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COVID-19 Patients with Hepatic Complications During the Third Wave of Pandemic in Egypt

Alzhraa M Fahmy[1], Marwa O Elgendy[2,3], Ahmed M Khalaf[4], Mona A Abdelrahman[5], Mohamed EA Abdelrahim[5]*, Ahmed O El-Gendy[6]

[1]Tropical Medicine and Infectious Diseases Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

[2]Department of Clinical Pharmacy, Teaching Hospital of Faculty of Medicine, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

[3]Department of Clinical Pharmacy, Faculty of Pharmacy, Nahda University (NUB), Egypt

[4]Internal Medicine Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

[5]Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

[6]Department of Microbiology and Immunology, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt

***Corresponding author:** Mohamed EA Abdelrahim, mohamedemam9@yahoo.com

Abstract: COVID-19 is a respiratory infection that has lately begun to affect other vital organs, including the heart, kidney, and liver. The purpose of this study was to investigate the hepatic complications in COVID-19 patients and the risk of being admitted to ICU or facing death. *Methodology:* Comorbidities (hypertension and diabetes), COVID-19 symptoms, laboratory findings (ALT level, AST level, and albumin), complications during hospitalization, treatment protocol used, and survival outcomes were all studied in 200 COVID-19 infected Egyptian patients who had virological symptoms and were followed up until they recovered or died. It was found that older people and those with higher blood glucose levels have a higher risk of developing liver-associated COVID-19 disorders. Also, the majority of patients who developed liver complications in the course of the infection had high mortality rates. Patients with diabetes, hypertension, or hepatic disease are at higher risk of ICU admission or death. Hence, it is important to pay attention to these problems in the diagnosis and treatment of COVID-19 to develop a suitable individualized treatment protocol. There was also a correlation between the mortality in COVID-19 patients and both, high blood glucose and liver enzyme levels. It can be attributed to the correlation between diabetes and liver disease as every disease may be a complication to the other; moreover, COVID-19 may lead to increased blood sugar levels in addition to ALT and AST levels. Another theory is that COVID-19 may affect the liver and hence people with chronic liver disease.

Keywords: COVID-19; Hepatic complications; Third wave

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a RNA virus, which was first detected in humans in Wuhan, China, in December 2019. The virus has spread worldwide, triggering the coronavirus 2019 (COVID-19) disease, which continues to leave a serious impact on global health [1-4]. Most SARS-CoV-2 patients are asymptomatic or have mild symptoms, such as cough, fever, headache, and anosmia. About 15% have severe respiratory symptoms that last more than 10 days, resulting in compromised

respiration, which can lead to multiorgan failure, coagulopathy, or even death. Oxygen supplementation, invasive ventilation, and other supportive measures constitute the standard care for hospitalized patients. However, the mortality rate remains high among patients with critical illness. Common risk factors associated with severe COVID-19 are well recognized, comprising of advanced age, male, and comorbidities, such as hypertension, heart diseases, diabetes, and malignancy [5,6].

Lately, there have been some insights into the impact of COVID-19 on other organs. A number of studies have shown that more than half of COVID-19 patients reported varying levels of liver disease. In addition, a recent study showed that SARS-CoV-2 has the tendency to attach to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes, resulting in their dysfunction and inducing a systemic inflammatory response that causes liver injury. As of March 10, 2020, seven large-scale hospital-based studies have shown the clinical characteristics of COVID-19 patients, providing some insights into the factors that induce liver damage in these patients. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were reported in these studies, ranging from 14% to 53% [7,8].

Moreover, a pathological study of a liver biopsy specimen belonging to a patient who succumbed to death from COVID-19 showed moderate microvesicular steatosis as well as mild lobular and portal activity, demonstrating that SARS-CoV-2 can cause liver injury. However, there is still limited research on the investigations of liver enzymes and clinical features of liver failure in COVID-19 patients [9,10].

In Chinese surveys, one of which was led by Guangzhou Medical University, which included 552 hospitals in 31 provincial municipalities in January 2020, many COVID-19 patients were found to have some changes in their liver function test results; 6.2% to 22.2% of patients had elevated serum AST levels, while 21.3% to 28.1% of patients had elevated serum ALT levels. From among six studies conducted in Wuhan, only four included data on the proportion of patients with elevated liver function test results. Specifically, in these four studies, the proportion of infected patients with elevated serum AST levels ranged from 24.1% to 36.6% [11-13].

In another survey in China, the proportion of patients with elevated serum AST levels was only 16.1%, whereas those with elevated serum ALT levels were not specified. It seemed that the proportion of infected patients with elevated serum AST levels in Wuhan was much greater than those reported cases outside Wuhan. It is reasonable to speculate that there might have been a higher load of virus in the patients in Wuhan since the infection started there and is concentrated in a larger percentage of the population [14,15].

1.1. Gender factor in relation to liver dysfunction among COVID-19 patients

A total of six case series indicating abnormal liver function test results among COVID-19 patients revealed that the proportion of infected men with elevated serum AST levels was higher than that of infected women. In these case series, the proportion of infected men with elevated serum AST levels were 68.7%, 58.2%, 58.1%, 72.4%, 62.8%, and 73.2%, respectively, whereas the percentage of infected women were 31.3%, 41.8%, 41.9%, 27.6%, 37.2%, and 26.8%, respectively. Hence, it can be hypothesized that infected men are more susceptible to developing COVID-19-related liver dysfunction compared to infected women [16,17].

