An evaluation of liver function tests in severe acute respiratory syndrome - Corona virus 2 (SARS-CoV-2) infection in the backdrop of chronic kidney disease

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ABSTRACT

Background: The SARS-CoV-2 pandemic has emerged as the most challenging global health problem of this century. The concomitant presence of co-morbidities like chronic kidney disease (CKD), diabetes, CHD, further complicates the problem. Aim: To assess the patterns of LFT abnormalities in patients of SARS-CoV-2 infection with and without CKD and evaluate the probable outcomes.

Materials and Methods: A cross-sectional retrospective observational study done on 600 patient samples (Group 1: SARS-CoV-2 without CKD, Group 2: SARS-CoV-2 with CKD and Group 3: CKD uninfected with SARS-CoV-2) which were processed for LFT and KFT.

Results: AST and ALT were significantly higher in all SARS-CoV-2 infected; Group 1 mean ± 2SD, (63.63 ± 42.89U/L & 50.25 ± 46.53U/L), group 2 (90.59 ± 62.51U/L & 72.09 ± 67.24 U/L) as compared to Group 3 (25.24 ± 7.47U/L & 24.93 ± 11.44U/L). A statistically significant elevation is seen in these two parameters in Group 2 as compared to Group 1. There was a negative significant correlation between eGFR and AST/ALT levels in Group 1 (p < 0.05). In Group 2, a weak positive correlation was seen with ALT. Group 3, eGFR’s showed strong correlations with AST and ALT levels; reduction in kidney function correlated well with increase in serum ALP levels.

Conclusions: This study establishes that SARS-CoV-2 infected, with CKD, show higher elevations in serum aminotransferase levels in comparison to those without CKD. In contrast, the CKD group not infected, shows a decline in serum aminotransferase levels. Serum ALT values in SARS-CoV-2 show significant correlation with eGFR. Also, elevated ALP values in CKD patients may be used as an indicator of declining kidney function.

Keywords: ALP, Amino-transferase (AST & ALT), CKD, eGFR, SARS-CoV-2
cardiovascular injury, and renal dysfunction. The concomitant presence of co-morbidities like chronic kidney disease (CKD), encompasses a huge gamut of conditions associated with a progressive decline in kidney function and abnormal glomerular filtration rate, making the task of patient management a daunting challenge for the attending physician.

The objective of this study is to compare the levels of the liver enzymes serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum alkaline phosphatase (ALP) levels among three groups of subjects. Group 1 comprised of SARS-CoV-2 RT-PCR positive patients without CKD, Group 2: SARS-CoV-2 RT-PCR positive patients with CKD, and Group 3 SARS-CoV-2 RT-PCR negative CKD patients.

In this tertiary care center level Indian study, the laboratory findings of Atal Bihari Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, have been presented in the context of severity of outcomes of CKD patients hospitalized for COVID-19, and compare them, with an in-house control group without kidney disease, and an unaffected CKD group. Our paper systematically assesses the patterns of liver test abnormalities in these patients and evaluates the probable outcomes and their application in the community at large. In our paper we also highlight the importance of monitoring liver function tests in patients of COVID-19 with and without CKD. Liver function tests are cost effective and available even in primary care centers and may be used in resource constrained settings to assess COVID-19 affected patients.

Methodology

This is a cross-sectional retrospective observational study conducted at the Department of Biochemistry, Dr. R.M.L. Hospital, New Delhi, India. The data was collected from laboratory reports obtained from the hospital database, by biochemical analysis of blood samples, from patients admitted to the different COVID-19 designated wards/ICUs and Nephrology Unit of the hospital. New Delhi, Data from the month of July 2020 to November 2020 was analyzed.

