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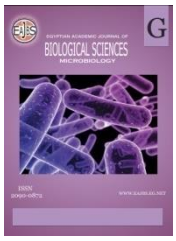

The Effect of Covid-19 on Liver

Huda Dakeel Ali, Asma Easa Mahmood and Batool Imran Theeb
Department of Pathological Analysis, College of Applaied Science, Samaraa University.
*E. Mail: batoolomran@yahoo.com

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ABSTRACT

Wuhan City, China has reported the identification of the first occurrence of the respiratory disease brought on by a new coronavirus since December 2019. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) shows variation symptoms such as fever (100%), cough (73%), headache (23%), sore throat (23%), sputum production (47%), chest pain (15%), Dyspnea (82%), diarrhea (33%), anorexia (65%), Fatigue (100%). The percentage of males from the total samples was (62.7%) while the females were (37.3%). The laboratory tests to confirm SARS-CoV-2 infection were positive RT-PCR, D-Diamer with rang 636.9-10000g/ml, and CRP rang 37-110 mg/L. Coronavirus causes damage to hepatocytes that elevated liver enzymes, ALT, AST, ALP and TSB with a range of 25%, 34.4%, 15% and 25% respectively.

INTRODUCTION

In December 2019, Wuhan City, Hubei Province, China, revealed the discovery of the first case of respiratory illness brought on by a novel coronavirus. The World Health Organization named the disorder coronavirus disease 2019 (COVID-19) dated February 11, 2020, despite the fact that it is still dangerous throughout the entire world (CDC, 2020). As SARS-CoV-2 infected the liver and cause dysfunction and damage to hepatocytes (Fan *et al.*, 2020). Symptoms included cough, fever, pneumonia, ,headache, diarrhea, hemoptysis, and, dyspnea, (Adhikari *et al*., 2020).

SARS-CoV-2 uses the host receptor angiotensin I converting enzyme 2 (ACE2) to infect human cells. Even though it has been claimed that ACE2 is expressed in the lung, liver, stomach, ileum, kidney, and colon, these tissues actually express it at relatively low levels, particularly in the lung(Qi *et al*., 2020; Lai *et al*., 2020).

When a disease is present, the innate immune system starts to react. Some innate immune cytokines increase, which may help in predicting the subsequent stages of the clinical period (Mason, 2020; Liu *et al*., 2020). Cytokine storms, which come from increased levels of proinflammatory cytokines and chemokines that affect numerous organs, are the cause of ARDS in COVID-19 disease (Zhang *et al.*, 2020; Merad and Martin, 2020). In the host cell, the type transmembrane protease, serine 2 (TMPRSS2) increases viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, which enables coronavirus entrance into host cells (Hoffmann *et al.*, 2020). ACE2 and TMPRSS2 are present in target cells of the host, specifically alveolar epithelial type II cells (Mancia *et al.*, 2020; Zou *et al.*, 2020).

A typical side effect of SARS-CoV-2 infection is liver damage, which can be brought on by a direct viral infection of liver cells (Zhang *et al.,* 2020) The most frequently reported symptoms of liver damage in COVID-19 patients are abnormal liver function and elevated levels of aspartate aminotransferase or alanine aminotransferase, which have appeared in 16.1-53.1% of SARS-CoV-2-infected individuals (Wang *et al.,* 2020; Huang *et al.,* 2020).

MATERIALS AND METHODS

Blood samples were collected from patients from October 2021 to April 2022 in Tikrit Hospital, and Digestive system and liver Hospital in Baghdad. All patients who suspect to have COVID-19 enrolled in this study and diagnosed according to the Iraqi National Guidelines for the diagnosis of COVID-19, Common symptoms included dizziness, headache, shortness of breath, runny nose, sore throat, diarrhea, decreased appetite and jaundice (Grant *et al*., 2020). The consent of the patients was obtained before collecting data and samples from them. The sample studied included (N=162) cases including 20 individuals from a control sample. The mean age was (52) years ranging between 20 to 79 years. To conduct medical tests, blood samples were drawn from patients as follows and an automatic hematology was used to measure, Total WBCs, monocytes, Lymphocytes Neutrophils, Eosinophils, basophils, and platelets. Others Blood samples in Gel-Tube used for Alanine transaminase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Bilirubin, C- reactive protein CRP, D- dimer, and IL-17.

