Renal and hepatic injury associated with COVID-19 infection; A prospective cohort analysis of renal and hepatic injury in patients infected with COVID-19

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Abstract

The current study evaluated the rate of progression of acute kidney and hepatic injury and its associated mortality rate in patients infected with COVID-19. For this study, a total of 397 COVID-19 positive adult patients were prospectively recruited. Routine medical examination, liver function tests (LFT) and renal function test (RFT) were performed at the time of hospitalization and this procedure was repeated for every two days until the hospital stay of the patient or till the death of the patient. The upper values (data obtained from the recovered patients or died patients during course of the disease) of LFT and RFT were compared to that of baseline values (recorded at the time of hospitalization) of recovered or died patients. The baseline values of both LFT and RFT values were not significantly varied between recovered 88.41% (n=351) *and died patients* 11.59% (n=46) *at the time of hospitalization. However, the baseline values of total serum bilirubin were significantly (P = 0.001) higher in died patients at the time of hospitalization as compared to the recovered patients. Moreover, majority (52.17%) of the died patients progressed to stage III and stage IV acute kidney injury prior to death. Furthermore, both LFT and RFT were abnormally elevated as compared to their baseline values among the died patients. COVID-19 patients possess high risk for the development of acute kidney and liver injuries, which can substantially enhance the mortality rate.*

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Introduction

COVID-19 emerged as a pandemic human infectious disease of SARS-CoV-2 origin (1). This disease is highly contagious, with varying signs and complications, causing high risk to public health. The predominant presentation of COVID-19 is an acute respiratory disease that may progress to pneumonia; it may also damage other organs, for instance, the kidneys, heart, gastrointestinal tract, liver, immune, blood, and nervous system (2).

Most of the COVID-19 patients are presented with mild-to-moderate respiratory manifestations and re-

covered usually with simple, supportive treatment. Unfortunately, old patients, particularly those having comorbidity such as diabetic, cardiovascular disease, chronic obstructive pulmonary disease (COPD), cancer, renal and hepatic diseases, are under higher risk of serious illness (3). Acute kidney injury (AKI) and liver injury are common in patients with COVID-19 and plays a vital role in the duration of therapy and clinical outcome (4). Various studies confirm that AKI is the one of the common life-threatening complications of COVID-19 and the incidence was found to be11.6% among Chinese adults hospitalized with COVID-19 and the incidence was higher (>50%) for patients admitted in the intensive care units (ICUs) (5). Moreover, other studies have shown that 17% of COVID-19 patients might develop AKI and the mortality rate was higher for such patients (6).

In the COVID-19 infection, the liver is not directly affected, as it seems to be spared by the virus; however, patients with the most severe form of the disease might result in liver injury mainly due to cytokine storm. Liver injury, as observed in hepatitis and/or cholestasis, is commonly noticed in 60% of patients suffering from SARS-CoV-2 infection (7). Moreover, studies suggested that the change in hepatic biochemistry might result from pneumonia-induced hypoxaemia, drug-induced hepatotoxicity and systemic inflammatory response, particularly for COVID-19 patients hospitalized with severe manifestation (8, 9). The other critical prognostic factors for COVID-19 patient's survival include early detection of development of AKI and hepatic injury. However, unlike other identified prognostic factors, AKI and hepatic injury are possibly curable by interventions (10). Therefore, the aim of the current study was to identify the association between markers of kidney and liver injuries that resulted from SARS-CoV-2 infection. *The current study evaluated the rate of progression of AKI , hepatic injury and its associated mortality rate in patients infected with COVID-19.*

Methods

This current prospective study was conducted (between 18/07/2020 to 28/09/2020 at Al-Shafaa center for corona pandemic in the medical city, Baghdad, Iraq) on patients diagnosed with COVID-19 infection. All adult patients (aged 18 years and above) confirmed to be having infected with SARS-CoV-2 by polymerase chain reaction were included in the study.

The study approved by the Institutional Higher Scientific Ethics Committee of Baghdad Teaching Hospital (No. 5648 dated 10/07/2020). Written consent was obtained from all the participants who were enrolled in this study. Further, all patients followed COVID-19 treatment protocol as approved by the Ministry of Health, Iraq.