A total of 600 patient samples were included in the study. 454 RT-PCR positive SARS-CoV-2 subjects, of age ≥18 years and of either sex, were included in the study. Among the study subjects 253 were cases of COVID-19 with and without CKD. Liver function tests are cost effective and available even in primary care centers and may be used in resource constrained settings to assess COVID-19 affected patients.

| Inclusion and exclusion criteria are listed as below |
|---------------------------------------------|
| **Inclusion criteria** | **Groups** |
|---------------------------------------------|-----------|
| 1. Patients who were symptomatic and tested positive for SARS-CoV-2 by RT-PCR test | + + - |
| 2. Sex. (Male/Female) | M/F M/F M/F |
| 3. Age≥18 years | + + + |
| 4. History of chronic kidney disease (CKD) | - + + |

Exclusion criteria - Pregnant and lactating females, patients on hemo-dialysis/ESRD as well as patients with previous history of CLD or preexisting cardiac disease (CHD).

All samples were collected adhering to bio-safety guidelines and received according to ICMR 2019 guidelines of COVID-19 management, in plain vacutainers with triple layer packaging. They were processed for liver function tests (LFT) - AST [ULN (upper limit of normal) - 41U/L], ALT [ULN-40U/L], ALP [ULN-135 U/L] and renal function tests (Serum Urea and Creatinine) in COVID-19 (Trauma center) Laboratory, Department of Biochemistry, Dr. RML Hospital New Delhi. The cases with elevated liver enzyme values were considered to have abnormal liver function. Those with ALT, AST values >3 × ULN, and ALP >2.5 × ULN, were classified as those having liver injury. Serum AST & ALT were estimated by ERBA Mannheim XL system Pack IFCC recommended without pyridoxal phosphate reagent; serum ALP was estimated by using ERBA Mannheim XL system Pack German society of clinical chemistry recommended ALP AMP method; serum Urea was estimated by urease GLDH method and serum creatinine was estimated by enzymatic method on the venous blood samples after separation of serum by proper centrifugation. The samples were processed on fully automated ERBA XL 640 Chemistry Analyzer (TRANSASIA Bio-medicals, India) after verification of two levels of internal quality controls. The present study was approved by the Institutional Ethics Committee [416 (65/2020)/IEC/ABVIMS/RMLH/222].

Statistical analysis

The data were analyzed using SPSS statistical software (v 24; IBM Corporation, Armonk, NY, USA). The data was checked for normality using Shapiro-Wilk’s test. Data is represented as mean and standard deviation for the serum levels of AST, ALT and ALP in all the three groups. The means of the different parameters in three groups were compared by one-way analysis of variance (ANOVA). These comparisons were followed by post-hoc comparisons between groups by means of the Tukey’s test and a $P < 0.05$ was considered statistically significant. The gender distribution was also compared among the three groups using Chi-square test. The linear relationship between the variables (test parameters) was assessed using the Spearman Rank Correlation analysis method. At 95% confidence interval, a $P$ value of $\leq 0.05$ was considered significant.
**Result**

The three groups age and sex matched. There was no statistically significant difference (P > 0.05) between the mean ages in the three groups. No significant difference (P > 0.05) was observed between the percentages of females in the three groups as shown in Table 1.

Of the 400 patients with COVID-19 whose test reports were analyzed, 61.5 (%) had abnormal liver function and 11.5 (%) had liver injury during hospitalization.

Tables 2 and 3 showing statistical comparisons of the means of the three groups made by one way ANOVA, followed by post-hoc analysis. A value of (P < 0.05) of the mean difference for the parameters in the 3 groups, was considered to be significant.

As described in Tables 2 and 3 AST levels were significantly higher in all COVID-19 positive patients irrespective of their renal function status. AST levels [Figure 1] were significantly higher in both Group 1 mean ± 2 SD (63.63 ± 42.89 U/L) and Group 2 (90.59 ± 62.51 U/L) as compared to Group 3 (25.24 ± 7.47 U/L) (P < 0.05). There was also a statistically significant elevation of serum AST levels in patients belonging to Group 2 as compared to patients in Group 1 (P = 0.002). Similarly, serum ALT levels [Figure 2] were also significantly higher in both Group 1, mean ± 2 SD (50.25 ± 46.53 U/L) and Group 2 (72.09 ± 67.24 U/L) as compared to Group 3 (24.93 ± 11.50 U/L) (P < 0.05). There was a significant difference seen between groups 1, group 2, and group 3 (p = 0.001, 0.002, 0.001) respectively.

