

# Impact of Treatment of Chronic HCV Patients by Direct-Acting Antiviral Drugs (DAADs) on COVID-19 Disease Frequency and Severity

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**Background and study aim:** Since both SARS-CoV-2 and Hepatitis C virus (HCV) are positive-sense RNA viruses, it is logical to consider those nucleotide analogs found to be successful against HCV could potentially demonstrate similar efficacy against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). The present study aims at estimating the frequency and severity of COVID-19 in HCV-treated patients.

**Patients and Methods:** A cross-sectional study was accomplished. The study enrolled 200 HCV-infected individuals who were eligible for DAADs therapy and had received treatment in 2019 before the COVID-19 pandemic. The treatment regimen for all patients in the study consisted of Sofosbuvir plus Daclatasvir for a duration of 3 months, except for three patients who received the same treatment for 6 months as a result of liver cirrhosis.

**Results:** The enrolled patients attained a mean age of 53.6 years. Most patients (74%) came from rural areas, and forty-

seven (23.5%) patients had different chronic diseases, with hypertension (17.5%) and diabetes mellitus (13%) being the most common. The majority, 183 (91.5%), of patients achieved sustained virological response (SVR). Only 12 (6%) patients developed COVID-19. In most patients (75%), the duration of infection till seroconversion was 10 days. All COVID-19 patients in the current study were ultimately improved with no mortality. Nine (75%) of SARS-CoV-2 infected patients developed infection one year after the last dose of DAADs. Most of those patients rarely follow the recommended hygienic measures.

**Conclusion and recommendations:** Previous treatment of chronic hepatitis C by Sofosbuvir plus Daclatasvir protects against infection of SARS-CoV-2. Future large, randomized trials are warranted to draw firm conclusions.

## INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has had a profound impact on the globe, with millions of people around the globe affected by the resulting coronavirus disease (COVID-19). The virus has caused several reported deaths and ongoing morbidity, making it a major global health challenge [1].

Both hepatitis C virus (HCV) and coronaviruses are positive-sense single-stranded RNA viruses, which depend upon an RNA-dependent

RNA polymerase (RdRp) for genome replication and transcription [2, 3].

Therefore, RdRp is considered a critical target for successful antiviral treatment due to its high conservation at the amino acid level in the active site. In vitro studies have shown that sofosbuvir is capable of binding to SARS-CoV-2 RdRp, which results in a reduction in the protein's function and ultimately leads to the eradication of the virus [4]. Antiviral agents that act by inhibiting polymerases through nucleotide and nucleoside analogs are a potential

class of therapeutic agents for treating COVID-19 [4, 5]. Sofosbuvir is an antiviral drug that has been affirmed for clinical use and has shown to be highly effective against different genotypes of the Hepatitis C Virus (HCV) [6]. The daclatasvir and sofosbuvir safety has been established in patients experiencing significantly impaired renal function [7].

In silico and in vitro studies have indicated that designates the binding of sofosbuvir/daclatasvir and ribavirin to the RNA-dependent RNA polymerase of SARS-CoV-2 [8-10].

Sofosbuvir and daclatasvir have the potential to be accessible and cost-effective treatment agents for COVID-19, considering their availability and affordability. Some authors were persuaded to conduct a clinical trial to appraise the consequence of direct-acting antiviral drugs (DAADs) such as Sofosbuvir, Daclatasvir, and Ribavirin on COVID-19. Published data showed challenging findings for combining Daclatasvir and Sofosbuvir in treating COVID-19 patients [11].

The present work intended to assess the COVID-19 severity and prevalence in HCV patients. Also, to judge the consequence of the previous treatment of HCV patients by (DAADs) on COVID-19 infection.

## PATIENTS AND METHODS

### Study setting and design:

A cross-sectional study was undertaken at Al-Rajhi Liver Hospital. It was conducted in the period between July 2021 and April 2022.

### Study population:

The study enrolled 200 individuals with known chronic HCV infections who were eligible for the DAADs in 2019.

### Inclusion criteria:

- 1) HCV patient with or without LC.
- 2) Age >18 years old.
- 3) Received the DAADs in 2019.

### Exclusion criteria:

Patients who experienced any of the following events were excluded; combined HCV with HIV

or HBV infection, age  $\leq$  18 years old, breast-feeding or pregnant patients, autoimmune liver disease, multiorgan failure, active cancer, and/or renal insufficiency, immunosuppressive drugs and/or confirmed diagnosis of SARS-CoV-2 before starting DAADs.

### Methodology

All patients were assisted using a questionnaire with 4 domains (**supplementary table 1**):

- 1- Personal and demographic data, socioeconomic status, and other comorbid diseases.
- 2- Drug therapy for HCV, its duration, type of response, and the period between the end of the last dose of HCV treatment and the emergence of symptoms of COVID-19.
- 3- Adherence of the patients to precautions against SARS-COV-2.
- 4- SARS-CoV-2 infection:
  - The definition of SARS-CoV-2 infection used in the study adhered to the suspected and confirmed case definitions provided by the Ministry of Health and Population.
  - Onset, course, duration, symptoms (Respiratory or GIT or others), hospital admission history, and need for oxygen therapy or ICU admission.
  - Clinical outcomes: time of hospital discharge or time of recovery, requirement for invasive mechanical ventilation, and/or death if occurred.