1.2. Age factor in relation to liver dysfunction among COVID-19 patients

Out of five case reports, three were concerning children, whereas the other two concerned adults. The children's age ranged from 3 months to 7 years, while the adult patients' age ranged from 35 to 56 years. None of these children had abnormal serum liver enzymes. Therefore, it can be hypothesized that elderly people are associated with a higher probability of liver dysfunction [17,18].

1.3. Angiotensin-converting enzyme (ACE) 2-mediated liver dysfunction

SARS-CoV-2 has direct adverse effects on the liver. Several studies have suggested that SARS-CoV-2

enters alveolar epithelial cells through human ACE2 receptors. Therefore, the lungs are supposed to be the main target organ of SARS-CoV-2 infection [18,19]. Previous studies have recorded that epithelial cells in the bile duct may also express ACE2 receptors, with a proportion of 20 times higher than hepatocytes. These reports suggest that SARS-CoV-2 infection could also lead to epithelial cell damage in the bile duct. However, significant elevations of serum alkaline phosphatase (ALP) level, bilirubin, and gamma-glutamyl transferase (GGT), which can also reflect bile duct injury, are rarely seen in COVID-19 patients. Liver histopathologic features from COVID-19 patients also did not record any significant hepatocyte or bile duct cell damage. Hence, it is reasonable to assume that COVID-19-related liver dysfunction is more likely due to secondary liver damage than the use of hepatotoxic therapies or the coexistence of systemic inflammatory response, respiratory distress syndrome-induced hypoxia, or multiple organ dysfunction [16-22].

Hence, we decided to perform a more detailed study focusing on the hepatic state and the treatment protocols of COVID-19 patients.

2. Patients and methods

The study was conducted on 200 hospitalized COVID-19 patients from Beni-Suef University Hospital in Egypt, after its approval by the Research Ethical Committee of the Faculty of Pharmacy, Beni-Suef University (REC-H-PhBSU-20010).

Data were collected from those patients from February 2021 to April 2021. The data were classified into six components: comorbidities (hypertension and diabetes), COVID-19 symptoms, laboratory findings (ALT level, AST level, and albumin), complications during hospitalization, treatment protocol used, and the survival outcomes.

3. Results

The data and specific health parameters of 200 COVID-19 patients were collected and analyzed for a more detailed correlation study between COVID-19 infection and the patients' health state, specifically focusing on liver disease patients.

In terms of gender, there were twice as many female patients as male patients (**Figure 1**).

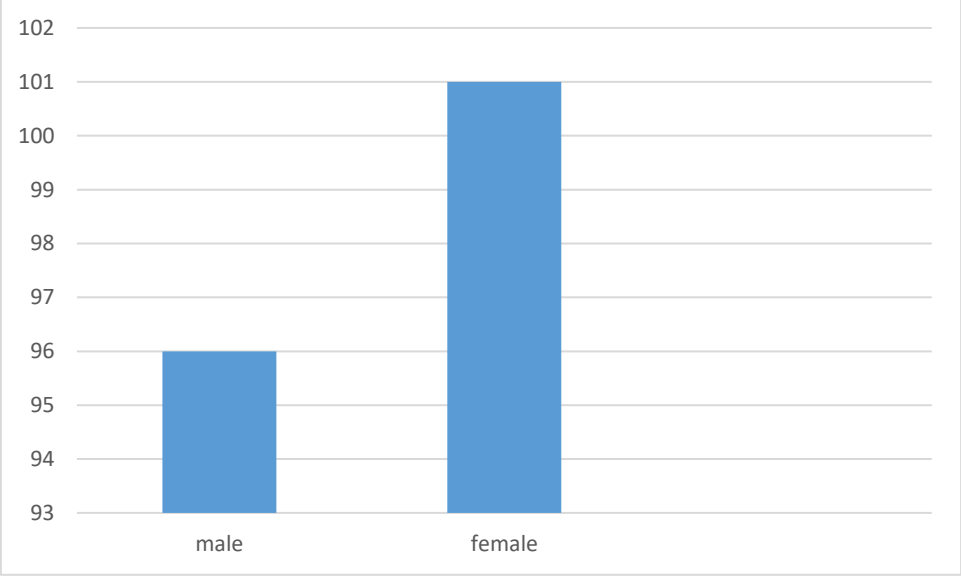

Figure 1. COVID-19 patients' gender

In terms of age, only 17% of the patients were between 25 to 45 years old. The majority of the patients were elderly patients, age ranging from 60 to 90 (**Figure 2**).