On the contrary serum ALP levels [Figure 3] were significantly lower in Group 1, mean ± 2 SD, (123.39 ± 78.31 U/L) (P < 0.05) as compared to Group 2 (185.38 ± 92.70 U/L) and Group 3 (186.22 ± 76.29 U/L). The average serum ALP levels of Groups 2 & 3 were more or less comparable, and no significant difference was seen (P = 0.378).

Correlation studies between eGFR values and liver enzyme levels were performed in all the three groups as represented in Table 4. There was a negative correlation between eGFR and AST levels in Group 1 (Spearman's ρ = 0.017 and P < 0.05). A similar but stronger trend was observed in case of ALT (ρ = 0.001, P < 0.01). However no significant correlation existed between eGFR and ALP In Group 2, no statistically significant correlation was seen between eGFR and AST or ALP values. However, a weak positive correlation was seen with ALT (ρ = 0.006, P < 0.01). In Group 3, eGFR showed strong positive correlations with AST and ALT levels (ρ = 0.001, P < 0.01; ρ = 0.001, P < 0.01) while reduction in kidney function correlated well with increase in serum ALP levels, (ρ = 0.001, P < 0.01).

**Discussion**

CKD is classified by the National Kidney Foundation guidelines, into 5 stages. This is based on the calculation of estimated GFR (eGFR). The Modification of Diet in Renal Disease (MDRD) Study equation is the most widely used equation for estimating GFR in patients aged 18 yrs. and over. [9]

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eGFR \, (\text{mL/min}/1.73\, \text{m}^2) = 1.86 \times (\text{PCr}^* - 1.154 \times (\text{age}) - 0.203
\]

[Multipled by 0.742 for women and by 1.21 for African Americans. PCr*=Plasma Creatinine.]

In Stage 1 eGFR is ≥ 90 mL/min/1.73 m² with presence of kidney damage like persistent proteinuria, abnormal blood, and urine chemistry etc., Stages 2, 3 and 4 correspond to eGFR of 60 – 89 mL/min/1.73 m², 30 – 59 mL/min/1.73 m² and 15 – 29 mL/min/1.73 m², respectively. The prime objective of treatment is to retard the progression of CKD, perform cardiovascular disease risk estimation and manage the complications. [9] CKD stage 5 corresponds to eGFR 15 mL/min/1.73 m² and is also known as end stage renal disease (ESRD).

In our study, CKD stage 3 and 4 patients were considered in Groups 2 & 3. The association of co-morbidities is a characteristic of chronic kidney disease. Derangements of hepatic function is one of the most important co-morbid conditions commonly seen with CKD and may be particularly confounding in cases with associated SARS-CoV-2. Numerous studies have shown that hepatic enzymes levels act as good prognostic markers in CKD including ESRD. [10,11] Several studies have concluded, that, there

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Table 1: Demographic characteristics of the three study Groups-1, 2, 3 (Group 1: SARS-CoV-2 without CKD, Group 2: SARS-CoV-2 with CKD, Group 3: CKD uninfected with SARS-CoV-2)

| Demographic parameters | Group 1 | Group 2 | Group 3 | P  |
|------------------------|--------|--------|--------|----|
| Age in years (mean±SD) | 49.29±18.52 | 54.84±15.01 | 53.61±14.49 | 0.724 |
| Range in years          | 18‑77  | 21‑79  | 29‑75  |    |
| Female (%)              | 37.8   | 42.2   | 36.7   | 0.578 |

