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Original article

A single centered study reveals association between liver injury and COVID-19 infection

Noha M. Elemam [a], Haifa Hannawi [b,c], Kashif Bin Naeem [b], Suad Hannawi [b,*]

[a] Sharjah Institute for Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates
[b] Ministry of Health and Prevention, Department of Medicine, Dubai, United Arab Emirates
[c] Mohammed bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates

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ABSTRACT

Background and aim: Despite the fact that it has been over a year with the pandemic COVID-19 infection, ongoing research and analysis reveal many complications and comorbidities associated with COVID-19. In this study, we aimed at investigating the clinical and laboratory assessments in COVID-19 patients with and without liver injury.

Methods: Symptomatic 541 COVID-19 positive patients, who were admitted to Al Kuwait Hospital, Dubai, United Arab Emirates (UAE), were recruited in this study. Their data was collected retrospectively, including demographic data, blood tests, symptoms, radiographical assessments, and clinical outcomes of COVID-19.

Results: Around 19% of the recruited COVID-19 patients displayed signs of acute liver injury. Also, there was an increase in the percentage of critical, ICU-admitted and mortality rates in COVID-19 cases with liver injury, as well as a higher percentage of septic shock and acute respiratory distress syndrome (ARDS). COVID-19 patients with liver injury had more pronounced bilateral consolidation, lymphopenia and neutrophilia. Additionally, these patients had higher levels of CRP, LDH, procalcitonin, ferritin and D dimer levels. Finally, there was a higher percentage of patients taking various COVID-19 therapies in the COVID-19 patients with liver injury group.

Conclusion: COVID-19 patients with acute liver injury are at a higher risk for serious outcomes including death.

1. Introduction

It has been more than a year since the discovery of the SARS-CoV-2 virus, that still remains a global pandemic till now. COVID-19 infection caused by SARS-CoV-2 was reported to be associated with various symptoms according to the stage, that could start off with fever, sore throat, loss of taste and smell, and could end in pneumonia and even acute respiratory distress syndrome (ARDS). However, COVID-19 complications were associated with multiple comorbidities including diabetes, hypertension as well as cardiac, gastrointestinal and renal dysfunction (Rismanbaf and Zarei, 2020, Wang, T. et al., 2020).

Although the lung is the main site of SARS-CoV-2 infection, previous reports indicated that around 10% of COVID-19 patients had liver damage as the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were abnormal (Garridoet al., 2020, Huang et al., 2020, Rismanbaf and Zarei, 2020, Zhang et al., 2020). More, severe and ICU-admitted COVID-19 patients exhibited liver dysfunction, as observed by elevated liver enzymes (Bangash et al., 2020, Fan et al., 2020, Guan et al., 2020, Wang, D. et al., 2020, Zhang et al., 2020). Previous liver biopsies obtained from COVID-19 patients showed leukocyte infiltration into the lobular and portal sites coupled with hepatocyte degeneration and focal necrosis, as well as microvascular steatosis, indicating liver injury upon infection with SARS-CoV-2 (Xu et al., 2020).

Various possible theories were suggested to be behind the liver dysfunction seen in COVID-19 patients (Zhang et al., 2020). One could be the inflammation caused by the immune dysfunction including the cytokine storm (Cao et al., 2020). A second possibility

* Corresponding author.
E-mail address: suad1@ausdoctors.net (S. Hannawi).

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could be direct viral entry through the known SARS-CoV-2 entry receptor angiotensin-2 converting enzyme (ACE2) (Wang, D. et al., 2020), that is present on cholangiocytes in liver tissues, thus causing bile duct dysfunction (Chai et al., 2020). Another possible proposition is the hepatotoxicity caused by drugs used for COVID-19 treatment (Cao et al., 2020). These drugs include the antiviral drugs oseltamivir, ritonavir/lopinavir, and remdesivir, as well as the anti-inflammatory chloroquine and hydroxychloroquine, all of which are metabolized in the liver and would cause hepatotoxicity (Yang, R.-X. et al., 2020, Yang, X. et al., 2020). Also, pneumonia and critical symptoms of COVID-19 could be a contributing factor in liver damage (Chand and Sanyal, 2007, Ghoda and Ghoda, 2020). Finally, some studies suggested that COVID-19 might trigger further liver damage in patients with pre-existing liver diseases (Ali, 2020).