RESULTS AND DISCUSSION

Symptoms and Laboratory Tests for Covid-19 Patients:

43 samples were collected from hospitalized patients from Baghdad Teaching Hospital-Gastroenterology and Liver Hospital and Tikirit Hospital, who are suspected of being infected with SARS-CoV-2.

SARS-CoV-2 patients were diagnosed based on clinical tests by a specialist doctor, laboratory results and PCR swab. Examinations and symptoms confirmed the infection as shown in Tables (1 &2).

Covid-19 samples were 43 samples (27 male and 16 female). Infected men composed (62.7%) of specimens. The results are close to the results of (Chang *et al*., 2020) who found that male patients composed and 67%, but decreased than (Huang *et al*., 2020) reached the percentage males was 73% from collected samples.

The patient infected with SARS-CoV-2 were exhibit various symptoms such as fever (100%), cough (73%), headache (23%), sore throat (23%), sputum production (47%), chest pain (15%), Dyspnea (82%), diarrhea (33%), anorexia (65%), Fatigue (100%), as shown in Table (1). The symptoms of the coronavirus were extremely diverse, ranging from non-symptomatic to extremely mild to severe symptoms that had an impact on multiple organ failure and even death. According to (Huang *et al.,* 2020), who stated that 98% of the infected patients experienced fever followed by cough (76%), dyspnea (55%) and loss of taste or smell, symptoms can include fever. The results corroborate with those of Wang et al. (2022) who discovered that diarrhoea was present in 34.0% of cases. Although Covid-19 has a number of mechanisms that can produce symptoms, the one that causes headaches is still unknown. First, some ideas contend that people with COVID-19 have greater amounts of certain cytokines in their serum, including tumour necrosis factor (TNF), interleukin 2 (IL-2), and granulocyte macrophage-colony stimulating factor (Wang *et al.,* 2020; Qin *et al.,* 2020; Neurath, 2020). Headaches could be brought on by these immune cell cytokines, which are produced in response to viral infections (Eccles, 2005; Marchioni and Minoli, 2010). Second, a coronavirus can produce anomalies in alveolar gas exchange when it enters lung tissue. These abnormalities can result in brain hypoxia, an

increase in anaerobic metabolism in mitochondrial cells, and an accumulation of acid metabolites. It will restrict cerebral blood flow, cause brain cells to expand, and widen the cerebral veins in addition to ischemia and congestion-related headaches (Wu *et al.,* 2020). Additionally, a coronavirus that directly attacks the nervous system may cause headaches. Along with headaches, some individuals also experienced neurological symptoms such as nausea, vomiting, and dizziness (Wang *et al.,* 2020; Mo *et al.,* 2020). According to autopsy findings on COVID-19 patients, certain neurons deteriorate in engorged and edematous brain tissue. Additionally, in the brain fluid of confirmed patients, other investigations found genome sequencing of Covid-19 (Wu *et al.,* 2020). Neuronal pathways are an important point of entry for neurotropic viruses. Two research studies showed that SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-COV) might enter certain brain regions when administered intranasally to transgenic mice (Netland *et al.,* 2008; Li *et al.,* 2016) Given that SARS-CoV-2, SARS-CoV, and MERS-CoV all have a common aetiology and structure (Li *et al.,* 2020) This approach can also be used to explain this unique coronavirus.

Another symptom that coronaviruses can cause, sore throat, was present in COVID-19 patients. Given that both SARS-CoV-2 and influenza can spread virally through the respiratory system and that their symptoms are similar (Xia *et al.,* 2020; Grant *et al.,* 2020) It's likely that SARS-CoV-2 causes sore throats in a manner similar to how influenza does. The SARS-CoV-2 infection may cause the body to produce inflammatory mediators in the airway, including prostaglandins and bradykinin, which may affect the sensory nerve in the layers of throat tissue and cause painful throat.

Interleukin-6 typically mediates myalgia during viral infection, which upregulates and results in myalgia or arthralgia (Manjavachi ., 2010; Drożdżal *et al.,* 2020). Myalgia may be brought on by skeletal muscle injury. According to Li et al. (2020), ACE2 is also present in skeletal muscle, and SARS-CoV-2 has the ability to bind to ACE2 and infect skeletal muscle. However, postmortem examinations of SARS-CoV patients' skeletal muscles did not reveal viral infection (Ding *et al.,* 2004).