Table 2: LFT outcomes amongst the 3 groups

| Test parameters (U/L) | Group 1 (n=200) | Group 2 (n=200) | Group 3 (n=200) |
|-----------------------|-----------------|-----------------|-----------------|
| AST                   | 63.63±42.89     | 90.59±62.51     | 25.24±7.47      |
| ALT                   | 50.29±46.53     | 72.09±67.24     | 24.93±11.44     |
| ALP                   | 123.39±78.31    | 185.38±92.70    | 186.22±76.29    |

Table 3: Correlation between LFT outcomes amongst the 3 groups

| Test parameters | Group 1 | Group 2 | Group 3 |
|----------------|--------|--------|--------|
| AST            | 2      | 0.002  | 1      | 0.002  | 1      | 0.002  | 1      | 0.001  |
| ALT            | 3      | 0.001  | 3      | 0.001  | 2      | 0.001  |
| ALP            | 2      | 0.002  | 1      | 0.002  | 1      | 0.001  | 1      | 0.001  | 2      | 0.998  |
is a decrease in the level of serum aminotransferases in patients with CKD compared to the normal population. Ray L. et al.\(^\text{[10]}\) concluded that serum aminotransferase levels tend to remain lower in ESRD patients compared to the normal population, and levels further reduce with the worsening of CKD. The patho-physiological mechanism for the reduction in the serum aminotransferase levels in patients with CKD remains controversial. The possible mechanisms include reduction in pyridoxal-5-phosphate which is a coenzyme of aminotransferase, presence of ultraviolet absorbing materials, and high levels of uremic toxins.\(^\text{[10]}\) Other possibilities included decreased synthesis and inhibition of release of AST and ALT from hepatocytes or accelerated clearance from serum.\(^\text{[12-16]}\) A low serum amino-transferase level could also be due to water retention and hemodilution in patients of CKD.\(^\text{[10]}\) However, this pattern is usually not maintained in CKD with SARS-CoV-2. In our study we included patients from this group.

Different meta-analytical and independent studies have shown, that, more than half of patients with SARS-CoV-2 showed varying levels of liver involvement. Several case reports have also indicated that a significant number amongst them show evidence of liver damage too.\(^\text{[17-19]}\) About 30% of all SARS-CoV-2, RT PCR positive admissions in our hospital, had abnormally high levels of serum creatinine at the time of presentation. This intensive derangement of renal function may have been due to the acute deterioration of renal function related to SARS-CoV-2 disease or increased susceptibility to secondary infection in them.\(^\text{[20]}\) Other possible reasons for the high prevalence of kidney involvement, is that some of the patients with COVID-19 infection, had a previously documented history of CKD (Group 2).

Liver damage in patients with corona virus infection might be directly caused by the viral infection of liver cells.\(^\text{[21]}\) Two recent studies showed that angiotensin converting enzyme 2 (ACE2) was the key receptor for SARS-CoV-2 cell entry\(^\text{[22,23]}\) which was mainly localized in the heart, kidney and testes, and expressed at a low level in many other tissues, especially in the colon and lung.\(^\text{[24]}\) A study showed that SARS-CoV-2 might directly bind to ACE2 positive cholangiocytes and cause liver damage, which may partially explain the contribution of SARS-CoV-2 infection to the liver test dysfunction in our patients.\(^\text{[11]}\) The virus may bind to angiotensin converting enzyme 2 (ACE2) cholangiocytes, leading to cholangiocytes dysfunction and inducing a systemic inflammatory response leading to liver injury.\(^\text{[23,25]}\) Moreover, the use of ACE-inhibitors and angiotensin receptor blocker (ARBs) drugs might also affect liver tests.\(^\text{[26]}\) Another possible reason behind this, is the use of hepatotoxic drugs like the antiviral remdesivir, oxidative stress, coexisting systemic inflammatory response, respiratory distress induced hypoxia and associated multi-organ dysfunction.\(^\text{[17,27,28]}\)