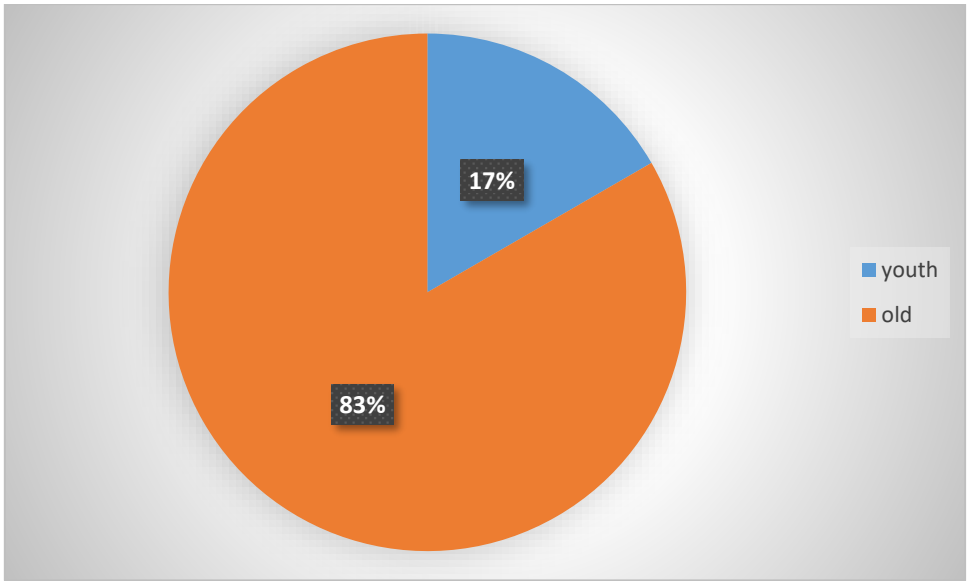

Figure 2. COVID-19 patients' age

From the data obtained, majority (n = 192) of the patients had normal blood pressure levels (120/80 mmHg), with only eight patients having high blood pressure (**Figure 3**).

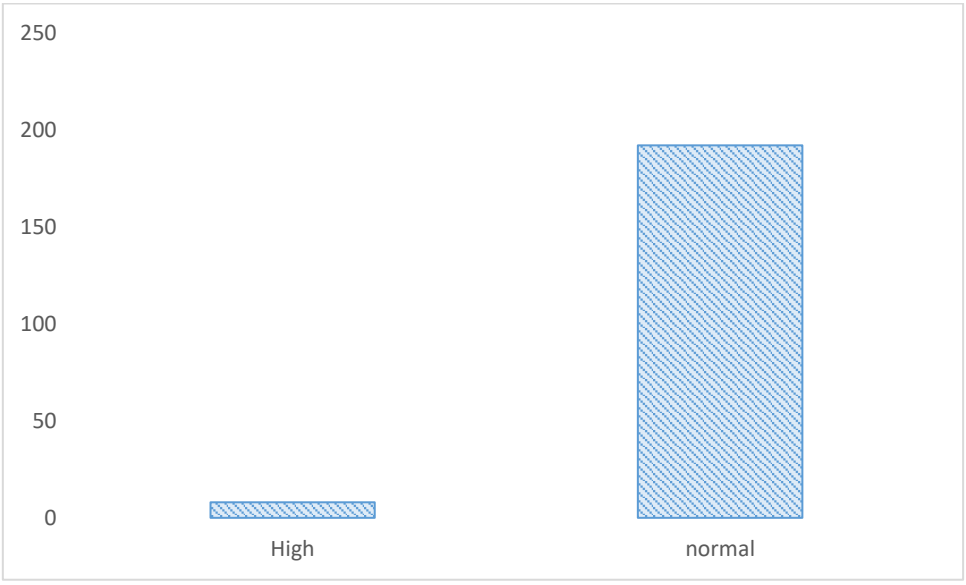

Figure 3. COVID-19 patients' blood pressure levels

As shown in **Figure 4**, all of the patients had anosmia (loss of the sense of smell) and ageusia (loss of the sense of taste) as the specific diagnostic symptoms for COVID-19 infection.

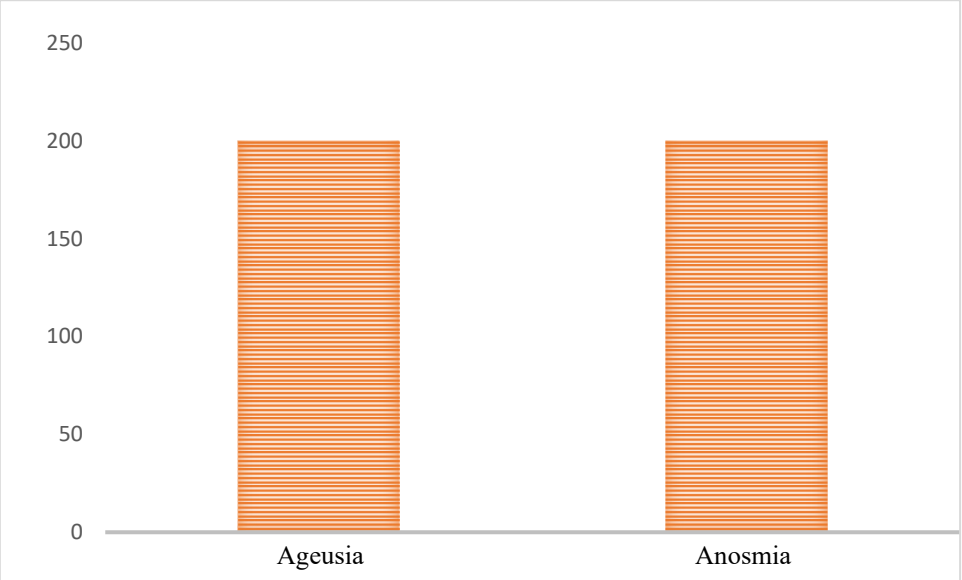

Figure 4. Anosmia and ageusia in COVID-19 patients

In terms of the patients' health state and symptoms, 19.9% of the patients had high blood glucose levels (n = 59), 11 patients had abdominal pain, 9 patients had diarrhea, 2 patients had nausea, and only one patient had episodes of vomiting (**Figure 5**). The rest of the patients had no specific symptoms except for anosmia and ageusia.