Thus, further investigation into the mechanism is still necessary. Furthermore, cytokines may also result in myalgia, when cytokines stimulate them, prostaglandin E2 is created, and by binding to peripheral pain receptors, prostaglandin E2 enhances pain. 2005's Eccles. Injuries to the skeletal muscles can also be a sign of neurological system damage. (Eccles, 2005; Mao *et al.,* 2020) SARS-CoV-2 can directly attack the nervous system by binding to ACE2 to cause skeletal muscle damage or indirectly attack the nervous system through peripheral nerves.

The exact mechanism through which SARS-CoV-2 causes chest discomfort is unknown. According to Li *et al.* (2020), cardiac injury or a pleural inflammatory illness may be the source of chest pain (Li *et al.,* 2020) In the heart, a high level of ACE2 expression has been seen (Li *et al.,* 2020). As a consequence of the autopsy, SARS-CoV viral RNA was discovered in the heart samples of individuals whose deaths were brought on by SARS. This discovery implies that the virus can enter cardiomyocytes directly and damage the heart through ACE.

Furthermore, inflammatory markers associated with the cytokine storm syndrome, such as C-reactive protein, leukocytes, and procalcitonin, sharply increase in people who have suffered a cardiac injury. Increased inflammatory cytokine release and activation can injure myocardial cells (Shi *et al.*,2020). Additionally, certain inflammatory mediators that are released into the pleural space and activate pain receptors on the pleura might cause chest pain (Reamy *et al.,* 2017) Heart difficulties can also be attributed to COVID-19-related breathing problems and hypoxia. (Zheng *et al.,* 2020), as shown in Tables (1 and 2).

The domino effect of viremia and inflammatory substances may affect the digestive system. According to studies, stool samples of up to 53.4% of individuals contain viral nucleic acid (Guan *et al.,* 2020; Huang *et al.,* 2020). More research is needed to confirm the hypothesis that enteropathic viruses directly damage the intestinal mucosa and cause digestive symptoms.

Third, the intestinal flora, which is both abundant and diverse, colonises the human intestine. The intestinal flora serves a number of important physiological roles in the body, including affecting how nutrients are metabolised by the body, regulating immune system maturation and development, and having an antibacterial effect. Changes in the intestinal flora brought on by the virus itself may result in symptoms of digestion. The intestines contain the body's most powerful immune system. Through the same mucosal immune system, changes in the digestive tracts composition and function have an impact on the respiratory tract, while respiratory tract flora diseases have an impact on the digestive tract through immunological control. This system is referred to as the "gut-lung axis." (Jeffers *et al.,* 2004; Gramberg *et al.,* 2005).

Table 1: Symptoms of SARS-2**.**

Symptoms	Percentage
Age	18-90
Gender males/females	68.5% / 31.5%
Fever	100%
Cough	73%
Headache	23%
Sore throat	23%
Sputum production	47%
Chest pain	15%
Dyspnea	82%
Diarrhea	33%
Anorexia	65%
Fatigue	100%

Based on the RNA extracted from respiratory specimens including oropharyngeal swabs, sputum, nasopharyngeal aspirate, bronchoalveolar lavage, or deep tracheal aspirate, RT-PCR is the most often used detection technique (Sahin *et al*., 2020). RT-PCR is used in diagnostic Corona assays to measure the quantity of unique genetic virus fragments present in an individual. The pro-inflammatory biomarkers C-reactive protein (CRP) and D-dimer are present in greater concentrations in COVID-19 patients. As shown in Table (2) the range of D-Dimer values in patients with COVID-19 are 636.93-10000ng/ml and CRP 37-110mg/l. Patients with COVID-19 may have a pulmonary endothelial injury with inflammation-related intra-alveolar fibrin deposits or systemic endothelial injury with widespread thrombosis of smaller arteries or larger veins. (Roncon *et al.,* 2020), and coagulopathy (Eriksson *et al.,* 2020; Onishi *et al.,* 2020; Spiezia *et al.,* 2020) as possible explanations for the rise in D-dimer values.

Thus, in-hospital trends of D-dimer and other coagulation markers could be a sign of disease activity in COVID-19 patients. In fact, an increase in D-dimer velocity can indicate venous thromboembolic (VTE) in cancer patients (Leonard-Lorant *et al*., 2020).

