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The Impact of COVID-19 Infection on Prognostic Effect of Liver Laboratory Markers and Disease Outcome

Randa R. Ghamyes*, Hayjaa M. Alhamadani and Mohammed I. Rasool[1]

Department of Medical Laboratory Techniques, College of Medical Technology, Al-Farahidi University, Baghdad, Iraq
[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Kerbala, Kerbala, Iraq
✉ randa_rasol@yahoo.com

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Abstract: Severe acute respiratory syndrome-related coronavirus 2 (SARS- CoV-2) is a viral pathogen that causes coronavirus disease 2019 (COVID-19). Angiotensin-converting enzyme 2 (ACE2), as a receptor, is crucial for SARS-CoV-2 to get access into the host cells. According to reports, ACE2 is expressed in the liver, placenta, heart, lungs and kidneys. This study sought to gain unique insights into the features of liver indicators in individuals suffering from COVID-19 disease in order to enhance their therapeutic care. The study groups included 50 people diagnosed with COVID-19 infection in the patient's group and 25 healthy people without any systemic diseases in the control group. Human serum samples were used to measure liver function enzymes, CRP, D dimer, and ferritin all samples by using automated quantitative tests. The results revealed a statically significant difference between AST, ALP, TSB, and study groups, where it is found that the mean levels of AST (88.04±33.00) and ALP (99.61±41.93) were high in patients than in controls, while the mean levels of TSB were low in patients (0.51±0.21) than the controls. A significant difference was also obtained for each ferritin, CRP, and D dimer between the study groups, where it found the mean concentrations of D dimer, ferritin and CRP, i.e., 1208.09±667.32, 60.53±23.91 and 204.52±90.62, respectively, were high in the patient's group than in controls.

Key words: COVID-19, angiotensin-converting enzyme 2, liver, liver injury, liver enzymes.

Introduction

Compared to the previous epidemics of SARS-CoV and respiratory syndrome-related coronavirus in the middle east, SARS-CoV-2 initially emerged in the Wuhan area in 2019 and spread rapidly among millions of people present globally (Chen et al., 2020; Soltani et al., 2020)

The number of fatalities and instances of infected individuals have risen rapidly because of the lack of specialised efficient antiviral medicines (Sohrabi et al., 2020). Since COVID-19 has a contagious and pathogenic nature, a greater knowledge of manifestations, etiology, and clinical features of COVID-19 possibly will enhance each prevention, treatment, and recovery programme for diseases.

ACE2 receptor is known to mediate the virus attachment to the host cell and hence an important factor for causing disease due to infection. Owing to the widespread distribution of ACE2, SARS-CoV-2 causes a systemic illness that may impact the heart, liver, pancreas, and kidneys, in addition to altering the immune system and circulating lymphocytes (Harmer et al., 2002; Pringle et al., 2011). Even though the lung is identified as the main involved organ, previous investigations revealed that SARS-CoV transmission to the liver can cause liver cell impairment along with liver test abnormalities in COVID-19 severe patients (Bangash et al., 2020; Huang et al., 2020). Liver problems that develop through the illness or

*Corresponding Author

treatment of COVID-19 in individuals who either with or without a history of liver disease are referred to as COVID-19-associated liver injury (Marabotto et al., 2021). The research findings suggest that multiple factors, including SARS-CoV-2 infection, lead to hepatic damage. Biliary duct cells and type II alveolar cells are susceptible to infection because ACE2 is expressed in these cells (Chau et al., 2004; Sungnak et al., 2020). Furthermore, the probability of the virus infecting the liver cell is reported. Likewise, a wide range of factors, including direct cytotoxicity from viral infection to indirect participation of the inflammatory cytokine storm, hypoxia alterations brought on by respiratory failure, endothelins, and drug-induced liver injury, could contribute to the pathogenesis of the disease (Saber-Ayad et al., 2020). Recent studies state that multiple abnormal liver function test results are present in 50% of COVID-19 patients, indicating that the individuals may have varying degrees of liver impairment (Marabotto et al., 2021).

Patients, Materials and Methods

Patients

This study comprised 50 Iraqi individuals diagnosed with COVID-19 infection and 25 healthy people from the same ethnicity without any systemic diseases were considered as the control group.