In this study, we aimed at investigating the effect of liver dysfunction on the laboratory blood tests, symptoms, clinical outcomes and mortality rate in COVID-19 patients that were admitted to the first hospital that had been devoted to COVID-19 cases.

2. Patients and methods

2.1. Subjects

A total of symptomatic 541 COVID-19 positive patients, who were admitted to Al Kuwait Hospital, Dubai, United Arab Emirates (UAE), were recruited in this study and their data was collected retrospectively. Ethical approval for this study was obtained from Ministry of Health and Prevention Research Ethics Committee (MOHAP/DXB-REC/MMM/NO.44/2020) and conforms to the provisions of the Declaration of Helsinki. The clinical data included age, sex, medical history of other organ dysfunctions including acute cardiac injury, and ARDS. Also, the duration of illness was recorded.

Symptoms associated with COVID-19 were documented including fever, myalgias, fatigue, anorexia, headache, confusion, rhinorrhea, shortness of breath, sore throat, cough, sputum production, hemoptysis, nausea, vomiting, and diarrhea. Blood tests including white cell count (WCC), platelets, neutrophil count, lymphocyte count, hemoglobin (Hb), HbA1c, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin, troponin and coagulation tests (D-dimer and the international normalized ratio; INR).

The data of liver function tests including albumin level, alanine aminotransferase (ALT), aspartate aminotransaminase (AST), serum bilirubin and alkaline phosphatase level (ALP) were collected. All the liver function tests were performed at the time of admission to the hospital. Liver injury was defined by the presence of high ALT and/or high AST by more than five times the upper limit of normal reference range.

Clinical outcomes of COVID-19 had been reported (intensive care unit admission; ICU, need for mechanical ventilation, acidosis, septic shock and death). COVID-19 patients were classified based on the following criteria, 1- mild to moderate; no pneumonia or mild pneumonia, 2- severe; presence of dyspnea, respiratory rate $\geq$ 30/min, blood oxygen saturation $\leq$ 93%, ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) < 300, and lung infiltrates > 50% within 24–48 h, and 3- critical; respiratory failure, septic shock, or multiorgan dysfunction/-failure. Besides, radiographical assessment using chest X-ray and computed tomography (CT) tests was performed for the investigated individuals. The treatment regimens used for management of COVID-19 therapy included hydroxychloroquine (HCQ), antivirals such as lopinavir-ritonavir and favipiravir, antibodies, steroids, interferon, anti-fungal agents and IL-6 receptor blocker Tocilizumab.

2.2. Statistical analysis

SARS-CoV-2 infected individuals suffering from acute liver injury were compared to those without liver injury. The values represent mean ± SEM for the continuous variables, or percentage relative to the total number of patients in each group for the categorical variables. Statistical analysis was performed using GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA). Student's *t*-test was used to assess the differences between the groups for the continuous variables, while Chi-square test was used for the categorical variables. P value < 0.05 was considered statistically significant. The demographic data of the cohort are listed in Table 1, while the other collected data along with the respective p values are listed in the supplementary tables.

3. Results

3.1. Liver dysfunction in COVID-19 patients

In order to categorize COVID-19 patients into 2 groups with and without liver dysfunction, the levels of liver enzymes, bilirubin and albumin were compared. As seen in Fig. 1A-C, elevated levels of ALT, AST and ALP were observed in those in the liver impairment COVID-19 group compared to those without ($p < 0.0001$, $p < 0.0001$ and $p = 0.0025$, respectively). Furthermore, bilirubin levels were elevated in COVID-19 patients with liver dysfunction ($p = 0.0003$), while hypoalbuminemia was found in those patients ($p < 0.0001$) as shown in Fig. 1D and 1E.

