a link exists between the disease of COVID-19 and the AST-ALT increase. The receptor of ACE2 could be among the many receptors contributing to hepatic injury observed in COVID-19. Subsequent investigations may uncover different liver cell receptors involved in hepatic damage because of COVID-19. This observation also suggests that the universal high inflammatory state may be the primary mechanism accountable for the rise in hepatic enzymes (Medetalibeyoglu et al. 2020).

The fundamental mechanism complicatedly implicated in liver damage in COVID-19 patients includes immune reformation because of SARS-CoV-2 infection and systemic inflammation caused by cytokine-storm. Current analyses draw attention to findings recognising reduced T-lymphocyte rift, chiefly CD8+ T and CD4+ T cells, and high cytokine levels, such as IL-6, in seriously ill and stern COVID-19 patients. Elevated (exceeding their normal limits) levels of these biological intermediaries cause inflammation and worsen clinical consequences in COVID-19 patients. IL-6, an inflammatory bioindicator, doles out as a marker of COVID-19 rigorousness, and tocilizumab drug has been used in clinical tests to treat gravely ill individuals. The proofs presented in this investigation suggest that patients having deranged hepatic biochemistry examinations at admittance are more likely to develop a serious sickness. This underscores the importance of monitoring hepatic profile, especially ALT and AST, and utilizing their levels to inform therapeutic dosages of medications prescribed for the management of COVID-19 (McGrowder et al. 2021).

Additionally, restricted studies have shown decreased albumin levels in patients with stern disease caused by COVID-19, in conjunction with cholestatic bio indicators like ALP and GGT, typically altered in individuals with the relentless illness. The abridged albumin level might be linked with disease advancement, mainly in COVID-19 patients with severe illness. Further investigation is warranted to explore the causes of reduced albumin, which can be attributed to changes in the permeability of blood vessels or the humoral response of the immune system (McGrowder et al. 2021).

In addition to the pulmonary cells of alveoli, numerous additional tissues, such as kidneys, heart and gut, exhibit significant levels of ACE2 expression (Ye et al. 2006). The National Center for Biotechnology Information (NCBI) database indicates that inside the human body, the organ in which ACE2 expression takes place at fourth rank is the kidney, surpassed only by the gall bladder, small intestine, and duodenum. The expression level of ACE2 is almost 100 times higher than in the kidney and in respiratory organs. In the kidney, the primary sources of ACE2 expression in proximal tubular cells are their brush border, with podocytes contributing to a smaller degree. The way SARS-CoV-2 infection affects kidney cells in which expression of ACE2 is still a subject of debate, even though numerous investigations have verified the occurrence of COVID-19 and acute kidney injury (AKI) (Cheng et al. 2020; Qian et al. 2020; Rudnick and Hilburg 2020; Zahid et al. 2020) sustain that SARS-CoV-2 may display an inclination towards the renal function.

In our study, the serum creatinine level in the control group was considerably increased compared to the experimental group, including the severe and moderate groups. However, uric acid and albumin levels were decreased significantly in both the moderate and severe patient groups when contrasted with the control group. Still, no significant disparity in renal profile between patients of experimental groups, i.e. moderate and severe patients.

In this consideration, the latest research by Diao et al. (2021) is pretty outstanding. They discovered that SARS-CoV-2 can precisely aim for tissues of the kidney. The researchers found the definite nucleocapsid protein of SARS-CoV-2 in kidney samples and recognized gathered virus antigens in kidney tubules through tissue analysis during postmortem. They reported that SARS-CoV-2 unswervingly impacts the kidney's tubules in humans, which results in acute damage to kidney tubules. In their elucidation, other than direct cell toxicity, it also activates complement and macrophage-interceded pathogenesis of tubules as a derived consequence of the mounted-up antigens of the virus.

The deficiency of mechanistic impending in the physiological effects of disease concerns like respiratory failure and hypouricemia, as well as the lack of efficient longitudinal follow-up for important bioindicators and biomarkers, are also causing problems.

CONCLUSION

Derangement in LFTs and RFTs in COVID-19 patients should regularly be accessed to avoid post covid complications.