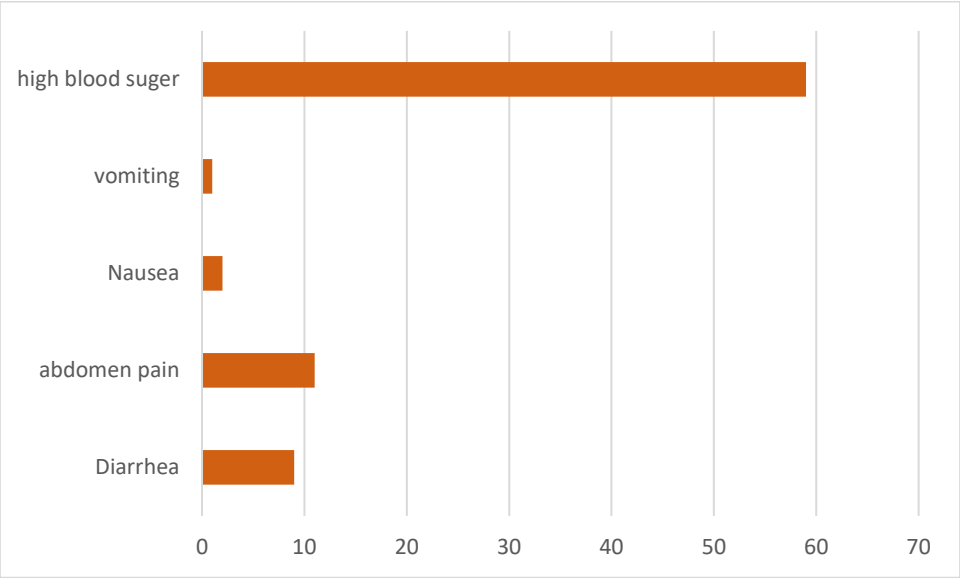

Figure 5. Health state and symptoms of COVID-19 patients

As shown in **Figure 6**, only 28% of the patients had elevated ALT and AST levels (liver enzymes), ranging between 90-160 U/L and 60-110 U/L, respectively, compared with 72% of the patients who had normal liver enzymes levels, ranging between 7-56 U/L and 10-40 U/L, respectively.

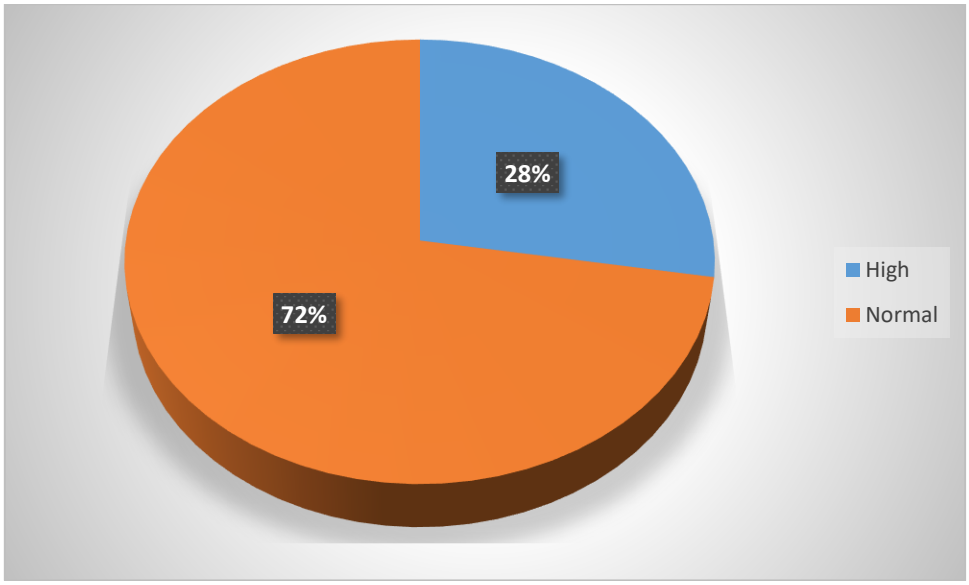

Figure 6. Liver enzyme (ALT and AST) levels of COVID-19 patients

In terms of albumin levels, 50% of the infected patients had 4 g/dL albumin, 32% had 3g/dL albumin, and only 18% had 4.5-5 g/dL albumin (**Figure 7**).