Demographic data of hospitalized COVID-19 patients were recorded. In the current study, a total of 397 patients (male: female ratio of 2.89:1) with an average age of 48.03 $\pm$ 14.09 years were *prospectively recruited. Routine medical examination (*Fever, systolic blood pressure, diastolic blood pressure, respiratory rate, pulse rate, blood sugar, white blood cells counts, hemoglobin), *liver function tests (LFT) and renal function test (RFT) were performed at the time of admission and these examinations repeated for every two days until the hospital stay of the patient or till the death of the patient. The upper values (data obtained from the recovered patients or died patients during course of the disease) of LFT and RFT were compared to that of baseline values (recorded at the time of hospital admission) of recovered or died patients.*

Based on the clinical presentation, severity of disease and computed tomography scan, the patients were categorized into four groups 1) mild case; CT scan negative for pneumonia 2) moderate case; CT scan positive for pneumonia 3) severe; patients having reduced oxygen saturation [?] 93%, respiratory rate [?] 30 breaths /min, or multi-organ failure with positive CT scan for pneumonia and 4) critical patients; patient admitted to ICU.

Serum creatinine (S.Cr.), blood urea nitrogen (BUN) and estimated glomerular filtration rate (eGFR) were assessed for all patients. According to Lin *et al* (11), a S.Cr. cut off normal upper level used was more than 1.2 mg/dL for women and 1.4 mg/dL for men. BUN cut off level more than 23.2 mg/dL (11). For male patients, the GFR was estimated from S.Cr. concentration using the Cockroft–Gault equation, and for female; the estimated creatinine was reduced by 15%. The stages of renal dysfunction were categorized according to Ostermann and Joannidis (12). Patient with eGFR of [?] 90 mL/min considered as normal (stage

1), eGFR= 60-89 mL/min reflected mild kidney disease, whereas, eGFR = 30-59 ml/min was subdivided into moderate stage 3A (for patients with GFR = 45-59 mL/min) and moderate stage 3B (for patients with GFR 30-44 mL/min). Severe cases of kidney disease described for patients with eGFR =15-29 mL/min, and the end-stage renal failure represents eGFR of less than 15 mL/min (12).

The cut off value of abnormal liver function test used are; alanine aminotransferase (ALT) >55 U/L, aspartate aminotransferase (AST) >48 U/L, alkaline phosphatase test (ALP) >129 U/L and total bilirubin >1.2 mg/dL (13).

The upper values of the data obtained from the recovered patients during disease period were compared to that of data recorded for patients at time of hospitalization (baseline) or prior to the death of the patient.

The results were analyzed using SPSS software (version 23.0; SPSS, Chicago, IL, USA) and Prism 8 for OS X (version 8.4.3 GraphPad Software, LLC) used for figures drawing. The continuous variables were expressed as Mean +- standard deviation (*SD).* The results were compared using paired student's t-test. Median [interquartile ranges (IQR)] was used as appropriate. The Chi-square test was used to analyze the categorical variables, and a 95% confidence interval (CI) was reported. The potential impact and risk of renal and hepatic injury described by Cox hazard regression model and 95% CI. All statistical analysis was significant at P value < 0.05.

Results

Patients' characteristics and study profile are depicted in Table 1 and Figure 1, respectively. Overall, 397 patients with COVID-19 were enrolled in this study with a median age of 47-year (range 20-75); IQR: 38-59, 74.31% (n=295) of patients were males, and 88.41% (n=351) patients were recovered, whereas 11.59% (n=46) were died. For the recovered patients, the hospitalization period for recovered patients was significantly shorter ($P < 0.001$) and the respiratory rate was higher ($P < 0.001$). However, all the died patients required admission to the ICU (*x2* test, $P < 0.001$).

Most of the recovered patients were presented as moderate and severe cases (34.76%, 23.93%, respectively; while the majority of the died patients (76.09%) presented as critical case. Among 46 patients, 30.43% (n=9) and 41.30% (n=19) were having history of COPD and hypertension, respectively; and was significantly higher in died patients as compared to patients recovered from COVID-19 infection (*x2* test, $P < 0.001$, $P = 0.10$, respectively) (Table 1).