After categorizing COVID-19 patients into two groups based on liver dysfunction, it was worth investigating if these patients had other organ dysfunctions such as cardiac injury. Indeed, COVID-19 patients with liver impairment, exhibited more cardiac injury ($p < 0.0001$), which was further supported by an increase in their troponin levels ($p = 0.0040$, Fig. 2A-B).

Table 1
Demographic data of the COVID-19 patients included in the study, with and without liver dysfunction. BMI: body mass index. Data represented as numbers of individuals or mean ± standard deviation.

	COVID-19 patients with liver dysfunction (n = 103)	COVID-19 patients without liver dysfunction (n = 438)
Demographic Data		
Gender (M/F)	92/11	324/114
Age at Diagnosis (years)	49.23 ± 13.87	48.50 ± 15.0
BMI	28.32 ± 5.461	28.62 ± 5.956
Travel History (Yes/No)	0/103	30/408
Contact History (Yes/No)	18/85	113/325
Duration of illness (days)	5.532 ± 2.622	5.768 ± 3.194

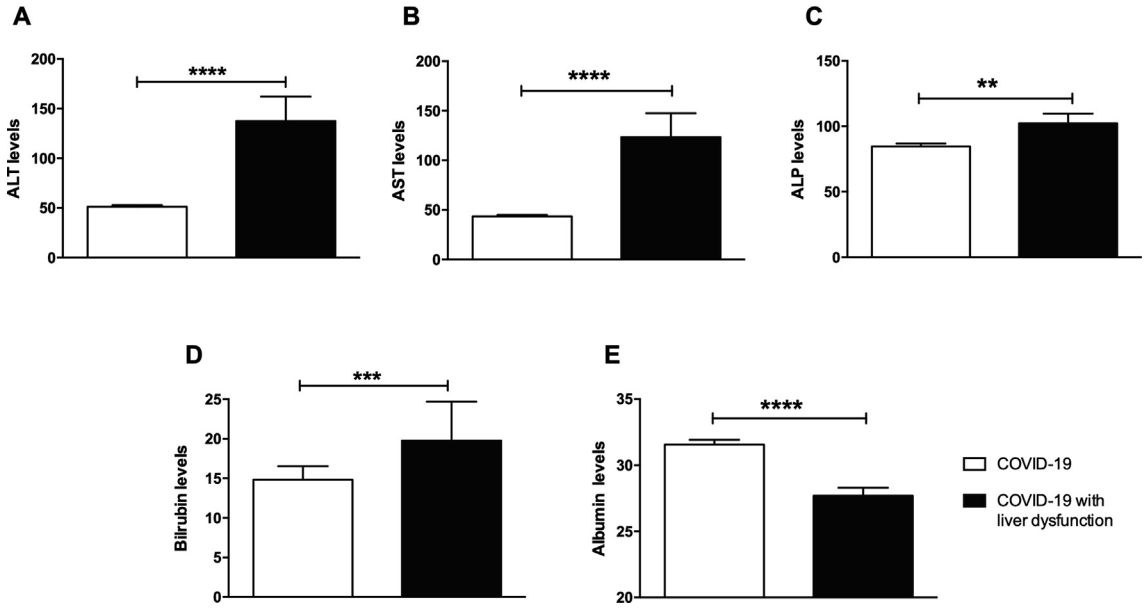

Fig. 1. Liver function tests in COVID-19 patients. COVID-19 patients categorized in the liver impairment group showed higher levels of (A) ALT, (B) AST, (C) ALP, (D) Bilirubin and lower levels of (E) Albumin compared to COVID-19 with no liver impairment. **p < 0.01, ***p < 0.001, ****p < 0.0001.

