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ORIGINAL ARTICLE

Outcomes for Co-infection of Chronic Hepatitis C and COVID-19: A Multicenter study

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ABSTRACT

Keywords HCV, Liver, COVID-19.

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Background The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The extreme rise in inflammatory cytokines resulting in significant morbidity and mortality, especially in presence of co-morbid illness such as chronic liver disease. **Methodology:** This was a case-control study, carried among the target population at Quarantine departments at Aswan governorate. Patients were subjected to complete history taking, physical examination and investigations including full labs, pelviabdominal ultrasound and chest computerized tomography (CT). Confirmation of COVID-19 infection done by PCR from nasopharyngeal swabs. Patients divided into two groups according to presence or absence of chronic hepatitis C virus (HCV) infection. **Results:** There was statistically significant correlation between severity of COVID-19 infection and presence of chronic HCV infection (P-value < 0.001). Severe and critically-ill COVID-19 cases are more among the HCV infected patients. There was a highly significant difference in Child-Pugh score before and after COVID-19 infection (P-value < 0.001).**Conclusion** HCV infection is associated with more severe disease and higher mortality in patients co-infected with COVID-19 virus. The severity of liver impairment was associated with poor clinical outcomes in COVID-19 patients.

BACKGROUND

Coronavirus is an enveloped single stranded RNA virus, belonging to the Coronaviridae family. Its name is due to the fact that microscopic images show a ‘ crown’ around it. Coronavirus was associated with specific diseases including severe acute respiratory syndrome (SARS) in 2003 and Middle Eastern Respiratory Syndrome (MERS) in 2012 which occurred by SARS-CoV and

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MERS-CoV, respectively. The current pandemic wave of coronavirus has been named as Severe Acute Respiratory Distress Syndrome Coronavirus 2 (SARS- CoV-2) [**1].**

There is wide variation of the clinical features of COVID-19 ranging from asymptomatic infection to acute respiratory distress syndrome and multi-organ failure. This progression was found to be associated with extreme rise in different inflammatory cytokines **[2].**

Hepatitis C virus (HCV) is a major health problem affecting more than 170 million people all over the world. Unfortunately, progression to chronic infection occurs in most of infected persons. Cirrhosis, portal hypertension, liver cell failure and hepatocellular carcinoma may occur as results of chronic HCV infection [**3].** It is a small enveloped RNA virus [**4]** & can be transmitted through many routes include blood-borne transmission, surgical interventions, intravenous drug use, sexual route, occupational exposure, or mother to baby transmission [**5].**

Manifestations of the infection by COVID-19 on the liver are generally mild, transient and have no effect on the course of COVID-19 disease except most severe forms resulting from the cytokine storm, which cause multi-organ failure including the liver **[6].**

PATIENTS AND METHODS

This was a case control study, carried among the target population at Quarantine departments of Aswan University Hospital, Aswan Specialized Hospital, Daraw General Hospital and Edfu General Hospital since 30th September 2020 to 30th June 2021.

In this study, 200 patients, older than 18 years, infected with COVID-19 virus were included. Accordingly, patients were categorized into 2 groups. Group I involves 100 patients with chronic HCV with 55 patients of them evident to have liver cirrhosis based on liver function tests and pelvi-abdominal ultrasound. Group II involves 100 patients who are negative for HCV infection.

An informed consent was obtained from all enrolled participants. Patients younger than 18 years and who have liver cirrhosis due to any cause rather than HCV were excluded from the study.

All enrolled patients were subjected to complete history taking, through physical examination especially of COVID-19 infection such as fever, dry cough, dyspnea, bone pain, headache, loss of taste, loss of smell, diarrhea, wheeze, hemoptysis, sore throat, rhinorrhea, palpitation, vomiting, anorexia, fatigue and myalgia and history of chronic HCV manifestations such as jaundice, hematemesis, melena, abdominal swelling, lower limb edema, and deterioration of conscious level.

From all enrolled patients, blood samples were taken and allowed to clot at room temperature (range 18°C to 20°C). Samples were collected for different blood tests like CBC, blood urea, serum creatinine, international normalized ratio (INR), liver function test, inflammatory Markers (erythrocyte sedimentation rate (ESR), C- reactive protein (CRP)) and D-Dimer. Carful history taking, good clinical examination and previously mentioned investigations were done to every enrolled patient. Polymerase chain reaction (PCR) through naso-pharyngeal swabs were done to all patients. Severity of COVID-19 infection was estimated for all patients according to National

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Institute of Health (Table 1). Imaging study in the form of abdominal ultrasonography was performed. Chest Computerized Tomography (CT) was also performed and COVID-19 Reporting and Data System (CO-RADS) classification was estimated to each patient (Table 2). Child-Pugh score was estimated to all cirrhotic patients before and after infection with COVID-19 (Table 3).