REFERENCES

1. Agarwal A, Chen A, Ravindran N, To C, Thuluvath PJ. 2020. Gastrointestinal and liver manifestations of covid-19. Journal of Clinical and Experimental Hepatology. 10(3):263-265.
2. Bielecka-Dąbrowa A, Cichocka-Radwan A, Lewek J, Pawliczak F, Maciejewski M, Banach M. 2021. Cardiac manifestations of covid-19. Reviews in Cardiovascular Medicine. 22(2).
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in wuhan, china: A descriptive study. The lancet. 395(10223):507-513.
4. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. 2020. Kidney disease is associated with in-hospital death of patients with covid-19. Kidney international. 97(5):829-838.
5. Diao B, Wang C, Wang R, Feng Z, Zhang J, Yang H, Tan Y, Wang H, Wang C, Liu L. 2021. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. Nature communications. 12(1):2506.
6. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. 2020. Abnormal liver tests in covid-19: A retrospective observational cohort study of 1,827 patients in a major us hospital network. Hepatology. 72(4):1169-1176.
7. McGrowder DA, Miller F, Anderson Cross M, Anderson-Jackson L, Bryan S, Dilworth L. 2021. Abnormal liver biochemistry tests and acute liver injury in covid-19 patients: Current evidence and potential pathogenesis. Diseases. 9(3):50.
8. Medetalibeyoglu A, Catma Y, Senkal N, Ormeci A, Cavus B, Kose M, Bayramlar OF, Yildiz G, Akyuz F, Kaymakoglu S. 2020. The effect of liver test abnormalities on the prognosis of covid-19. Annals of hepatology. 19(6):614-621.
9. Qian J-Y, Wang B, Liu B-C. 2020. Acute kidney injury in the 2019 novel coronavirus disease. Kidney diseases. 6(5):318-323.
10. Rudnick MR, Hilburg R. 2020. Acute kidney injury in covid-19: Another challenge for nephrology. American journal of nephrology. 51(10):761.
11. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J. 2020. Lancet infect dis. Elsevier Ltd.
12. Specific A. 2020. Expression in cholangiocytes may cause liver damage after 2019-ncov infection [preprint] chai x. Hu L, Zhang Y, et al bioRxiv.
13. Sultan S, Lim JK, Altayar O, Davitkov P, Feuerstein JD, Siddique SM, Falck-Ytter Y, El-Serag HB. 2020. Aga rapid recommendations for gastrointestinal procedures during the covid-19 pandemic. Gastroenterology. 159(2):739-758. e734.
14. Wei H, Wang Z, Kuang Y, Wu Z, Zhao S, Zhang Z, Li H, Zheng M, Zhang N, Long C et al. 2020. Intercellular adhesion molecule-1 as target for car-t-cell therapy of triple-negative breast cancer. Front Immunol. 11:573823.
15. Wu Z, McGoogan JM. 2020. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in china: Summary of a report of 72 314 cases from the chinese center for disease control and prevention. jama. 323(13):1239-1242.
16. Xu L, Liu J, Lu M, Yang D, Zheng X. 2020. Liver injury during highly pathogenic human coronavirus infections. Liver international. 40(5):998-1004.
17. Xu Z. 2020. Shi l, wang y. Zhang J, Huang L, Zhang C, et al Pathological findings of COVID-19 associated with acute respiratory distress syndrome Lancet Respir Med. 8:420-422.
18. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T. 2020. Clinical course and outcomes of critically ill patients with sars-cov-2 pneumonia in wuhan, china: A single-centered, retrospective, observational study. The lancet respiratory medicine. 8(5):475-481.
19. Ye M, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. 2006. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: Implications for albuminuria in diabetes. Journal of the American Society of Nephrology. 17(11):3067-3075.
20. Zahid U, Ramachandran P, Spitalewitz S, Alasadi L, Chakraborti A, Azhar M, Mikhalina G, Sherazi A, Narh JT, Khattar P. 2020. Acute kidney injury in covid-19 patients: An inner city hospital experience and policy implications. American journal of nephrology. 51(10):786-796.

21. Zhang H, Pan J, Yao P, Hanqing H, Huilai M, Xie S. 2015. Investigation and response for the first case of group x meningococcal disease in zhejiang province. Chinese Journal of Preventive Medicine. 49(6):579-580.
22. Zhang J, Xie B, Hashimoto K. 2020. Current status of potential therapeutic candidates for the covid-19 crisis. Brain, behavior, and immunity. 87:59-73.