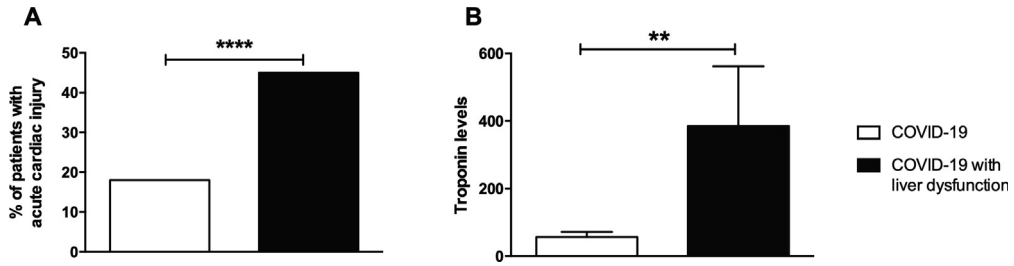

Fig. 2. Cardiac injury in COVID-19 patients with liver injury. (A) There was a higher percentage of COVID-19 patients with cardiac injury along with liver damage. (B) This was supported by higher troponin levels in the COVID-19 patients with liver injury. **p < 0.01, ****p < 0.0001.

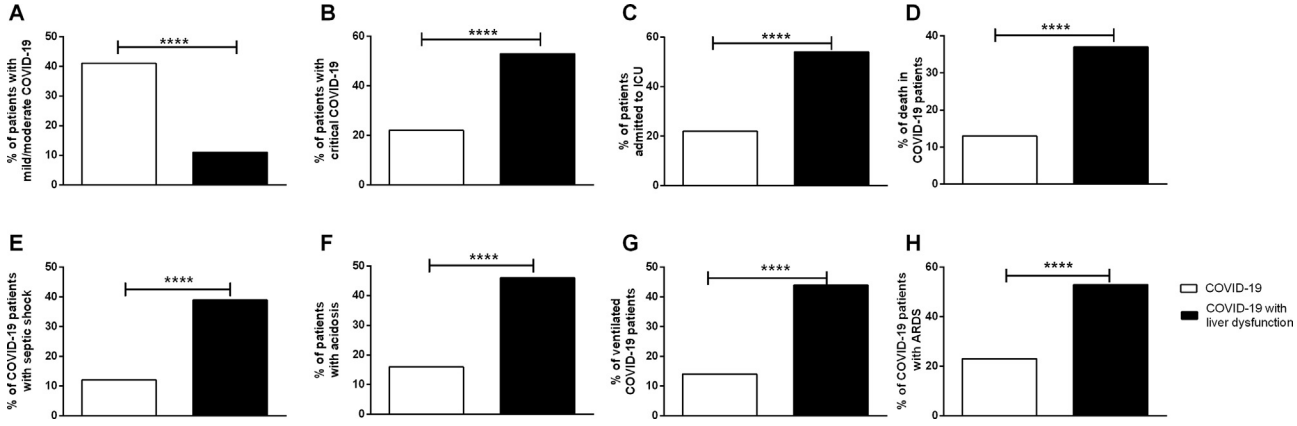

Fig 3. Clinical outcomes and disease severities in COVD-19 patients with liver dysfunction. (A) Lower percentage of mild/moderate cases of COVID-19 patients were observed in the liver damage group, while there was a higher percentage of (B) critical, (C) ICU-admitted, and (D) death. COVID-19 patients with liver damage were more likely to (E) go in septic shock, (F) have acidosis, (G) need ventilation and (H) suffer from ARDS. **** p < 0.0001.

3.2. Clinical outcomes and disease severity in COVID-19 patients

It seems that liver dysfunction might be a contributing factor that is associated with severity and mortality of COVID-19 infection. As illustrated in Fig. 3A, there was a decline in the percentage of mild-moderate patients with acute liver injury while there was a concomitant increase in the percentage of critical, ICU-admitted and death of COVID-19 patients (Fig. 3B-D, p < 0.0001 for all). It was quite interesting that along with liver damage, it was noted that there was a higher percentage of patients with septic shock (Fig. 3E), acidosis (Fig. 3F), ventilated individuals (Fig. 3G), and ARDS (Fig. 3H, p < 0.0001 for all).