1.1 Abnormal Kidney Function Test and Clinical Outcomes

At the time of hospitalization, majority of recovered and died patients (97.99%) had normal kidney (stage I) (n= 338, 85.14%) and mild (stage II) AKI (n=51, 12.85%), respectively (Table 2). The baseline S.Cr and eGFR was not significantly varied between died and recovered patients (Mean +- *SD,* 0.91 +- 0.09 versus 0.86 +- 0.28; *t-test*, $P = 0.184$), (Mean +- *SD,* 126.17 +- 30.51 versus 139.39 +- 54.19, *t-test*, p=0.106), respectively. BUN for both recovered and died patients at time of hospitalization was not significantly differed (Mean +- *SD,* 20.19 +- 9.74 versus 21.22 +- 7.60; $P = 0.459$) (Table 3, Figure 2).

Of the total died patients (n= 46), 52.17% patients progressed to stage III and IV AKI one or two days prior to death (Table 2). While comparing the renal function test of recovered patients with that of dead patients, S.Cr (Mean +- *SD,* 2.07 +- 1.49 versus 0.86 +- 0.28; $P < 0.001$)and BUN (Mean +- *SD,* 34.43 +- 12.19 versus 20.19 +- 9.74; $P < 0.001$) were significantly higher on the day before death. The eGFR was relatively low for patients the day before death when compared to patients recovered from COVID-19 infection (Mean +- *SD,* 67.99 +- 42.26 versus 139.39 +- 54.19; $P<0.001$) (Table 3, Figure 2).

Of the total died patients(n=46); all of the kidney function tests were abnormally elevated from baseline values one or two days before death. The mean of S.Cr was increased by more than 47% from the baseline (Mean +- *SD,* 0.98 +- 0.10 versus 2.07 +- 1.49; $P < 0.001$). Consequently, the eGFR decreased from baseline by more than 63% (Mean +- *SD,* 109.12 +- 24.69 versus 67.99 +- 42.26; $P < 0.001$). Similarly, BUN was

increased more than 61% from the baseline value (Mean +- *SD,* 109.12 +- 24.69 versus 67.99 +- 42.26; $P <$ 0.001) (Table 3, Figure 2).

Abnormal Liver Function Test and Clinical Outcomes

For all the patients AST, ALT, ALP and total serum bilirubin was estimated. The upper-recorded values for the recovered patients were compared to that of baseline and one or two days before death of patients as well. The baseline value of total serum bilirubin was higher in died patients when compared with recovered patients (Mean +- *SD,* 0.81 +- 0.24 versus 0.63 +- 0.36; *P* [?] 0.001), however, AST (Mean +- *SD,* 23.09 +- 9.69 versus 21.87 +- 12.04; $P = 0.436$), ALT (Mean +- *SD,* 29.65 +- 20.49 versus 27.46 +- 10.37; $P =$ 0.476), and ALP (Mean +- *SD,* 100.85 +- 68.01 versus 104.57 +- 46.65; $P = 0.719$) were not significantly differed between both groups (Table 4).

The liver function test results were abnormally elevated in died patients one or two days before death when compared to recovered patients AST (Mean +- *SD,* 36.98 +- 10.92 versus 23.09 +- 9.69; p< 0.001); ALT (Mean +- *SD,* 40.28 +- 12.92 versus 29.65 +- 20.49; $P < 0.001$); ALP (Mean +- *SD,* 122.35 +- 40.43 versus 100.85 +- 68.01; $P = 0.037$) and total bilirubin (Mean +- *SD,* 1.36 +- 0.96 versus 0.63 +- 0.36; $P <$ 0.001)}. Further, among the died patients, the AST (Mean +- *SD,* 36.98 +- 10.92 versus 21.87 +- 12.04; $P < 0.001$), ALT(Mean +- *SD,* 40.28 +- 12.92 versus 27.46 +- 10.37; $P < 0.001$) and total bilirubin levels (Mean +- *SD,* 1.36 +- 0.96 versus 0.81 +- 0.24; $P < 0.001$) were significantly higher one or two days prior to death as compared to their baseline value (Table 4, Figure 3).