| Table 4: Correlation between eGFR and LFT amongst the 3 group |
|---------------------------------|----------------|----------------|----------------|
| LFT Parameters                  | eGFR (Group 1) | P              | eGFR (Group 2) | P              | eGFR (Group 3) | P              |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| AST (SGOT)                      | -0.151         | 0.017          | 0.134          | 0.061          | 0.786          | 0.001          |
| ALT (SGPT)                      | -0.200         | 0.001          | 0.194          | 0.006          | 0.807          | 0.001          |
| ALP                             | 0.121          | 0.055          | 0.019          | 0.786          | -0.438         | 0.001          |
In our study serum AST levels were significantly higher in all SARS-CoV-2 positive patients irrespective of their renal function status. In a study by Currier et al.[29] it was observed that in COVID-19 positive patients with elevated and super elevated liver enzyme levels have significantly higher rates of complications. Similarly in a study by Hwaiz et al.[30] it is stated that that most of the patients with SARS-CoV-2 have deranged hepatic enzymes. Also, there was a statistically significant elevation in Group 2 as compared to Group 1 (P < 0.05). Similarly, serum ALT levels were also significantly, higher in both Group 1, and Group 2 as compared to Group 3 (P < 0.05). Also, there was a significant difference seen between group 1 and group 2 (p < 0.05). Thus, the findings of serum AST and ALT levels are not in consonance with those seen in non-COVID-19 CKD patients and show an increase rather than a decrease. However, serum ALP levels were significantly lower in Group 1 as compared to Group 2 and 3, thereby indicating a higher strength of association of ALP values with CKD than non-CKD cases. The average serum ALP level of Groups 2 and 3 were comparable. ALP levels in both the latter groups show a rising trend with a marginal increase in the mean of group 3 (185.38 ± 92.70 U/L) in comparison to group 2 (186.22 ± 76.29 U/L).

In Group 1 a negative correlation is seen between eGFR and AST (p < 0.05). A similar but stronger trend was observed in case of ALT (p < 0.01). In Group 2, both AST and ALT showed a weak positive correlation with eGFR; it was statistically significant only with the latter (ALT) (p < 0.01), signifying a reduction in ALT levels with deteriorating kidney function, in the SARS-CoV-2 positive CKD cases. A positive correlation existed between eGFR and ALP in groups 1 and 2, but this was not significant. In Group 3, eGFRs showed strong positive correlations with AST and ALT levels (p < 0.01) and reduction in kidney function correlated well with increase in serum ALP levels, (p < 0.01).

The association between ALP and renal damage may be, at least in part, explained by endothelial dysfunction, a strong and independent predictor of cardio-vascular events in different clinical conditions, including essential hypertension[31] which is one of the leading causes of CKD stage 4. Mechanisms linking ALP to endothelial dysfunction may include inhibition of tyrosine kinase activity into endothelial cells with consequent impairment of endothelial NO synthase function, promotion of high production of reactive oxygen species (ROS), and apoptosis due to increased degradation of pyrophosphate promoting atherosclerotic lesions in vascular wall.[19,32-34] Thus, elevated ALP values in CKD patients may be used as an indicator of declining kidney function as corroborated by Angela Sciacqua et al.[35] who in their study have shown a significant negative correlation between eGFR and ALP.

The studies by Ray et al.[10] and Sabouri et al.[16] have emphasized that the use of standard reference values for amino-transferases to help detect liver disease, is less useful in CKD patients, and have proposed that separate normal (lower) reference ranges of serum aminotransferases in different stages of CKD need to be determined. However, in stark contrast to their findings there is a paradigm shift with respect to serum ALT/AST levels in SARS-CoV-2 afflicted CKD patients, who show elevations from baseline levels that lie beyond normal conventional laboratory ranges. This is quite in contrary to CKD that is not infected with SARS-CoV-2 and have values that are either low normal or below baseline. Mean ALT values, though elevated, have shown a negative and positive correlation with e-GFR in group 1 and 2 respectively there by signifying a proportionate fall in enzyme levels with progressive decline in kidney function in Group 2 patients of CKD, with SARS-Cov-2 infection.