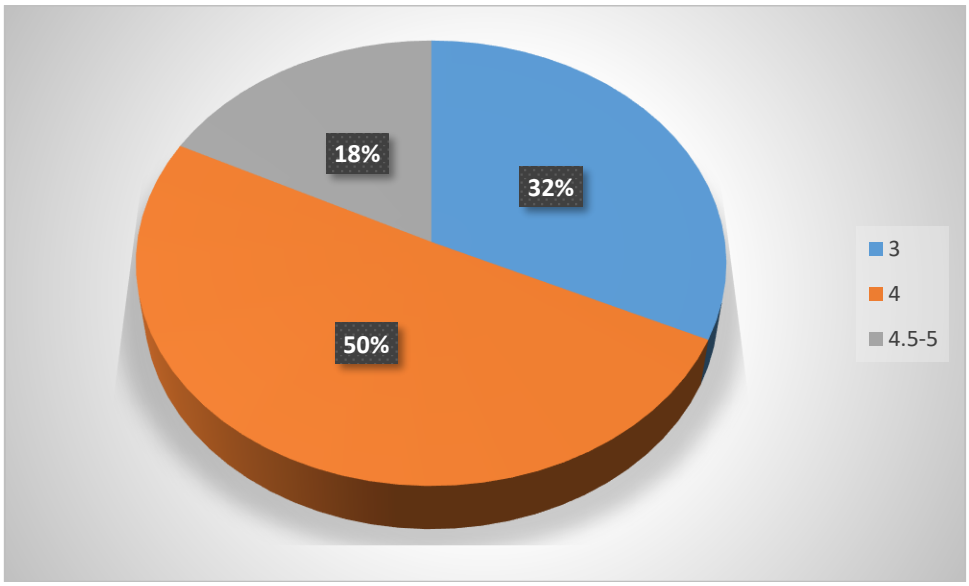

Figure 7. Albumin levels of COVID-19 patients

According to the treatment protocol in the hospital, all 200 infected patients received ceftriaxone (Rocephin), azithromycin (Xithrone), and zinc; in addition to that, Controloc was given to 189 patients, while Peptazol was given to 15 patients. About 166 patients received enoxaparin sodium (Clexane); 136 received paracetamol (Perfalgan); 179 were given hydroxychloroquine (Plaquenil); 91 patients were given levofloxacin (Tavanic); 4 patients were given epoetin alfa (EPREX); 89 were given Becozyme; 10 were given prednisolone (Solupred) (**Figure 8**).

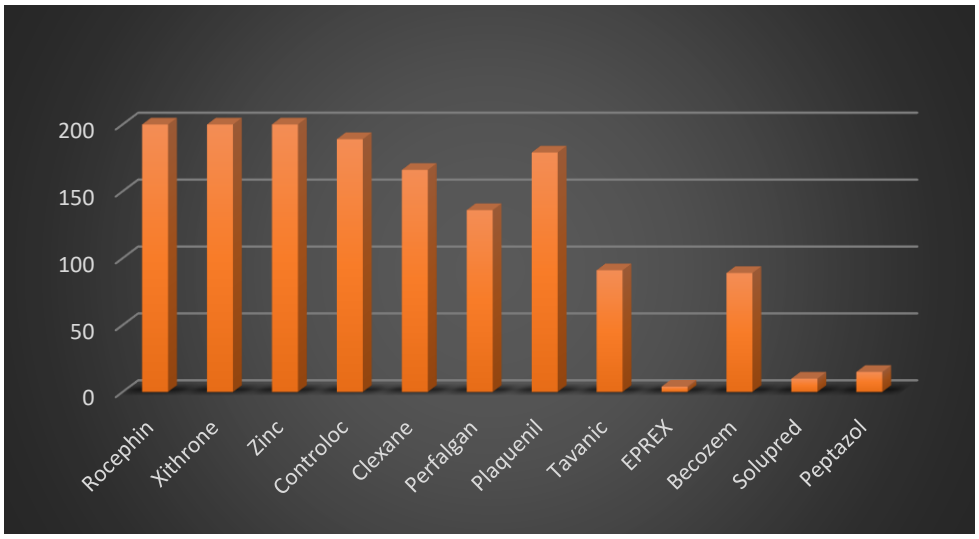

Figure 8. Treatment protocol for COVID-19 patients

According to the severity of the patients, it was recorded that only 10% of the cases needed to be transferred to ICU, while the rest of the patients were managed in normal hospital rooms (**Figure 9**).

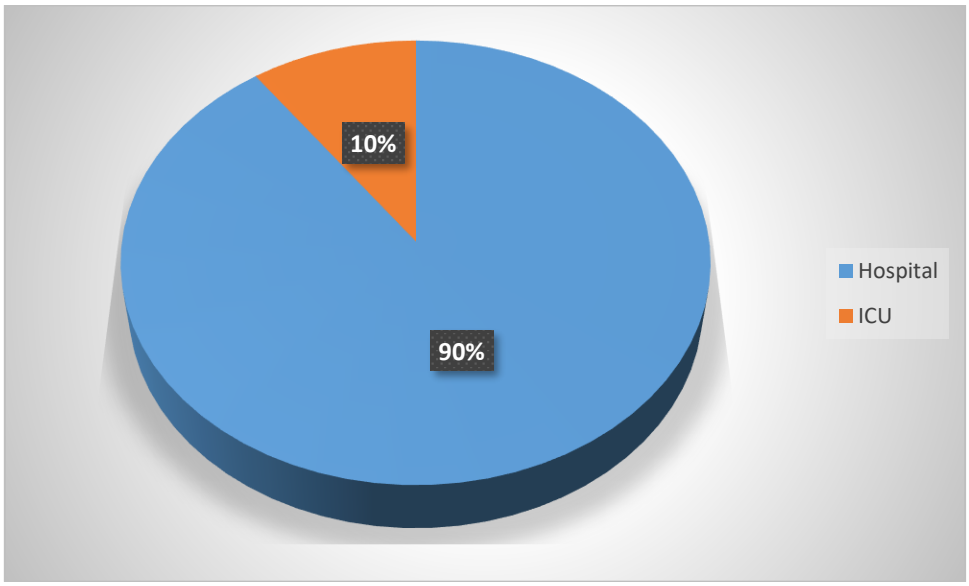

Figure 9. State of COVID-19 patients

According to **Figure 10** and **Figure 11**, only 3% of COVID-19 patients succumbed to death, of which 67% were male, and 33% were female.