All the patients and control are aged between 13 and 81 years. The patients were recruited from Dar Al-Salam Hospital, Baghdad, Iraq. The healthy control were volunteers.

Materials and Methods

For the liver function test, approximately 5 ml of venous blood sample was utilised to separate sera. Serum samples were analysed for liver function test (ALP, ALT, AST, TSP) along with C- reactive protein and D dimer by Cobas c111 Analyser. While the Ferritin test was analysed using Cobas E 411 Analyser.

Statistical Analysis

The Chi-square (X^2) test was used to compare percentages in the data of the current investigation. (Mean SD) was used to describe numerical dates. The F-test (ANOVA) was used to compare three or more numerical variables, whereas the T-test was used to compare two numerical variables. To describe the nature and intensity of the link between variables, Pearson correlation (R) was used. The test's level of significance was set at 0.05. Programmes like (SPSS v.22 and GraphPad Prism v.6) are utilised to evaluate recent data.

Results and Discussion

Results of present study revealed no significant differences between gender and age in study groups (Table 1).

In countries where sex-disaggregated data were available, these studies demonstrate no considerable gender difference in the overall number of confirmed COVID-19 cases, comparable to global statistics. However, as older males are fewer in absolute numbers

Table 1: Chi-square tests were used to compare gender and age groups with study groups

			Groups		*Total*	*P value*
			Patients	*Controls*		
Age groups (years)	1-20	N	0	1	1	*P*>0.05
		%	0.0%	4.0%	1.3%	
	21-40	N	15	14	29	
		%	30.0%	56.0%	38.7%	
	41-60	N	20	6	26	
		%	40.0%	24.0%	34.7%	
	61-80	N	13	3	16	
		%	26.0%	12.0%	21.3%	
	>80	N	2	1	3	
		%	4.0%	4.0%	4.0%	
Gender	Males	N	25	10	35	*P*>0.05
		%	50.0%	40.0%	46.7%	
	Females	n	25	15	40	
		%	50.0%	60.0%	53.3%	

than their female counterparts due to their short life expectancy, this may indicate a higher incidence in men in the older age categories where there are similar absolute numbers of cases in both genders (Gebhard et al., 2020).

In the age group over 40 years, where practically all COVID-19 deaths occur, an exponential rise with age is a useful model to explain and evaluate both COVID-19 and all-cause mortality. Furthermore, COVID-19 mortality has a stronger age dependence than all-cause mortality, and men are at an elevated risk relative to women, but this risk is more prominent in aged people (Jakhmola et al., 2021). Recent reports have established evidence is of a rise in disease risk in men over 60 years (Robert Koch Institute, 2020). Elderly people are at a significant risk of COVID-19 infection, which may be probably brought on by an impaired immune system, chronic illnesses, malnutrition, elevated ACE-2 expression, and organ damage.

In Kirkuk city, it was found that men have higher rates of infection, particularly those over 61 years of age and those with concomitant conditions such as diabetes, high blood pressure and cardiovascular disease (Faiq et al., 2021).

Men are 50% more likely than women to be hospitalised, according to new statistics on disease severity and course. In previous studies, male patients are more than females, which is due to several causes such as genetics, ACR2 receptors, hormones disorders, immune status, and majorly because of COVID-19 infection. In addition, the infection with COVID-19 increases with age progression because of the decrease in immune efficacy in the elderly (Grasselli et al., 2020). Additionally, three studies showed that in comparison to males, females exhibit more potent and robust innate immune responses. The greater degree of IL-6 receptor expression in male lung epithelial cells shows that males are more exposed to the cytokine storm that can exacerbate COVID-19 disease. Additionally, males have stronger levels of pro-inflammatory cytokines and chemokines (Gemmati et al., 2020).

Results of the present study showed that there is no significant difference between ALT with study groups. In contrast, our study showed significant differences between AST, ALP, TSB, and study groups, where it found the mean levels of AST (88.04±33.00) and ALP (99.61±41.93) were high in patients than in controls, while the mean levels of TSB were low in patients (0.51±0.21) than controls (Table 2).