Risk of Mortality with Kidney and Liver Injury for COVID-19

Based on the number of patients, who developed abnormally elevated values (above the cut off value) of S. Cr and BUN showed high risk for death as compared to the recovered patients (43.48% versus 1.71%, hazard ratio (HR) 44.23; 95% CI: 16.34-19.70, $P < 0.001$) and (13.04% versus 2.28%, HR 5.59, 95% CI: 1.86-16.84, $P = 0.020$). Furthermore, the abnormal elevation of liver function test above cut off value when compared with recovered patient increases the probability of liver injury related death (AST 3.70% versus 17.39%, HR 5.47; 95% CI: 2.13-14.05, $P = 0.001$), ALT (10.87% versus 3.42%, HR 3.45; 95% CI: 1.16-10.27, $P = 0.038$), ALP (58.70% versus 12.82%, HR 9.66; 95% CI: 4.97-18.79, $P < 0.001$), and bilirubin 1.71% versus 52.17%, HR 62.73; 95% CI: 23.24-169.32, $P < 0.001$) (Table 5, Figure 4).

Discussion

In the current study, laboratory findings of both kidney and liver function were compared between patients who recovered or died of COVID-19. This study primarily aimed to investigate the possible cause of death (other than respiratory failure) in patients with COVID-19 infection. Moreover, to our knowledge, this is the first kind of study that compared the functioning of both kidney and liver functioning in COVID-19 infected patients.

Various studies have been conducted to investigate the risk factors for the development of AKI among COVID-19 patients. Old age (>50 years) and gender (male) have been confirmed to be associated with a higher rate of AKI as compared to young and female patients (14). Coca concluded that increase in ten years of age could be associated with more than 10% increase in the risk of AKI (15). Besides, other independent factors related to the development of AKI and mortality rate in COVID-19 patients include diabetes mellitus, hypertension, white blood cells count, respiratory rate during disease episode, COPD, and previous history of chronic kidney diseases (16). These were consistent with our result as well wherein patients died were older than recovered patient, and 76.09% were male. Meanwhile, the respiratory rate at the time of hospitalization was higher among the patients. The presence of COPD and hypertension could be the direct cause of death and indirectly AKI may also have predisposed to death (Table 1).

Literatures suggest that the pathogenies of COVID-19 virus involve various mechanisms to cause clinical manifestations (17). Therefore, COVID-19 patient with underlying AKI, indeed required mechanical ventilation or ICU admission and might prognoses with worst outcomes as compared to healthy kidney patients (18, 19). In this study, all of the patients were admitted to the ICU at least two days before death and in most

of the cases the patients' data were collected one day prior to death. Although patients with renal diseases have higher risk to be infected with COVID-19. However, patients infected with SARS-CoV-2 without a history of renal complications might not have severe kidney injury or less likely to progress to renal failure. Unfortunately, there was a less renal recovery in patients diagnosed with COVID-19 as compared to the patient with negative result for COVID-19 (19). Furthermore, COVID-19 patients with advanced stage of AKI (stage III and more) were reported to have more than 30% higher incidence for death as compared to patient with normal or subnormal kidney function (20). Considering the earlier findings, the results of the current study confirms that the renal function of patients ranged between normal to mild renal insufficiency at the time of hospitalization and progressed to critical stage III and IV before death. Further, a non-significant difference in S.Cr level and eGFR were observed between the died and recovered patients at time of hospitalization. However, an abnormal elevation in S.Cr (>2.1 fold), BUN (> 62.2%) and reduction in eGFR (>62.3%) were observed in died patients when we compared to baseline values. Overall, these results indicate an association between AKI and mortality among COVID-19 patients (Table 2). Although studies showed that low recovery rate of renal replacement therapy for COVID-19 patients with advanced AKI (21). The results of current study substantiate the fact that high rate of mortality may be possible in patients SARS-CoV-2 infection, who are having comorbidity with advanced renal diseases. This study describes the rate of mortality in COVID-19 patients were intensely related to AKI (S.Cr 43.48% versus 1.71%, HR 44.23; 95% CI: 16.34-119.70, $P < 0.001$) and (BUN 13.04% versus 2.28%, HR 5.59, 95% CI: 1.86-16.84, $P = 0.020$) (Table 5, Figure 3). Incidentally, continuous monitoring of renal function accompanied by preventive and supportive therapies for renal disease is vital to minimize the mortality rate in COVID-19 patients.