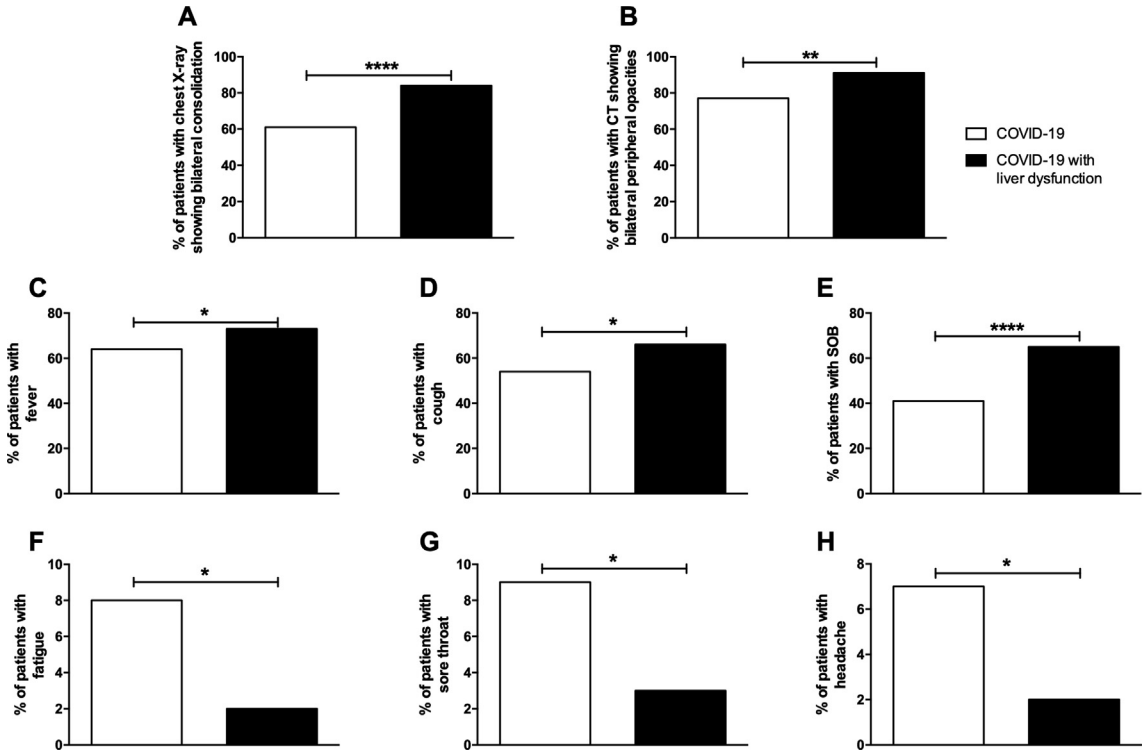

Fig. 4. Radiological tests and symptoms of COVID-19 patients with liver injury. COVID-19 patients with liver dysfunction showed more (A) bilateral consolidation in their chest X-ray, and more (B) bilateral peripheral opacities in their CT scans. (C) Fever, (D) cough, and (E) shortness of breath/SOB were reported more in COVID-19 patients with liver injury, while (F) fatigue, (G) sore throat, and (H) headache were much lower in those patients. *p < 0.05, **p < 0.01, ****p < 0.0001.

3.3. Radiographic assessment and symptoms in COVID-19 patients

It was revealed that a higher percentage of COVID-19 patients had bilateral consolidation and bilateral peripheral ground opacities in their chest X-ray and CT scans (Fig. 4A-B, $p < 0.0001$ and $p = 0.0023$, respectively). In parallel with the previous findings, COVID-19 patients with liver impairment showed more tendency to have symptoms of lower respiratory tract infection with a higher percentage of fever ($p = 0.04$), cough ($p = 0.0127$), and shortness of breath ($p < 0.0001$) (Fig. 4C-E). On the other hand, they tend to have less symptoms of upper respiratory tract infection such as fatigue (Fig. 4F, $p = 0.0189$), sore throat (Fig. 4G, $p = 0.0156$), and headache (Fig. 4H, $p = 0.033$).