Liver function Tests form an integral part of the panel of routine biochemical laboratory investigations available in the most peripheral of laboratories in both urban and rural settings. They are relatively cheap to perform and are well standardized. The use of LFT abnormalities as a marker of disease severity[29,30] may provide a valuable cost effective tool in the hands of the family physician, especially at the community level, to gauge the severity of morbidity in CKD complicated with COVID-19.

Limitations

This study had limitations, including extracting patients’ information from medical records, using a threshold of 40 IU/L as the normal transaminase level for all groups, and not considering unidentified hepatitis especially in the form of hepatitis C, which is common in CKD patients.

Conclusion

Our study is the first of this kind on the Indian population, and most comprehensively describes that SARS-CoV-2 positive CKD patients show more elevations in serum aminotransferase levels as compared to their SARS-CoV-2 positive non-CKD counterparts. This is in contrast to the CKD group not infected with SARS-CoV-2, which shows a decline in serum aminotransferase levels. Serum ALT values in all SARS-CoV-2 patients show significant correlation (positive or negative) with calculated eGFR values. Thus, ALT may be used as a marker to assess severity of disease and monitor therapeutic response during management of these patients. Also, elevated ALP values in CKD patients with SARS-CoV-2 infection may be used as an indicator of declining kidney function.

However, more studies in this direction are needed.

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IEC -Institutional ethical committee.

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Conflicts of interest
There are no conflicts of interest.