The other potential mechanisms of AKI involve SARS-CoV-2 related cytokine storm which, is related to immune response deregulations. It is a cytokine related systemic inflammatory response causing variety of clinical manifestations such as uncontrolled high fever, central nervous system abnormalities, hepatic injury, lymphadenopathy and kidney toxicity related to the massive release of cytokines such as IFN-c, TNF, IL-1, IL6 and IL-18, and, if untreated progression to multiple organ failure (22). Patient with cardiac comorbidity (particularly right ventricular failure secondary to COVID-19 pneumonia), or other predisposing factors for hypovolemia, sepsis or nephrotoxicity; besides, macrophage activation syndrome, and the development of micro emboli and micro thrombi in the context of hypercoagulability and endotheliitis might lead to kidney and liver congestion and subsequent development of AKI and liver injury (23). The results of the current study confer that the role of cytokine storm may result in concurrent deterioration of renal and hepatic functions in COVID-19 patients.

The liver biochemistry changed dynamically in patients infected by SARS-CoV-2 during the clinical course. ALT and total bilirubin founded to be elevated 28% and 18%, respectively (24) in an early study conducted in Wuhan, and 53% in a subsequent study (25). The degree of acute liver injury was different in COVID-19 patients. The patients demonstrated high levels of ALT/AST, ALP and total bilirubin required ICU admission. Further, it was noted that the prevalence of abnormal liver biochemistry was noted in COVID-19 patients at the time of admission and increased during the disease course (26). Importantly, these changes in hepatic parameters have a potential impact on COVID-19 patients and independently resulted in admission to ICU. Moreover, many studies showed that patients with the chronic hepatic disease were more liable to develop severe COVID-19 disease (27). The previous facts are consistent with our results as well, wherein bilirubin was significantly higher at the time of hospital admission among patients, whereas, just before death, extreme elevation in AST, ALT, and bilirubin were observed (Table 4, Figure 2).

Previous data suggest that the abnormal liver function can result from infection of bile duct cells by SARS-CoV-2; however, presence of ALP indicate that presence of the bile duct injury-related condition rather than COVID-19 infection (28). Interestingly, acute liver injury was believed to be due to the adverse drug reaction in patients using medication for the severe stage of COVID-19 (29). Currently, many reports focus on the systemic inflammation, which is associated with COVID-19 as a cause of liver injury (30). This finding confirms our insights about the role of cytokines storm, which could be responsible for kidney and liver injury subsequently increasing mortality rate in COVID-19 patients. Although, the available data about the effect of different antiviral drug on hepatic function not available, it is also foreseen that the use

of corticosteroid in COVID-19 patients also seemed to induce acute hepatic injury (31). This study was conducted on patients administered uniform protocol of therapy to exclude the side effect of the drug on the results, taking into consideration the variability in the duration of therapy and doses used. Though no patients had recorded for short-term mortality due to liver injury, studies were focused on the role of regular hepatic biochemistry monitoring on hospitalization period and COVID-19 patient's outcome (32). Notably, because of a large number of infected patients recorded daily worldwide, the effect of liver injury on COVID-19 patient outcomes is valuable, and its predictors can improve a patient's health (3). Therefore, in our study, besides AKI, we focused on the prognostic role of liver injury in COVID-19 patients and observed significant-high hepatic parameters indicative for liver injury among patient.

Conclusion

Although COVID-19 affects mainly the lungs, it can also cause multiple organ damage. Acute kidney and liver injuries are vital complications in patients with COVID-19 infections, which may further progress to chronic stage causing death of the patient. Therefore; increased awareness , timely detection and prompt treatment of acute kidney and liver injuries are essential to minimizes the mortality rate among COVID-19 patients.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

No conflict of interest to declare and the study received no fund.

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