Statistical analysis:

The patients were grouped into two groups: group I is formed of 100 patients with chronic HCV infection, group II is formed of 100 patients negative for HCV infection. Data were collected, coded, revised and entered to the Statistical Package for Social Science (SPSS) version 23. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non-parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5. The comparison between more than two groups with quantitative data and parametric distribution was done by using One Way Analysis of Variance (ANOVA) test and Kruskall-Wallis test was used in the comparison between more than two groups with quantitative data and non-parametric distribution. Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters in the same group. The P-value was considered significant as the following: $P > 0.05$: Non significant, $P < 0.05$: Significant, $P < 0.01$: Highly significant.

RESULTS:

This study included 200 patients infected with COVID-19 infection; who attended at Quarantine departments of many hospitals in Aswan governorate, from 30th September 2020 to 30th June 2021. Based on the presence or absence of HCV, the studied patients were categorized into 2 groups. The mean age was 53.5 years ± 16.5 years, the minimum age was 19 years and the maximum age was 93 years. 117 patients were men (53.5%) and 83 patients were females (46.5%). Only one third of participants were smokers. 23% & 50% of patients of group I were diabetic and hypertensive respectively, however 20% & 33% of patients of group II were diabetic and hypertensive respectively. As regard COVID-19 symptoms, Figure (1) shows that symptoms of COVID-19 infection were more frequent in group I. Regarding the complete blood count (CBC), the mean ± SD of hemoglobin, white blood cells (WBCs) count, lymphocytes count and platelets count in patients of group I were 9.99 ± 1.29 g/dl, 16.44 ± 6.16 /mm^3, 3.38 ± 1.88 /mm^3 and 162 ± 65.08 /mm^3 respectively, and in patients of group II were 11.3 ± 1.83 g/dl, 15.25 ± 8.81 /mm^3, 2.7 ± 1.8 /mm^3 and 228.71 ± 101.17 /mm^3 respectively. There was statistically significant difference between both groups as regard hemoglobin level and platelets count. As regard other laboratory investigations, there was no statistically significant difference between the two groups as regard Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), D-dimer and serum creatinine while there was statistically significant difference as regard bilirubin, ESR and CRP, being at higher levels in group I patients. Also, group I patients showed significant decrease in

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serum albumin level and increase in INR value in comparison to group II patients (P-value < 0.00001).

There is highly significant correlation between HCV infection and severity of COVID-19 infection (P-value < 0.00001). Severe and critically-ill COVID-19 cases are more among the HCV infected patients. There was a significant difference in chest CT findings between (group 1) and (group 2) (P-value < 0.01) **(Table 4)**. There was a highly significant difference in Child-Pugh score in patients with liver cirrhosis before and after COVID-19 infection (P-value < 0.0001) with more raise in the score points after COVID-9 infection.

According to COVID_19 outcome, it is significantly related to the HCV infection (P-value < 0.001). Mortality and morbidity rates were more common among HCV infected patients **(Table 5).**

DISCUSSION:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in late December 2019, with the epicenter in Wuhan, China, and, since that time, it has infected more than 135 million people, resulting in significant morbidity and mortality worldwide **[10].** Many studies were concerned with clinical outcomes of patients with chronic liver disease (CLD) and COVID-19 infection. According to the Centers for Disease Control, patients with CLD might be at increased risk for severe illness with COVID-19 infection **[11].**

Mirzaie et al. **[12]** found that the most common symptoms in patients with SARS-CoV-2 and HCV were fever (77.3%), cough (63.6%), dyspnea (40.9%), and gastrointestinal symptoms (31.8%). Moreover, in a study by Cerbu et al., **[13],** it was found that the patients in the active HCV group experienced more signs and symptoms, with fatigue being significantly more prevalent (83.8% vs. 64.2%, P-value < 0.0001), followed by myalgia (54.8% vs. 34.7%, P-value < 0.0001), and fever (87.0% vs. 72.6%, P-value < 0.0001)**.** In study in our hands, we demonstrated that severity of COVID-19 infection is significantly correlated to presence of HCV infection (P-value < 0.0001), in which severe and critically ill COVID-19 cases were more among the HCV infected patients with fever (98%) & dry cough (99%) as predominant symptoms.