References
1. Wu GZ, Wang JW, Xu JQ. Voice from China: Nomenclature of the novel coronavirus and related diseases. Chin Med J (Engl) 2020;133:1012–4.
2. World Health Organization. 2020a. Naming the coronavirus disease (COVID-2019) and the virus that causes it [WWW Document]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. [Last accessed on 2021 Apr 19].
3. India Situation Report. Available from: https://www.who.int/india/emergencies/coronavirus-disease-(covid-19)/india-situation-report. [Last accessed on 2021 Jul 07].
4. Yuki K, Fujigoi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020;215:108427. doi: 10.1016/j.clim.2020.108427.
5. Behzad S, Aghaghasvini L, Radmard AR, Gholamrezaezhad A. Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview. Clin Imaging 2020;66:35–41.
6. Lee I-C, Huo T-I, Huang Y-H. Gastrointestinal and liver manifestations in patients with COVID-19. J Chin Med Assoc 2020;83:521–3.
7. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–60.
8. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137-47. doi:10.7326/0003-4819-139-2-200307150-00013. Erratum in: Ann Intern Med. 2003; 139:605.
9. Levey A, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Int Med 1999;130:461-70.
10. Ray L, Nanda SK, Chatterjee A, Sarangi R, Ganguly S. A comparative study of serum aminotransferases in chronic kidney disease with and without end-stage renal disease: Need for new reference ranges. Int J Appl Basic Med Res 2015;5:31.
11. Oyelade T, Alqahtani J, Canciani G. Prognosis of COVID-19 in patients with liver and kidney diseases: An early systematic review and meta-analysis. Trop Med Infect Dis 2020;5:80.
12. Goicoechea M, Sánchez Cámara LA, Macías N, Muñoz de Morales A, Rojas AG, Bascuñana A, et al. COVID-19: Clinical course and outcomes of 36 hemodialysis patients in Spain. Kidney Int 2020;98:27-34.
13. Hung KY, Lee KC, Yen CJ, Wu KD, Tsai TJ, Chen WY. Revised cutoff values of serum aminotransferase in detecting viral hepatitis among CAPD patients: Experience from Taiwan, an endemic area for hepatitis B. Nephrol Dial Transplant 1997;12:180–3.
14. Lopes EP, Sette LHBC, Sette JBC, Luna CF, Andrade AM, Moraes M, et al. Serum alanine aminotransferase levels, hematocrit rate and body weight correlations before and after hemodialysis session. Clinics 2009;64:941–5.
15. Sette LHBC, de Almeida Lopes EP. Liver enzymes serum levels in patients with chronic kidney disease on hemodialysis: A comprehensive review. Clinics (Sao Paulo) 2014;69:271–8.
16. Sabouri S, Afzal Aghaee M, Lotfi Z, Esmaaily H, Alizadeh M, MosannenMozafari H. Evaluation of liver enzymes in end-stage renal disease patients on the renal transplant-waiting list in North-West of Iran. Nephro-Urol Mon 2020;12:e107859.
17. Bzeizi K, Abdulla M, Mohammed N, Alqamish J, Jamshidi N, Betjes MGH. Immune cell dysfunction and inflammation in COVID-19: Clinical features and treatment management. Virol J 2021;18:121.
18. Yu D, Du Q, Yan S, Guo X-G, He Y, Zhu G, et al. Liver injury in COVID-19: Clinical features and treatment management. Virol J (Engl) 2020;133:1012–4.
19. Wu Z, Yang D. A meta-analysis of the impact of COVID-19 on liver dysfunction. Eur J Med Res 2020;25:54.
20. Betjes MGH. Immune cell dysfunction and inflammation in end-stage renal disease. Nat Rev Nephrol 2013;9:255–65.
21. Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol Hepatol 2020;5:428–30.
22. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80.e8.
23. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020;367:1444-8.
24. Clarke NE, Turner AJ. Angiotensin-converting enzyme 2: The first decade. Int J Hypertension 2012;2012:307315.
25. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv 2020;2020.02.03.931766. doi: 10.1101/2020.02.03.931766.
26. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. J Hepatol 2020;73:566–74.
27. Fan Z, Chen L, Li J, Tian C, Zhang Y, Huang S, et al. Clinical features of COVID-19-related liver damage. medRxiv 2020;2020.02.26.20026971. doi: 10.1101/2020.02.26.20026971.
28. Yang L, Wang W, Wang X, Zhao J, Xiao L, Gui W, et al. Creg in hepatocytes ameliorates liver ischemia/reperfusion injury in a TAK1-dependent manner in mice. Hepatology 2019;69:294–313.
29. Currier EE, Dabaja M, Jafri SM. Elevated liver enzymes portends a higher rate of complication and death in SARS-CoV-2. World J Hepatol 2021;13:1181-9.
30. Hwaiz R, Merza M, Hamad B, HamaSalih S, Mohammed M, Hama H. Evaluation of hepatic enzymes activities in COVID-19 patients. Int Immunopharmacol 2021;97:107701. doi: 10.1016/j.intimp.2021.107701.
31. Sciacqua A, Tripepi G, Perticone M, Cassano V, Fiorentino TV, Pititto GN, et al. Alkaline phosphatase affects renal function in never-treated hypertensive patients: Effect modification by age. Sci Rep 2020;10:9847.
32. Perticone F, Perticone M, Maio R, Sciacqua A, Andreucci M, Tripepi G, et al. Serum alkaline phosphatase negatively affects endothelium-dependent vasodilation in naïve hypertensive patients. Hypertension 2015;66:874-80.
33. Schultz-Hector S, Balz K, Böhm M, Ikehara Y, Rieke L. Cellular localization of endothelial alkaline phosphatase reaction product and enzyme protein in the myocardium. J Histochem Cytochem 1993;41:1813-21.
34. Romanelli F, Corbo A, Salehi M, Yadav MC, Salman S, Petrovian D, et al. Overexpression of tissue-nonspecific alkaline phosphatase (TNAP) in endothelial cells accelerates coronary artery disease in a mouse model of familial hypercholesterolemia. PLoS One 2017;12:e0186426.