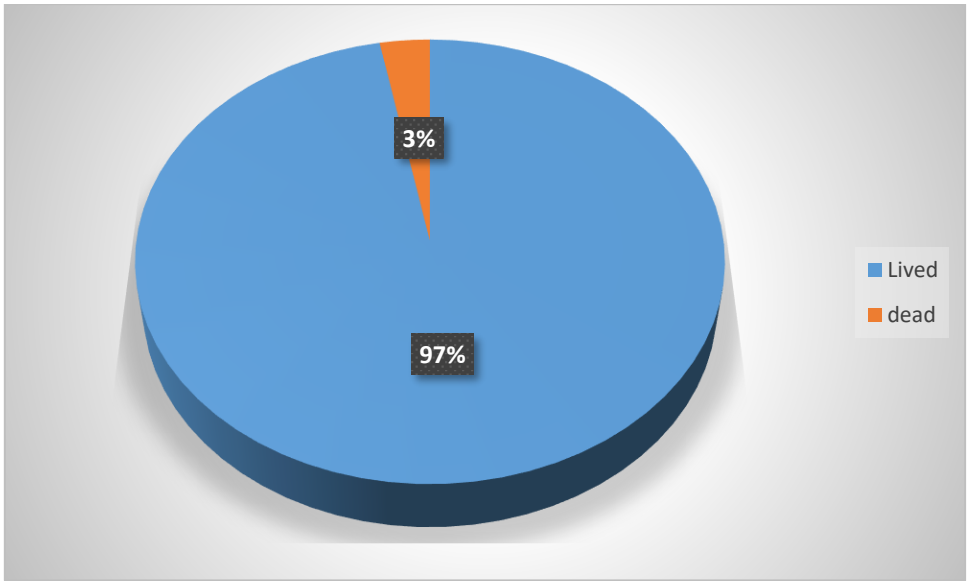

Figure 10. Mortality rate among COVID-19 patients

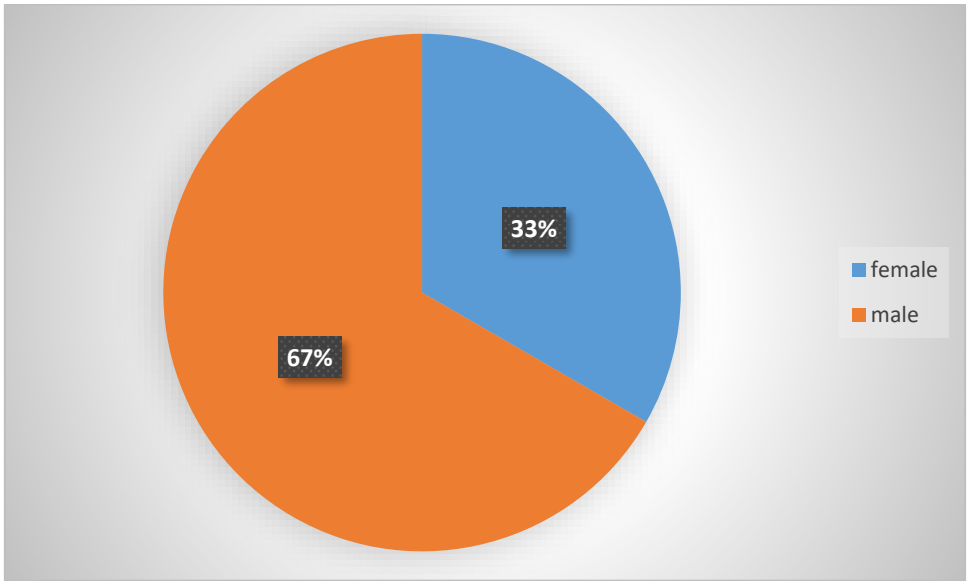

Figure 11. Gender of COVID-19 patients who succumbed to death

In regard to COVID-19 mortality, it was recorded that 67% of the patients who passed away were managed in ICU, while only 33% of the patients were managed in general wards (**Figure 12**).

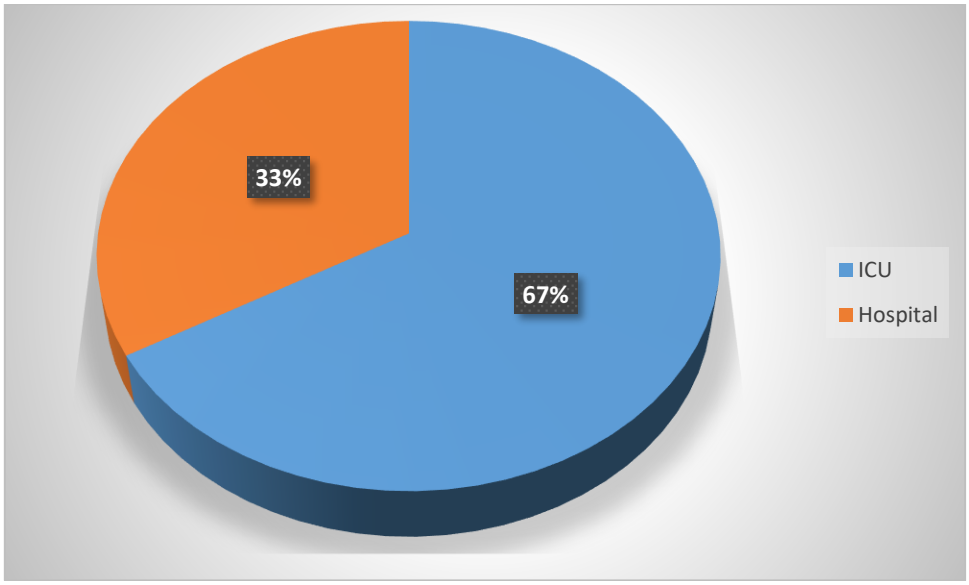

Figure 12. Management location of COVID-19 patients who passed away

According to **Figure 13**, **Figure 14**, and **Figure 15**, 67% of the patients who passed away had high blood glucose levels and liver enzyme (ALT and AST) levels, with normal serum albumin; on the other hand, 33% of the patients who passed away had normal liver enzyme levels and glucose levels, with low albumin levels.