3.4. Blood laboratory tests in COVID-19 patients

COVID-19 was associated with an increase in the white cell count (WCC) as well as lymphopenia and neutrophilia. As shown in Fig. 5A-C, this was further highlighted in patients with liver damage as they had a higher white cell count ($p = 0.002$) and exhibited much more significant lymphopenia and neutrophilia ($p < 0.0001$ for both). Additionally, those patients had higher levels of inflammation markers associated with COVID-19 including CRP (Fig. 5D, $p < 0.0001$), LDH (Fig. 5E, $p < 0.0001$), procalcitonin (Fig. 5F, $p < 0.0001$), ferritin (Fig. 5G, $p < 0.0001$) and D dimer levels (Fig. 5H, $p = 0.0002$). Similar to D-dimer levels, other coagulopathy related factors were different in COVID-19 patients with liver damage as observed in the decrease in the INR levels (Fig. 5I, $p = 0.0002$) in liver-impaired COVID-19 patients.

3.5. Treatment profile of COVID-19 patients

It was crucial to investigate if there was a difference in the drugs used for therapy of COVID-19 patients with and without liver injury. Different therapies included tocilizumab, favipiravir, antifungal agents, interferon, steroids and IV antibodies. As shown in Fig. 6A-C, there was a higher percentage of patients taking tocilizumab, steroid and IV antibodies in the COVID-19 patients with liver injury group ($p < 0.0001$ for all). Furthermore, a higher percentage of COVID-19 patients with liver injury took interferon ($p = 0.0172$), favipiravir ($p = 0.0017$), and antifungal agents ($p = 0.0032$) (Fig. 6D-F).

4. Discussion

The global pandemic COVID-19 caused by SARS-CoV-2 virus still remains a mystery to many researchers around the world. Despite the fact that it primarily affects the pulmonary system, several studies reported that COVID-19 infection affects other organs including renal, cardiovascular, gastrointestinal and hepatic systems (Guan et al., 2020, Huang et al., 2020, Wang, D. et al., 2020, Wang, T. et al., 2020, Yang, X. et al., 2020). In this study, out of the 541 recruited COVD-19 patients, 103 (19%) were reported to have acute liver injury. These patients had elevated levels of ALT, AST, ALP and bilirubin along with hypoalbuminemia, indicating liver damage. This goes in line with previous studies indicating abnormal liver function tests in COVID-19 patients (Cai et al., 2020, Phipps et al., 2020), due to the inflammatory status in COVID-19 that could cause elevated serum transaminase levels, jaundice and hepatic injury (Yang, R.-X. et al., 2020).

Elevated liver function tests were previously linked to non-alcoholic fatty liver disease (NAFLD) and obesity, however, there was no statistical difference between the body mass index (BMI) levels of COVID-19 in both groups (Table 1). As expected, COVID-19 patients with liver dysfunction had damage in other organs such as cardiac injury, further suggesting that inflammation and SARS-CoV-2 affect multiple organs especially in severely critical patients (Phipps et al., 2020, Sun et al., 2020).