The inflammatory biomarkers CRP and D-dimer showed a link with disease severity, with CRP showing a particularly close relationship with hypoxemic respiratory failure and cytokine storm. Numerous investigations provided evidence that the inflammation seen in the cytokine storms and

CRP levels of COVID-19 patients may have aided in the disease's development. CRP levels demonstrated a positive link with lung lesions in the early stages of COVID-19, which may suggest the severity of the disease given the significant cytokine levels caused by SARS-CoV-2 (Wang.2020).

Table 2: Laboratory test results for covid-19 patients.

Tests (43) cases	Results
RT-PCR	Positive
D-Diamer	636.96-10000ng/ml
CRP	37-110mg/l

Liver Function Test for Covid-19:

In this study, the total covid-19 samples were 43. The increased level of ALT are 8(25%), AST 11(34.4 %), ALP 5(15%) and TSB 8(25%), as show in the Table 3. The 43 COVID-19, positive patients were admitted. Recruited, patients, for the study who were, analyzed, for, their, liver, function enzyme levels, (ALT, AST, ALP and TSB) in, this, study, (75%, 65.6%, 85%, 75%) in the order, were found, with, enzyme, levels, within, normal, range.

Evaluated, Levels of ALT were,8 (25%), in patients with, raised, levels of these, enzymes which are similar to, ALT results of (Zeng *et al*., 2021) when reached to the percentage of ALT was 10 (14.3%), but decreased results of, aspartate aminotransferase (AST) alkaline phosphatase, (ALP), and, total, bilirubin, (TBIL) values, then the results, in this study, were 7 (10%), 2 (2.9%), and 4 (5.7%) respectively. Cai *et al.*, *(*2020) reached to increase in ALT, ALP and TSB percentage values similar to the value in this study were 49 (23.4%), 31 (14.8%), 24 (11.5%) and 51 (24.4%) in the order, but AST percentage value was 31 (14.8%) lower than has been reached. The results of this study were upper than those of (Qian *et al*., 2020) who found 7 (7.69%), 9 (9.8%), and slightly decreased than (Wan *et al*., 2020) who found elevated AST, and ALT percentages results were 25%. Increased level of TSB accepted (Aldhaleei *et al*., 2020).

Table 3: Elevated liver enzymes in patients with Covid-19 with IL-17.

Blood biochemistry	Patients of Covid-19 (n=32 /43)
ALT	8 (25%)
AST	11 (34.4%)
ALP	5(15.6%)
TSB	8 (25%)
IL-17	147.13±51.74

Some theories contend that liver damage in COVID-19 individuals may originate from the virus itself or from extra details including medication toxicity and systemic inflammation (Yang *et al*., 2020). Several investigations have revealed that the primary receptor for SARS-CoV-2 entry into cells is ACE2 (Clarke and Turner, 2012), The liver damage may be caused by the direct interaction of SARS-CoV-2 with ACE2 receptors in cholangiocytes (Zhang *et al.*, 2020).

The alteration of hepatocyte damage biomarkers, such as alanine aminotransferase,(ALT), aspartate, aminotransferase,(AST),,and bilirubin is,a common laboratory finding in patients with COVID-19 infection, many reports reached liver impairment had been showing elevation of aspartate transaminase (AST) or alanine transaminase (ALT) in around 10%–58%, mild bilirubin elevation in 3%–23%, slight alkaline phosphatase (ALP) elevation in 1%–10% and gamma-glutamyl transferase (GGT)

elevation in 13%–54% in patients with COVID-19.(Fan *et al*., 2020; Vespa *et al*., 2020; Arentz *et al*., 2020).

Although complicated, the pathomechanism of liver damage during infection is still not entirely understood. (Garrido *et al*., 2020). It is unclear if the liver damage indicates a more serious inflammatory response with hepatic injury or if it results from the direct viral action. (Feng *et al*., 2020). According to reports, the SARS-CoV binding site was shown to be the angiotensin-converting enzyme 2 (ACE2) (Feng *et al.,* 2020). The availability of this data allowed for the confirmation that SARS-CoV-2 may also directly infect host cells by binding to ACE2 on their surface with its S protein, although with 10–20 times more affinity, and producing Direct cytotoxicity as a result of active viral replication in hepatic cells (Feng et al., 2020)

Many organs, including the lungs, heart, and kidney, express the ACE2 receptor more strongly than other cell types (Ali and Hossain, 2020).