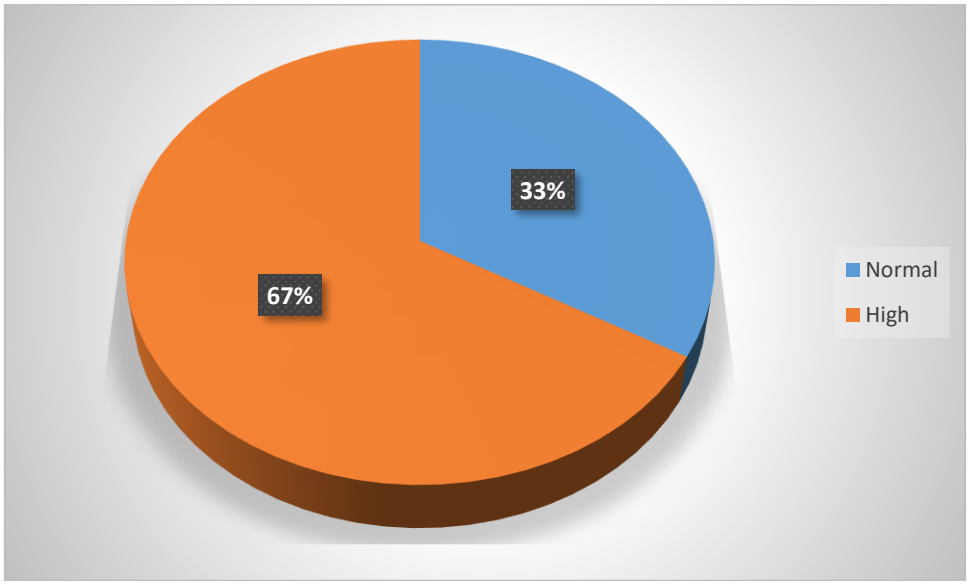

Figure 13. Blood glucose levels of COVID-19 patients who passed away

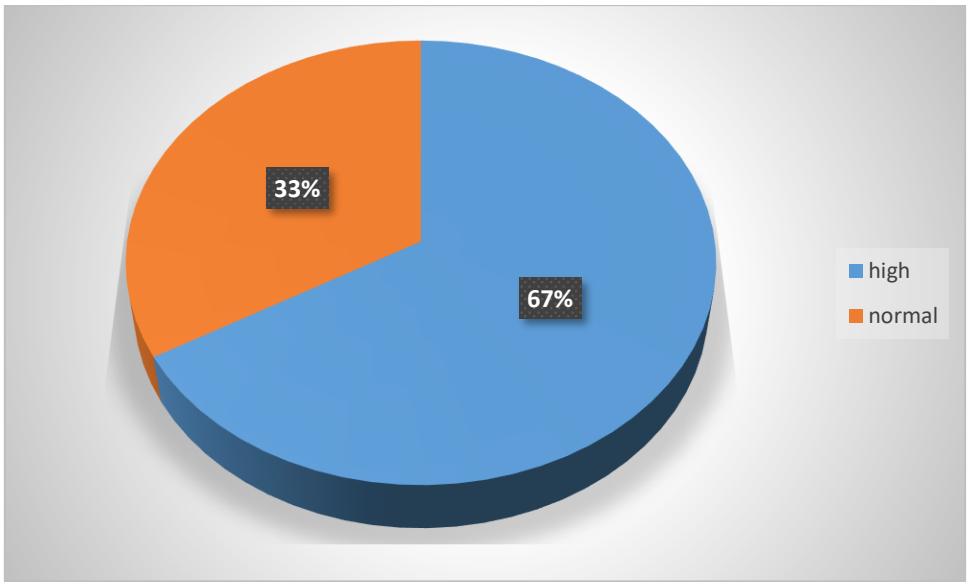

Figure 14. Liver enzyme levels of COVID-19 patients who passed away

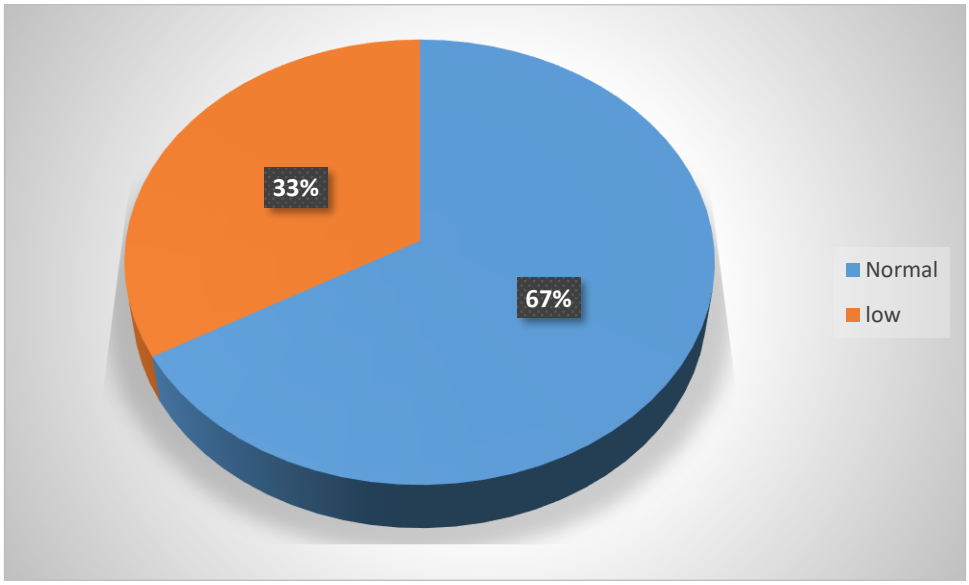

Figure 15. Serum albumin levels in COVID-19 patients who passed away

According to **Figure 16**, only 17% of the patients who passed away were from the younger age group (22-40 years old), whereas 83% of them were elderly patients (55-90 years old).