In a study by Ronderos et al., patients with HCV presented to the hospital earlier than patients without HCV, and, on hospital admission, had higher lymphocytic count and lower CRP, however, had worse serum creatinine, aspartate aminotransferase (AST), conjugated bilirubin, lower hemoglobin, and lower platelet count. In study in our hands, we found that platelets count and albumin level were significantly lower in group I while level of bilirubin (total and direct), ESR, CRP and INR values were significantly higher **[14]**. These changes may be explained by higher serum pro-inflammatory cytokines and levels in patients with abnormal liver function compared to those with normal liver function **[15, 16]**.

CT chest findings are usually correlated with severity of COVID-19 infection. Cerbu et al., **[13]** found that lung involvement of more than 40% of the lung parenchyma affected by the SARS-CoV-2 infection on chest CT imaging was significantly more prevalent in patients with active HCV infection (32.2% vs. 7.3%, P-value < 0.0001)**.** Also this is consistent with what Afify et al. **[17]** found. They found that patients with liver cirrhosis were more likely to show combined

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ground-glass opacities and consolidations in their chest CT findings: 28 (43.75%) vs 4 (6.55%), respectively (P-value < 0.001)**.** We illustrated that there is a significant difference in CT chest findings between both groups, being more advanced in group I patients (P-value < 0.01).

It was found that patients with SARS-CoV-2 infection who have pre-existing cirrhosis, 96% require hospital admission or a prolongation of hospital stay, and infection is frequently associated with deterioration of liver function and higher mortality **[11].** In a recent study, Afify et al., **[17]** found that mortality was higher in patients with liver cirrhosis with severe COVID-19 infection: 33 (51.56%) versus 9 (14.75%), respectively (P-value < 0.001)**.** In addition, a study by Xiao et al., **[18]** showed that COVID-19 patients with cirrhosis had larger proportion of more severely disease and higher mortality**.** It was concluded also that Child-Pugh score at hospital admission may predict COVID-19 severity and also, Child-Pugh score was highly associated with non-survival among those patients**.** Marjot et al., **[19]** found that there was highly significant difference among COVID-19 patients who survived versus who died as regards Child-Pugh score (P-value < 0.001). In our study we illustrated that there was a highly significant difference in Child-Pugh score before and after COVID-19 infection (P-value < 0.001).

It remains unknown whether hepatic injury is caused by the direct viral cytopathic effect or due to severe inflammatory response resulting in liver damage **[20]**. Angiotensin-converting enzyme 2 (ACE2), is expressed by hepatocytes and bile duct cells and they act as receptors of the virus **[21]** resulting in disturbance of liver functions **[22]**. Moreover liver biopsies showed a significant increase in mitotic process and hepatocytes swelling, suggesting that it may induce apoptosis of liver cells. Additionally, virus was detected in liver tissue **[23]**.

Conclusion HCV infection is associated with more severe disease and higher mortality in patients co-infected with COVID-19 virus. The severity of liver impairment was associated with poor clinical outcomes in COVID-19 patients.

Abbreviations

ACE2	Angiotensin-converting enzyme 2
ALT	Alanine aminotransferase
ANOVA	One Way Analysis of Variance
AST	Aspartate aminotransferase
CBC	Complete blood count
CO-RADS	(COVID-19)-Reporting and Data System
COVID-19	Coronavirus disease 2019
CRP	C- reactive protein
CT	Computerized tomography
ESR	Erythrocyte sedimentation rate
HCV	Hepatitis C virus
INR	International normalized ratio
IQR	Inter quartile range
IRB	Institutional Review Board

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MERS	Middle Eastern Respiratory Syndrome
PCR	Polymerase chain reaction
WBCs	White blood cells
SARS- CoV-2	Severe Acute Respiratory Distress Syndrome Coronavirus 2
SD	Standard deviation
SPSS	Statistical Package for Social Science

Declarations

-Ethics approval and consent to participate:

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki after approval from Institutional Review Board (IRB) for human subject research at Aswan University Hospital. (Serial: 342/2/19). An informed consent was obtained from all enrolled participants before enrolment to the study. Hazards about COVID-19 infection especially HCV patients also discussed with the participants.

-Consent for publication:

Non applicable.

-Availability of data and material:

Data & material were available for the study.

-Competing interests:

The authors have no conflict of interest to declare.

-Funding:

None.

-Authors' contributions:

All authors read and approved the final manuscript. MT is a Lecturer of Tropical medicine & Gastroenterology department at the faculty of medicine, Aswan University (The first & corresponding author of the work). EFM is a Professor of Tropical medicine & Gastroenterology department at the faculty of medicine, Assuit University, and revised the work. AAA is a Lecturer of Tropical medicine & Gastroenterology department at the faculty of medicine, Aswan University, and interpreted the data of the work. KBD is a Resident physician of Tropical medicine & Gastroenterology department at the faculty of medicine, Aswan University, and collected the data of the work.

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LIST OF TABLES:

Table (1): Severity of COVID-19 infection **[*7*]**.

Mild	• No pneumonia • No hypoxia
Moderate	• Pneumonia • No hypoxia
Severe	If any of the following criteria is met: - • SpO2 <92% on room air. • PaO2/FiO2 <300 mm Hg. • Respiratory rate >30 breaths/min. • Chest Radiology showing lung infiltrates >50% or progressive lesion within 24 - 48 hours.
Critically-ill	• SpO2 <92% on room air, or • Respiratory rate >30 breaths/min, and • PaO2/FiO2 <200 mm Hg. Despite oxygen therapy and/or organ dysfunction

Table (2): CO-RADS classification **[8]**.

CO-RADS Category	**Level of Suspicion for Pulmonary**	**Involvement of COVID-19 Summary**
1	**Very low**	**Normal or noninfectious**
2	**Low**	**Typical for other infection but not COVID-19**
3	**Equivocal/unsure**	**Features compatible with COVID-19 but also other diseases**
4	**High**	**Suspicious for COVID-19**
5	**Very high**	**Typical for COVID-19**

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Table (3): Child-Pugh score **[*9*]**.

Parameter	**Assign 1 point**	**Assign 2 points**	**Assign 3 points**
Ascites	Absent	Slight	Moderate
Bilirubin	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2 (Mild to moderate)	Grade 3-4 (Severe)

Class A=5-6 points, Class B=7-9 points, Class C=10-15 points.

Table (4): Comparison between the study groups as regards severity of COVID-19 infection & Chest CT Findings

		Group I	Group II	Total	P-value
Severity of COVID-19	Mild	8	24	32	< 0.00001
	Moderate	25	38	63	
	Severe	45	25	70	
	Critically-ill	22	13	35	
Chest CT Findings	CO-RADS 1	10	27	37	< 0.01
	CO-RADS 2	0	0	0	
	CO-RADS 3	31	26	57	
	CO-RADS 4	9	14	23	
	CO-RADS 5	50	33	83	

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Table (5): Relation between HCV infection and COVID-19 outcome

		Group 1	Group 2	Total
Outcome	Improved	57	77	134
	Detoriated	10	0	10
	Death	33	23	56
Total		100	100	200

LIST OF FIGURES

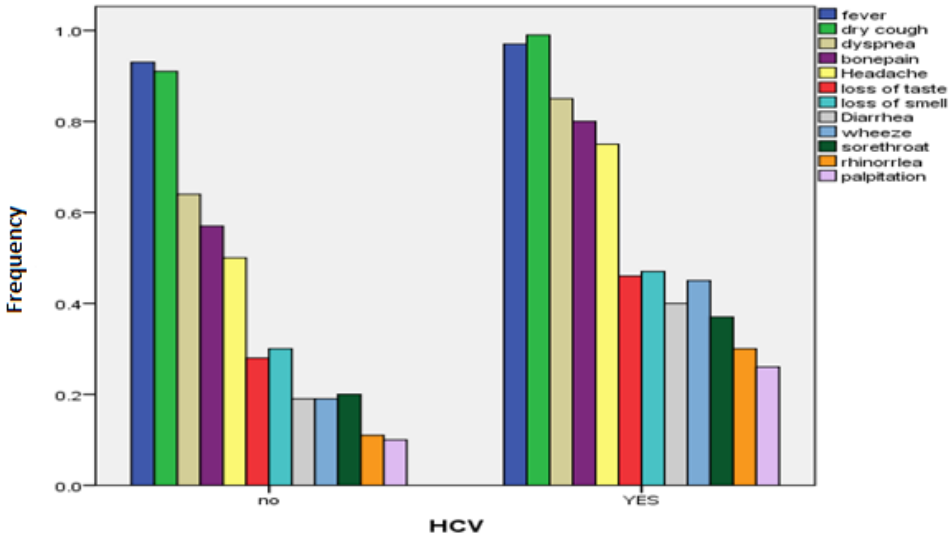

Figure (1): Comparison of COVID-19 symptoms frequency between the two groups.

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