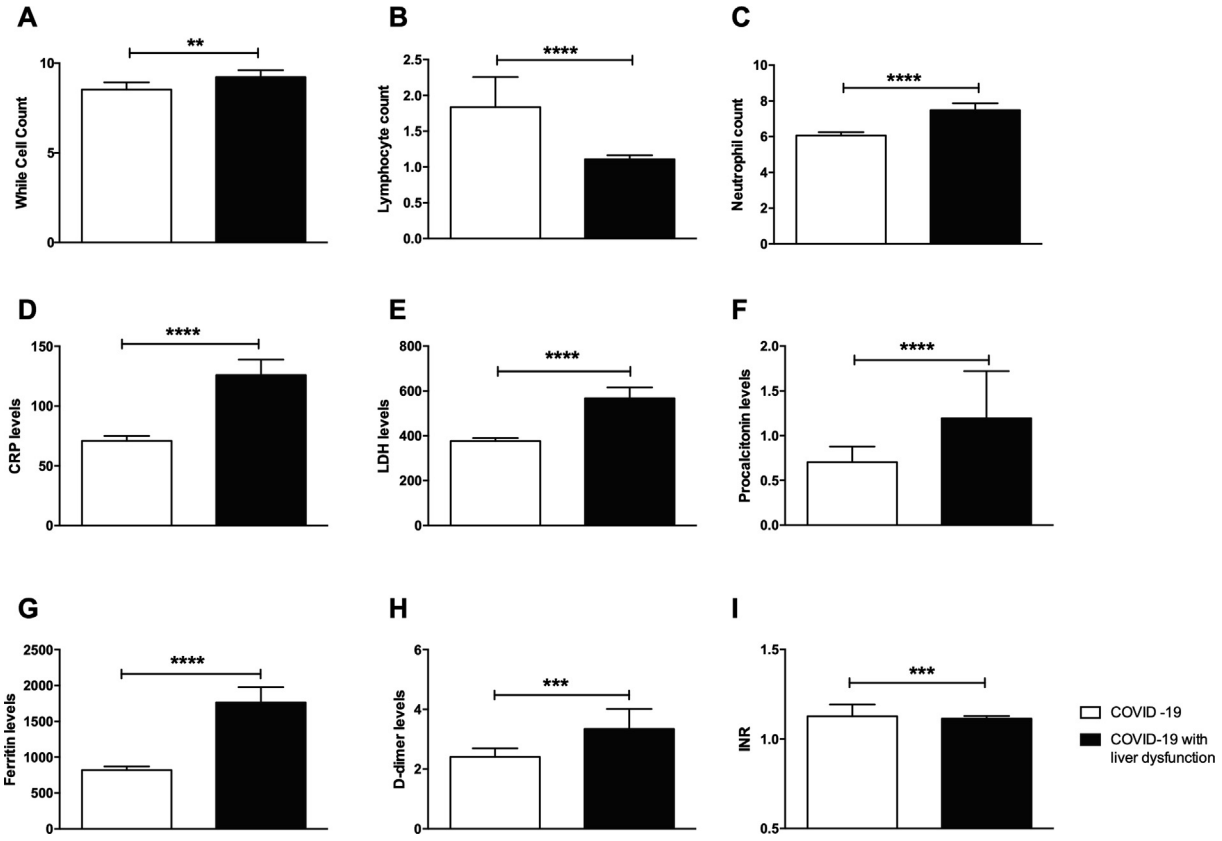

Fig. 5. Blood laboratory tests in COVID-19 patients with liver injury. There was a difference in the count of (A) white cells, (B) lymphocytes, and (C) neutrophils in COVID-19 patients with and without liver injury. Also, COVID-19 patients with liver dysfunction showed higher levels of (D) CRP, (E) LDH, (F) procalcitonin, (G) ferritin, and (H) D-dimer, while there was a decrease in the levels of (I) INR.**p < 0.01, ***p<0.001, ****p < 0.0001.