**The following investigation was obtained from each patient.**

#### a) Laboratory:

- Complete blood count.
- Liver enzymes.
- PCR for HCV, C-Reactive Protein, ESR, LDH, serum ferritin.
- Nasopharyngeal Swab for SARS-COV-2 results if were done.

**b) Imaging** included chest X-ray and computed tomography if needed.

**Supplementary Table 1**

<b>Questionnaire for Chronic HCV treated patients to detect COVID-19</b>
<b>Patient name:</b>
<b>Age:</b>
<b>Social Status:</b>
<input type="radio"/> Married <input type="radio"/> Single <input type="radio"/> Divorced <input type="radio"/> Widow
<b>Gender:</b>
<input type="radio"/> Male <input type="radio"/> Female
<b>Residence:</b>
<input type="radio"/> Urban <input type="radio"/> Rural
<b>Occupation:</b>
<b>What is the highest academic qualification?</b>
<b>Do you smoke?</b>
<input type="radio"/> Yes <input type="radio"/> No
<b>Do you have any chronic disease?</b>
<input type="radio"/> Yes <input type="radio"/> No
<b>The chronic health problems and what are the daily medications</b>
<input type="radio"/> ? <input type="radio"/> Diabetes, hypertension, chest disease <input type="radio"/> s, cardiac diseases, or others and the drugs used for the patient's condition
<b>Do you have current HCV symptoms?</b>
<input type="radio"/> No <input type="radio"/> Sore muscle <input type="radio"/> Joint pain <input type="radio"/> Fever <input type="radio"/> Nausea or poor appetite <input type="radio"/> Itching <input type="radio"/> Jaundice or dark urine
<b>Do you have Liver cirrhosis?</b>
<input type="radio"/> Yes <input type="radio"/> No
<b>What about the virological response after treatment?</b>
<input type="radio"/> SVR <input type="radio"/> Failure of response <input type="radio"/> Relapse <input type="radio"/> NO PCR had been done
<b>What regimen of therapy for HCV and its duration?</b>
<input type="radio"/> Sofosbuvir and Daclatasvir 3 months. <input type="radio"/> Sofosbuvir and Daclatasvir 6 months. <input type="radio"/> Sofosbuvir, Daclatasvir, and ribavirin 3 months. <input type="radio"/> Sofosbuvir, Daclatasvir, and ribavirin 6 months.
<b>What is the period between the end of the last dose of DAADs and the emergence of symptoms of Coronavirus if happens?</b>
<input type="radio"/> <3 months <input type="radio"/> 3-6 months <input type="radio"/> 6-9 months <input type="radio"/> 9-12 months <input type="radio"/> >1 year <input type="radio"/> No COVID-19 infection happened
<b>In the last months, Did you attend social gatherings outside your home?</b>

<ul style="list-style-type: none"> <li><input type="radio"/> Most days (&gt; 8 days)</li> <li><input type="radio"/> Some days (4-7days)</li> <li><input type="radio"/> Few days (&lt; 3 days)</li> <li><input type="radio"/> Not had any other social interaction</li> </ul>
<p><b>Did you wear a facial mask in your daily activity?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Always</li> <li><input type="radio"/> Usually</li> <li><input type="radio"/> Rare</li> <li><input type="radio"/> Never</li> <li><input type="radio"/> Others</li> </ul>
<p><b>In the past month, have you been in contact with a person known to have been diagnosed with COVID-19?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Yes</li> <li><input type="radio"/> No</li> </ul>
<p><b>How often are you doing the recommended pandemic hygiene, like washing your hands frequently, avoiding touching your face, covering coughs, and avoiding frequently touched surfaces in public places?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> All the time, I am being extra careful.</li> <li><input type="radio"/> Most of the time. I am trying to do my best.</li> <li><input type="radio"/> Sometimes, I do it if I remember it.</li> <li><input type="radio"/> Rarely, I don't worry about these things.</li> </ul>
<p><b>How often have you used public transport?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Most days (&gt;8 days).</li> <li><input type="radio"/> Some days (4-7 days).</li> <li><input type="radio"/> Few days (&lt; 3 days).</li> <li><input type="radio"/> Not using public transport.</li> </ul>
<p><b>Did you have COVID-19?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Yes (confirmed)</li> <li><input type="radio"/> Yes (but suspected)</li> <li><input type="radio"/> No</li> </ul>
<p><b>During the past months, did you have an illness that you think might have been COVID-19, the novel Coronavirus?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Yes</li> <li><input type="radio"/> No</li> </ul>
<p><b>When did the illness Start?</b></p>
<p><b>Have you been told by a physician or healthcare provider that you have had covid 19?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Yes</li> <li><input type="radio"/> No</li> </ul>
<p><b>Were you tested for COVID-19 by PCR?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Yes</li> <li><input type="radio"/> No</li> </ul>
<p><b>What is the result of the PCR test for Coronavirus?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Positive</li> <li><input type="radio"/> