Acute kidney and liver injury could be the cause of death in patients with COVID-19

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Abstract

We evaluated the increase in the risk of developing acute kidney and hepatic injury. Moreover, we investigate the association between kidney and liver biomarkers with poor prognosis and mortality rate. Methods: This was a prospective cohort study of 397 adult patients with an average age of 48.03 ± 14.09 were diagnosed with COVID-19 of whom, 46 (11.59%) died in hospital. The upper values of the kidney and liver biomarkers were obtained from the recovered patients during the disease period and are compared to the data for dead patients at admission (Baseline) and one day before death. Results: At admission to the hospital, the baseline S.Cr, BUN, and eGFR were not significantly varied between recovered and dead patients. Furthermore, the baseline values for AST, ALT, and ALP were not significantly differed between both groups. Whereas, baseline value of total serum bilirubin was higher in died compared to the recovered patients. For dead patients, the day before death, 52.17% of the patients had progressed to stage III and stage IV AKI. S.Cr and BUN were significantly higher, and eGFR was lower compared to the recovered patients. All of the kidney and liver function tests were abnormally increased from baseline to the day before death. The AST, ALT, and total bilirubin one day before death were significantly higher compared to their baseline value. Conclusions: COVID-19 patients have a high risk for the development of AKI and liver injury that can be progressed to a chronic stage and increase the mortality rate.

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died compared to the recovered patients. For dead patients, the day before death, 52.17% of the patients had progressed to stage III and stage IV AKI. S.Cr and BUN were significantly higher, and eGFR was lower compared to the recovered patients. All of the kidney and liver function tests were abnormally increased from baseline to the day before death. The AST, ALT, and total bilirubin one day before death were significantly higher compared to their baseline value.

Conclusions: COVID-19 patients have a high risk for the development of AKI and liver injury that can be progressed to a chronic stage and increase the mortality rate.

What's already known about this topic?

There is no confirmation about whether COVID-19 is associated with AKI and liver disease. In this research we investigate the association between COVID-19 with renal and hepatic disease. Furthermore, the risk of mortality in COVID-19 patients due to renal or hepatic disease.

What does this article add?

COVID-19 patients have a high risk for the development of AKI and liver injury that can be progressed to a chronic stage and increase the mortality rate.

INTRODUCTION

COVID-19 is a newly emerging human infectious disease of SARS-CoV-2 origin that is becoming a pandemic and has spread rapidly worldwide [1]. This disease is highly contagious, with varied signs and complications, and leads to a 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 recovered with simple, supportive treatment. Unfortunately, old patients, particularly those having comorbidity such as diabetic, cardiovascular 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].

Many studies confirm that AKI is the most critical complications of COVID-19 and the incidence was 11.6% of Chinese adult hospitalized with COVID-19 and was higher (>50%) for patients in the intensive care unit (ICU) [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].

The liver is not affected directly, as it seems to be spared by the virus; however, cytokine storm in patients with the most severe form of the disease might cause liver injury. Liver injury, in the form of hepatitis and/or cholestasis, is commonly observed in up to 60% of patients suffering from SARS [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].

One of the critical prognostic factors for COVID-19 patients survival is the development of AKI and hepatic injury. However, unlike other identified prognostic factors, AKI and hepatic injury are possibly curable by interventions [9].

Our objective was to identify the association between markers of kidney and liver disease with the death in patients infected with SARS-CoV-2.

METHODS

Study design

We performed a prospective cohort study on a patient diagnosed with COVID-19 admitted to Al-Shafaa center for corona pandemic in the medical city, Baghdad, Iraq from July 18, 2020, to August 28, 2020. All

patients included were adults (age >18 years) and confirmed to be infected with SARS-CoV-2 by polymerase chain reaction testing of a nasopharyngeal or oropharyngeal swab sample.

The study approved by the institution's higher scientific Ethics Committee of Baghdad teaching hospital. All patient were signed an official consent form to enrolled in this study and agree to use their results. All patients follow COVID-19 treatment protocol approved by the ministry of health in Iraq.

Data collection and measurements

The study included 397 patients (male:female= 2.89) with an average age of 48.03 ± 14.09. Demographic data for all patients enrolled collected, including comorbidity. Baseline biological tests and followed up until hospital discharge or death according to the protocol applied in Al-Shafaa center. Fever, SBP, DBP, RR, PR, blood sugar, WBCs, HG, S.Cr, BUN, AST, ALT, ALP, and total bilirubin were measured periodically throughout the disease course.

Based on the clinical presentation and investigations, patients categorized into four groups according to the severity of the disease. CT scan negative for pneumonia indicated mild case, whereas a positive CT scan designated moderate case. For patients having reduced oxygen saturation [?] 93%, respiratory rate [?] 30 breaths /min, or multi-organ failure with positive CT scan for pneumonia signifies the severe case and critical cases involved patient admitted to ICU.

Renal and liver function test

Serum creatinine, BUN and estimated glomerular filtration rate were assessed for all patients. According to Lin *et al* ., a creatinine cut off normal upper level used was more than 1.2 milligrams/deciliter (mg/dL) for women and 1.4 mg/dL for men. BUN cut off level more than 23.2 mg/dL [10]. For male patients, the Glomerular filtration rate was estimated from serum creatinine 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. Patient with eGFR of [?] 90 mL/min considered normal (stage 1), eGFR= 60-89 mL/min reflected mild kidney disease (KD), 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. reflected mild kidney disease (KD). Severe cases of KD described for patients with eGFR =15-29 mL/min, and the end-stage renal failure represents eGFR of less than 15ml/min [11].

The cut off value of abnormal liver function test used are; ALT >55 U/L, AST >48 U/L, ALP >129 U/L and total bilirubin >1.2 mg/dL [12].

The upper values of the data obtained from the recovered patients during disease period were compared to that recorded for died patients at admission (Baseline) and one day before death.

Statistical Analysis:

The results were analyzed using SPSS software (version 23.0; SPSS, Chicago, IL, USA) and Prism 8 for OS X (version 8.4.3 GraphicPad Software, LLC) used for figures drawing.

The continuous variables were expressed as Mean +- *SD* . The results were compared using a 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 was reported. The potential impact and risk of renal and hepatic injury described by Cox hazard regression model and 95% Confidence Interval. All statistical analysis was significant at p-value < 0.05.

RESULTS

Patient characteristics

Patients' characteristics are described in Table 1. Overall, 397 patients with COVID-19 were enrolled in this study with a median age 47-year (range 20-75); interquartile range (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. Comparing to the recovered patients, the hospitalization period for died patients was significantly shorter (p=0.000), the respiratory rate was higher (p=0.000), and all died patients have required admission to the ICU ($x2$ test, p=0.000).

Most of the recovered patients were presented as moderate and severe cases (34.76%, 23.93%) respectively; while the majority of died patients (76.09%) were presented as a critical case. Among 46 died patients, 30.43% (n =9) and 41.30% (n =19) had history of COPD and hypertension, respectively; and was significantly higher than patients recovered from COVID-19 ($x2$ test, p=0.00, p=0.10, respectively) (Table 1).

Abnormal kidney function test and clinical outcomes

At admission to hospital, 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%) (Table 2). The baseline S.Cr and consequently, eGFR was not significantly varied between died and recovered patient (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 recovered and died patients at admission was not significantly differed (Mean +- *SD,* 20.19 +- 9.74 versus 21.22 +- 7.60; p=0.459) (Table 3, Fig. 1).

For died patients, the day before death shows 24 (52.17%) patients had progressed to stage III and IV AKI (Table 2). Comparing to the recovered patients, S.Cr and BUN were significantly higher one day before death (Mean +- *SD,* 2.07 +- 1.49 versus 0.86 +- 0.28; p=0.000) and (Mean +- *SD,* 34.43 +- 12.19 versus 20.19 +- 9.74; p=0.000) respectively. The estimated GFR was lower for patients the day before death comparing to those who have been recovered from COVID-19 (Mean +- *SD,* 67.99 +- 42.26 versus 139.39 +- 54.19; p=0.000) (Table 3, Fig. 1).

Of 46 died patients; all of the kidney function tests were abnormally changed from baseline to the day 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=0.000). Consequently, the estimated GFR decreased from baseline by more than 63% (Mean +- *SD,* 109.12 +- 24.69 versus 67.99 +- 42.26; p=0.000). Similarly, BUN was increased more than 61% from the baseline value (Mean +- *SD,* 109.12 +- 24.69 versus 67.99 +- 42.26; p=0.000) (Table 3, Fig. 1).

Abnormal liver function test and clinical outcomes

All patient had a serial measurement of AST, ALT, ALP and total serum bilirubin. The upper-recorded values for the recovered patients were compared to the baseline and one day before death values for died patients. The baseline value of total serum bilirubin was higher in died compared to the recovered patients (Mean +- *SD,* 0.81 +- 0.24 versus 0.63 +- 0.36; p=0.001), whereas AST, ALT, and ALP were not significantly differed between both group (Mean +- *SD,* 23.09 +- 9.69 versus 21.87 +- 12.04; p=0.436), (Mean +- *SD,* 29.65 +- 20.49 versus 27.46 +- 10.37; p=0.476), and (Mean +- *SD,* 100.85 +- 68.01 versus 104.57 +- 46.65; p=0.719), respectively (Table 4).

Comparing to recovered patients, the entire liver function test one day before death were high in died patients {AST (Mean +- *SD,* 36.98 +- 10.92 versus 23.09 +- 9.69; p=0.000); ALT (Mean +- *SD,* 40.28 +- 12.92 versus 29.65 +- 20.49; p=0.000); 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=0.000)}. Furthermore, for died patients, the AST, ALT, and total bilirubin one day before death was significantly higher comparing to their baseline value [AST, (Mean +- *SD,* 36.98 +- 10.92 versus 21.87 +- 12.04; p=0.000); ALT (Mean +- *SD,* 40.28 +- 12.92 versus 27.46 +- 10.37; p=0.000); and total bilirubin, (Mean +- *SD,* 1.36 +- 0.96 versus 0.81 +- 0.24; p=0.000)] (Table 4, Fig. 2).

Risk of mortality with kidney and liver injury for COVID-19

Based on the number of patients who developed abnormal recording above the cut off value, the elevated values of S.Cr and BUN shows high risk factor for death comparing to the recovered patients (43.48% versus

1.71%, HR 44.23; 95% CI: 16.34, 119.70, p=0.000) and (13.04% versus 2.28%, HR 5.59, 95% CI: 1.86, 16.84, p=0.020). Furthermore, the spark elevation in liver function test above cut off value in died comparing to recovered patient increase 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=0.000), and bilirubin 1.71% versus 52.17%, HR 62.73; 95% CI: 23.24, 169.32, p=0.000)} (Table 5, Fig. 3).

DISCUSSION

We compare laboratory finding for kidney and liver function between patients who were recovered from COVID-19 with the died patient during the same period. To our knowledge, this is the first study that has made such a comparison. Our goal was to investigate the possible cause of death other than respiratory failure for the patient with COVID-19.

Many studies conducted to investigate the risk factors for the development of AKI among COVID-19 patients. Old male gender (>50 years) have been confirmed to associated with a higher rate of AKI compared to young and female patients [13]. Another study concluded that increased ten years of age could be associated with a >10% increase in the risk of AKI [14]. Besides, other independent factors related to the development of AKI and mortality rate in COVID-19 patients include DM, hypertension, WBCs count, respiratory rate during disease episode, COPD, and previous history of chronic kidney diseases [15]. These were consistent with our result in which, died patients were older than recovered patient, and 76.09% were male. Meanwhile, the respiratory rate at admission was higher among died patient. The presence of COPD and hypertension could be the direct cause of death and the causative for AKI (Table 1).

Based on the previous researches and the wide spectrum of the involved mechanisms, COVID-19 patient with underlying AKI, indeed required mechanical ventilation and ICU admission and might prognoses with worse outcomes compared to healthy kidney patients [16]. In this study, all of them died patients were admitted to the ICU at least two days before death and died patients' data were collected for this study a day before death was reported in the ICU.

Although patients with renal diseases have more risk for infection with COVID-19, patient infected by SARS-CoV-2 without a history of renal problems might opposite a burden for severe kidney injury and may progress to renal failure. Unfortunately, there was a less renal recovery in patients diagnosed with CVID-19 comparing to the patient with a negative result for COVID-19 [17]. Furthermore, COVID-19 patients with an advanced stage of AKI (Stage III and more) were reported to have more than 30% higher incidence for death compared to a patient with normal or subnormal kidney function [18]. Based on the previously mentioned facts, our result confirms that the renal function of died patients was ranged from normal to mild renal insufficiency at admission and then progressed to critical stage III and IV before death. Further, the non-significant difference in S.Cr level and eGFR between the died and recovered patients at admission and the progression of renal injury that is confirmed by spark elevation in S.Cr (>2.1 fold), BUN (> 62.2%) and reduction in eGFR (>62.3%) when we compare renal function test one day before death with the values obtained on admission. Altogether, these results indicate an association of AKI and mortality among COVID-19 patients (Table 2). Although studies showed a low rate of renal replacement therapy for COVID-19 patients with advanced AKI [19], this result explained by the high rate of mortality in advanced renal disease among patients suffering from SARS-CoV-2 infection. By this study, the risk of mortality in COVID-19 patients was strongly related to AKI (S.CR HR 44.23; 95% CI: 16.34, 119.70, p=0.000) and (BUN 13.04% versus 2.28%, HR 5.59, 95% CI: 1.86, 16.84, p=0.020) (Table 5, Fig. 3). In this regard, continuous monitoring of renal function with preventive and supportive therapies of renal disease is crucial for COVID-19 patients.

Another potential mechanism of AKI involves SARS-CoV-2 related cytokine storm that is related to immune response deregulations. It is a cytokine related systemic inflammatory response resulting in a variety of clinical manifestations such as uncontrolled high fever, CNS 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 (MOF) is almost inevitable [20]. Patient with

cardiac comorbidity (particularly right ventricular failure secondary to COVID-19 pneumonia), or other predisposing factors for hypovolaemia, sepsis or nephrotoxicity; besides, macrophage activation syndrome, and the development of microemboli and microthrombi in the context of hypercoagulability and endotheliitis might lead to kidney and liver congestion and subsequent AKI and liver injury [21]. The results of this study confess the role of cytokine storm in the concurrent deterioration of renal and hepatic functions in COVID-19 patients death.

The liver biochemistry changed dynamically in patients infected by SARS-CoV-2 during the clinical course. ALT and total bilirubin founded to be an increase in 28% and 18%, respectively [22], in an early study in Wuhan, and 53% in a subsequent study [23]. The degree of acute liver injury was different in COVID-19 patients. The need for ICU was more prevalent in patient demonstrate high levels of ALT/AST, ALP and total bilirubin. Furthermore, the prevalence of abnormal liver biochemistry is high in COVID-19 patients at admission and increased during the disease course [24]. 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 developed severe COVID-19 [25]. The previous facts are consistent with our results, in which only bilirubin was significantly higher at admission among died patients, whereas, just before death, extreme elevation in AST, ALT, and bilirubin were observed (Table 4, Fig. 2).

Studies were conducted and suggested that abnormal liver function can result from an infection of bile duct cells by SARS-CoV-2; however, alkaline phosphatase (ALP) founded not specific for COVID-19 patient as the bile duct injury-related index [26]. 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 [27]. Currently, many reports focus on the systemic inflammation that is associated with COVID-19 as a cause of liver injury [28]. These confirm our insights that cytokines storm could be the causative for kidney and liver injury with subsequent mortality in COVID-19 patients. Although the available data about the effect of a different antiviral drug on hepatic function, the use of corticosteroid in COVID-19 patients also seemed to induce acute hepatic injury [29]. This study was conducted to patients administered uniform protocol of therapy to exclude the effect of the drug on the results, taking into consideration the variability in the duration of therapy and doses used.

Even 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 patients outcome [30]. More importantly, 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 who are died.

CONCLUSION

Although COVID-19 affects mainly the lungs, it can also cause multiple organ damage. Acute kidney and liver injury are crucial complication in patients with COVID-19, which could be progressed to chronic stage and resulted in poor prognosis and increase the rate of mortality. It is therefore; we should increase our awareness towards the importance of timely detection of AKI and liver injury and consider all available treatment options for maintenance of kidney and liver functions to prevent death in COVID-19 patients.

ABBREVIATIONS**:** SBP, systolic blood pressure; DBP, diastolic blood pressure; RR respiratory rate; PR pulse rate; WBCs white blood cells count; HG; hemoglobin; S.Cr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

CONFLICT OF INTEREST:

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

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