Additionally, numerous investigations showed that patients with SARS and MERS infections had elevated liver enzyme values and varying degrees of liver impairment (Chau *et al*., 2004; Lee *et al*., 2017)

Interleukin 17 (IL-17):

Interleukin 17 values increased in groups of patients compared to the control group. The highest significant increase of interleukin-17 was within the group of patients infected with Covid-19 as shown in Table (1).

The results were corresponding with (Du *et al*., 2013; Ghazavi *et al*., 2021; Avdeev *et al*., 2021; Huang *et al.,* 2020) who confirm the elevated IL-17 levels in patients infected with Covid-19. SARS-CoV-2 infection can cause a systemic inflammatory response that is characterized by a cytokine storm and associated with an exaggerated release of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin 6 (IL-6), and therefore IL-17, all of which can affect the liver. IL-17 had an increased level of SARS-CoV-2 due to its systemic disease that may lead to multiple organ failure and death (Luo *et al*., 2020; Chen *et al*., 2020). Therefore, it is essential to manage and avoid cytokine storms. In this regard, there is an emerging discussion on whether inhibiting other cytokines could lessen the impact of Covid-19 (Bashyam and Feldman, 2020). IL-17 is one of the essential cytokines produced by Th17-lymphocytes. It is well known that excessive IL-17 synthesis triggers the T-cell response and promotes the production of inflammatory mediators including IL-1, IL-6, TNF, growth factors like G-CSF and GM-CSF, and other chemokines (Pacha *et al*., 2020).

Additionally, it was postulated that IL-17 may have contributed to the development of endothelial dysfunction and thrombophilia in Covid-19 infected individuals in a mechanism that made IL-17 dangerous for SARS-CoV-2 patients (Raucci *et al*., 2020) which the purpose of IL-17 was to assess the cytokine profiles of individuals with the coronavirus disease.

Complete Blood Count (CBC):

It is clear from Tables (4) that there is a statistical difference in the values of WBC groups. The highest values were for the group infected with Covid 19. The majority of patients showed significantly reduced lymphocyte counts on laboratory tests. This research suggests that T cells, in particular, may be the primary target of SARS-CoV. Virus particles travel through the respiratory mucosa to other cells, triggering a cytokine storm, a series of immunological reactions, and changes in peripheral white blood cells and immune cells like lymphocytes. Some patients progressed rapidly with acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failure.

Huang *et al.* (2020) draw attention to the finding that elevated neutrophil counts in the blood of patients with severe illness are a salient clinical hallmark of SARS COV 2 disease. Severe COVID-19 is now known to have an increased neutrophil-to-lymphocyte ratio when concurrent lymphopenia is present. Furthermore, low oxygen saturation in the blood of severity COVID-19 patients

may activate hypoxia-inducible factor 1 (HIF-1) signaling in circulation, contributing to COVID-19 patients increased neutrophil function (Guan *et al.*, 2020; Qin *et al.*, 2020).

According to certain studies, the coronavirus, which is believed to devour a significant number of immune cells, inhibits the body's cellular immune system. Patient exacerbations may have T lymphocyte destruction as a significant contributing factor (Liu, 2016). Few theories can be considered in such situations, When COVID-19 is serious, it can lead to pneumonia, hypoxemic respiratory failure, and viremia affecting a number of organ systems. Significant cytopenia is brought on by it, primarily severe lymphopenia and excessive CD8+ T cell depletion, leading to an immunocompromised condition and cytokine storm (Erdinc *et al*., 2021).

Table 4: CBC of patients with Covid-19.

Groups / CBC	Control	Corona
WBC	6.00±2.2 b	9.7±3.5 a
LYM	1.9±1.0 a	1.2±0.6 a
MON	0.36±0.1 b	0.67±0.1 a
GRA	2.9±0.9 a	3.8±0.6 a
RBC	4.4±0.8 a	4.5±0.9 a
HGB	13.2±1.9 a	12.7±2.1 a
MCV	88.2±6.4 a	87.9±9 a
PLT	265±81 a	228.7±48 a

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