Table 2: Comparative liver functions and TSB parameters with study groups were calculated by using the *t*-test

Groups		*N*	*Mean*	*SD*	*P value*
AST	Patients	50	88.04	33.00	*P*<0.001
	Controls	25	18.86	5.05	
ALT	Patients	50	114.06	44.78	*P*>0.05
	Controls	25	19.28	9.61	
ALP	Patients	50	99.61	41.93	*P*<0.05
	Controls	25	71.16	20.75	
TSB	Patients	50	4.55	0.21	*P*<0.01
	Controls	25	11.56	5.08	

Hwaiz et al. (2021) show high levels of ALT, AST, ALP, and low levels of TSB in COVID-19 patients than controls that could be connected to liver virus replication, which agreed with the current study results.

The SARS-CoV-2 virus targets the ACE2 receptor in liver cells', which is also the factor that enables the infection to enter liver cells. Furthermore, it has been demonstrated that ACE easily attaches to the SARS-CoV-2 spike protein (Pirola and Sookoian, 2020).

A recent study showed that the virus directly causes cytotoxicity while it is actively replicating in the liver, which results in liver damage because of the extreme inflammatory response in COVID-19 patients. Along with many factors including hypoxic alterations brought on by respiratory failure, vascular changes brought on by coagulopathy, endothelium, or heart failure-related congestion, drug-induced liver injury, and exacerbation of underlying liver disease (Mizumoto et al., 2020).

Liver viral replication in COVID-19 individuals may explain the prevalence of increased liver transaminases (ALT and AST). Patients with COVID-19 usually have slight abnormalities in plasma liver function tests (LFTs) upon admission. These LFTs, particularly AST as well as ALT, are linked to serious illness and elevated inflammatory signs. The pathogenetic process for abnormal LFTs is poorly understood; they are probably complex and could be influenced by microthrombotic endothelialitis, immunological imbalance, drug-induced liver injury, and hepatic ischemia brought on by hypoxia and MOF (Nadro et al., 2021).

Patients with COVID-19 frequently exhibit liver function test (LFTs) abnormality at admission; it is connected to organ dysfunction and an independent predictor of transfer to the intensive care unit (ICU) or death (Piano et al., 2020).

The researcher evaluated the clinical features of COVID-19 pneumonia in patients who showed abnormal liver function test results and found that these patients had a higher risk of experiencing a serious illness. Another study revealed a prolonged hospital stay is correlated to the impaired liver function that is present in more than one-third of SARS-CoV-2 infected patients who are admitted to the hospital. This revealed that most of the symptoms are present in COVID-19 individuals with abnormal liver function tests (Fan et al., 2020). From 48 cases of aberrant LFT, of which 31 cases were symptomatic. Nardo et al. (2021) revealed that the severity of SARS-COV-2 is correlated with hepatic abnormalities. Essa et al. (2020) showed high levels of TSB in patients with COVID-19 as compared to controls, and these results are not compatible with current study results.

Results of the current study showed there is a significant difference between ferritin, CRP, and D dimer with study groups. It was found that ferritin, CRP, and D dimer mean levels, such as 1208.09±667.32, 60.53±23.91, and 204.52±90.62, respectively, were elevated in patients than in controls (Table 3).

Table 3: Comparative ferritin, CRP and D dimer parameters with study groups were calculated by student's *t*-test

Groups		*N*	*Mean*	*SD*	*P value*
Ferritin	Patients	50	1208.09	667.32	$P<0.001$
	Controls	25	138.69	45.50	
CRP	Patients	50	60.53	23.91	$P<0.001$
	Controls	25	6.38	2.63	
D dimer	Patients	50	204.52	90.62	$P<0.05$
	Controls	25	0.45	0.08	

Kaushal et al. (2022) showed high levels of ferritin in patients with COVID-19 as compared to controls, and these results are compatible with the current study results. Elevated serum levels of CRP, D-dimer and ferritin were linked to infection due to COVID-19, in a meta-analysis (Huang et al., 2020). Increased iron or iron substitution favours the rapid expansion of numerous viruses including immunodeficiency virus (HIV) and hepatitis C virus (HCV) (Drakesmith and Prentice, 2008). Iron is required for many crucial SARS-CoV-2 operational and regulatory proteins, and too much of it can cause fibrin aggregation and a procoagulant condition (Colafrancesco et al., 2020). According to the authors, an elevated serum ferritin concentration was linked to a progression of the condition and an extremely poor favourable result in COVID-19. As a result, the serum iron level can be used as a crucial prognostic biomarker in the therapy of COVID-19 and patient triage (Kaushal et al., 2022).