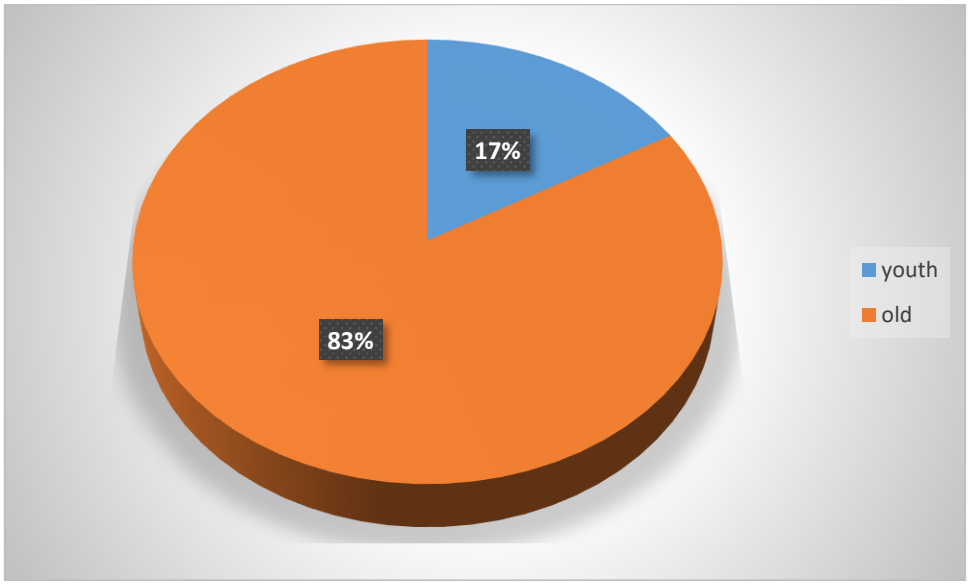

Figure 16. Age group of COVID-19 patients who passed away

4. Discussion

The data analysis revealed that the majority of COVID-19 patients were elderly patients. This was also seen in other studies that reported higher prevalence of COVID-19 infection in elderly male [23-25].

Almost a third of the patients had high blood glucose levels. Diabetes is considered to be a factor that increases the risk of COVID-19 infection as it facilitates viral entry into cells and causes poor immune response in patients [26,27]. Moreover, these patients have a higher risk for ICU admission.

Other than that, 5% of the patients were hypertensive. In a previous study, hypertensive patients who were infected with COVID-19 had stronger inflammatory response, higher CRP levels, higher risk of ICU admission, longer hospital stay, and a need for longer oxygen therapy compared to non-hypertensive patients [28].

All infected patients in this study had anosmia and ageusia as specific symptoms for COVID-19 infection. It is noticed that these two symptoms are early symptoms of COVID-19, and they frequently occur in patients infected with COVID-19 [29].

In regard to the state of the liver in COVID-19 patients, 28% of them had elevated liver enzymes (ALT and AST), and 32% showed a decrease in serum albumin. These abnormal test results indicate the severity of the cases [30,31].

Liver injury in COVID-19 patients may be due to a direct attack in response to the inflammatory cytokine storm triggered by the infection. Second, it may be related to the side effects of COVID-19 drugs used during hospitalization, which should be evaluated and monitored on a regular basis. Third, COVID-19 patients who have concomitant liver disease may be at risk of developing severe liver injuries [31,32].

Furthermore, only 10% of the cases were managed in ICU, while the rest of the patients were managed in normal hospital rooms. The mortality rate in this study was 3%, and it was significantly high among elderly male patients with high blood glucose level and liver enzymes as well as those managed in normal hospital rooms.

That indicates that the incidence of liver injury in severe cases of COVID-19 is higher than those with mild illness. Liver disease is a risk factor that worsens in patients with COVID-19, and hence it is necessary to pay attention to the occurrence of liver disease in the diagnosis and treatment of COVID-19, in order to

develop effective individualized treatment protocol [33].

Although laboratory abnormalities in liver function tests are widespread in COVID-19 patients, we can rule out the possibility that liver dysfunction is not a significant characteristic of COVID-19 and may not have serious clinical effects. This was also reported in a study conducted by Yafei Zhang [34].

This explains the reduced mortality and lower percentage of patients who progressed into severe illness requiring ICU admission.

5. Conclusion

Patients with diabetes, hypertension, or liver disease are at high risk of ICU admission or death. Hence, it is important to pay attention to these problems in the diagnosis and treatment of COVID-19, in order to develop a suitable individualized treatment protocol. There was a correlation between the mortality in COVID-19 patients and both, high blood sugar and liver enzymes levels. It can be attributed to the correlation between diabetes and liver disease as every disease may be a complication to the other. As recorded in many studies [16-22], COVID-19 can lead to increased blood sugar levels in addition to ALT and AST levels. Another theory is that COVID-19 may affect the liver and hence people with chronic liver disease [16-22].

Disclosure statement

The authors declare no conflict of interest.

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