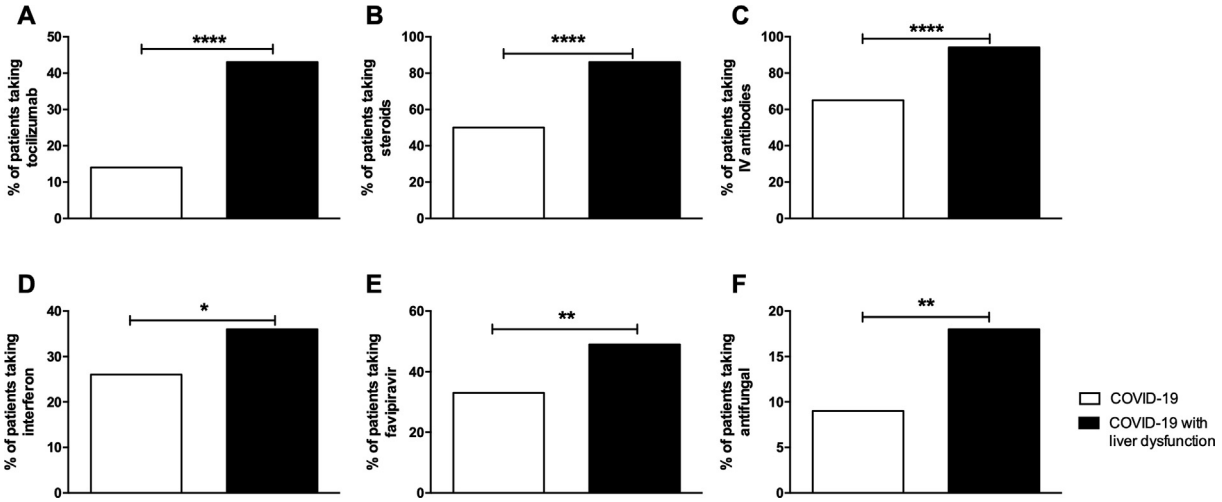

Fig. 6. Treatment profile of COVID-19 patients. A higher percentage of COVID-19 patients taking (A) tocilizumab, (B) steroids, (C) IV antibodies, (D) interferon, (E) favipiravir, and (F) antifungal drugs was found in the liver dysfunction group. *p < 0.05, **p<0.01, ****p < 0.0001.

Indeed, there was a high percentage of critical COVID-19 and ICU-admitted cases in the category that had liver injury. Furthermore, their chest X-ray and CT scans indicated pulmonary opacities and a more critical stage of infection. This goes in line with a previous study by Cai Q. et al where a similar observation was reported (Cai et al., 2020). Furthermore, a higher mortality rate was documented in COVID-19 patient suffering from liver damage. Several complications of COVID-19 infection include acidosis, sepsis and septic shock as well as pulmonary complication such as ARDS that could lead to the necessity of external ventilation (Chen et al., 2020, Wang, D. et al., 2020, Zhou et al., 2020). We observed that COVID-19 patients with acute liver injury are more likely to develop such complications, as shown in Fig. 3. This could be attributed to hypoxia and reperfusion that may trigger liver injury (Yang, R.-X. et al., 2020).

Interestingly, we found that COVID-19 patients with liver injury had milder COVID-19 symptoms such as headache, fatigue, and sore throat. While there was a higher percentage of COVID-19 patients had fever, cough and shortness of breath (SOB). Again, this could be due to the finding that more critical and ICU admitted

patients fall in the liver dysfunction group. This was further supported by the blood test findings with more pronounced lymphopenia and neutrophilia along with elevation of the inflammatory associated markers in COVID-19: CRP, LDH, procalcitonin, and ferritin. COVID-19 patients had multiple coagulation problems and it seems that they are more profound in patients with liver injury. High D-dimer and low INR, indicate a higher probability of thrombosis and coagulation problems that is a cause or result of liver damage (Phipps et al., 2020).

A possible cause of liver injury in COVID-19 is the drugs used in therapy. We observed in this study that a higher percentage of COVID-19 patients that took different classes of antiviral and anti-inflammatory agents, suffered from acute liver injury. This supports previous studies (Bangash et al., 2020, Yang, R.-X. et al., 2020), and highlights that care should be taken in the therapeutic use of various types of medications, doses, and durations of medicines in order to reduce the chance of drug-induced liver injury, as well as maintain liver function and protection. This supports previous studies that reported that acute liver injury and hepatotoxicity observed in COVID-19 could be due to either the drugs or might be a synergistic effect between the virus and the used drugs. Whether patients with a background of liver impairment prior to COVID-19 acquisition are more likely to contract the viral infection and to exhibit more liver impairment is a question that needs to be further investigated.

5. Conclusions, limitations and future perspectives

COVID-19 infection could lead to multiple organ dysfunctions, that should be monitored and deeply investigated during and post-COVID-19 infection. In this study, we reported that COVID-19 patients presenting with acute liver injury are at a higher risk for serious outcomes including death. However, this study has some limitations where pre-existing elements of liver impairment cannot be ruled out. This could be further investigated in future studies. Also, it would be interesting to investigate if elderly patients are at a higher risk of developing impaired liver functions. Future work would be needed to understand the short- and long-term effects of SARS-CoV-2 and used therapeutics on the various systems of the human body.

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Author contributions

Conception or design: N.M.E and S.H, Acquisition, analysis, or interpretation of data: H.H, K.B.N, and S.H, Drafting the work or revising: N.M.E and S.H., Final approval of the manuscript: N.M.E, H.H, K.B.N, and S.H.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2021.06.064.

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