Huang et al. (2020) show high concentrations of D dimer and CRP in COVID-19 patients as compared to controls, and these results are compatible with the current study results. In the study by Siddiqi and Mehra (2020), the COVID-19 stage of systemic hyperinflammation proposed inflammatory cytokines, and indicators including interleukin (IL)-7, IL-2, and IL-6, TNF-α, CRP, ferritin, and D-dimer were significantly elevated.

CRP is a liver-produced acute inflammatory protein that may be increased in several situations, including inflammation, cardiovascular disease, and infection (Sproston and Ashworth, 2018). An increased CRP level was linked to acute COVID-19 and the requirement for ICU treatment in a meta-analysis of 13 studies, but not with survival. Although there is no consensus on a threshold for judging COVID-19 severity, most research employed a limit of 10 mg/L (Koozi et al., 2020). According to the CRP distributional features, an ideal cut-off of 40 mg/L was linked to mortality.

The duration of the serum CRP elevation, which peaks 72 hours after the initial insults, made the serum CRP assessment period important. Despite its effectiveness in predicting a negative outcome in COVID-19 patients, it needs to be mentioned that a variety of variables including gender, age, smoking habits, obesity, cholesterol levels, blood pressure, and liver disease, could influence serum CRP levels. These factors should be considered while interpreting the serum CRP level. Additionally, recent research has demonstrated that serum CRP levels could be utilised to track the development and improvement of COVID-19 patients (Li et al., 2020).

The intensity of COVID-19 pneumonia was significantly linked with plasma CRP level. Study results may help to differentiate patients with severe to moderate COVID-19 pneumonia from those with mild ones based on the patient's CRP concentration for transfer to the intense care unit (Chen et al., 2020). A previous study revealed that the demand for mechanical ventilation was mainly predicated on the maximum amount of IL-6, followed by the level of CRP. This indicates that patients with COVID-19-related hyperinflammatory syndrome may be treated more quickly by utilising IL-6 or CRP levels as a guide (Herold et al., 2020).

In the present study, results also revealed that a higher D-dimer was linked to increased composite poor outcomes, especially severe COVID-19 and deaths. This observation confirms the theory that (SARS-CoV-2) disease might cause haemostatic system failure, resulting in a hypercoagulable state, a condition that is frequently seen in sepsis. The best cutoff value for high D-dimer in individuals with COVID-19 has not yet been determined because the reasons for increased serum D-dimer levels are multifactorial. In accordance with the recommendations of the International Society of Thrombosis and Hemostasis (ISTH), serum D-dimer levels that are significantly higher suggest enhanced thrombin generation. Hospitalisation may be necessary for COVID-19 patients with noticeably increased D-dimer values, regardless of how severe their clinical signs are (Thachil et al., 2020).

Hyperfibrinogenaemia, lymphopenia, elevated D-dimer, and leukopenia were among the common aberrant haematological COVID-19 indicators found upon admission, and they were considerably different between the mild and severe COVID-19 groups. Furthermore, changing neutrophil-lymphocyte ratios and D-dimer levels can be used to differentiate between severe and relatively mild COVID-19 cases (Fu et al., 2020). Patients with COVID-19 who had D-dimer on arrival at levels higher than 2.0 g/ml were more likely to die in hospitals, suggesting that D-dimer might be used as an important indicator to help with patient care (Zhang et al., 2020).

The blood parameter indicates that the ferritin levels will rise in the second week after being affected by COVID-19 and that other variables, including ESR, C.R protein, and D-Dimer, will vary in accordance with the typical range. These levels will vary as a result of receiving two 500 ml doses of paracetamol twice a day in the hospital, which has an impact on liver function, according to a prior case study (Hussein et al., 2021). In conclusion, COVID-19 infection has an impact on liver function and liver function enzymes.

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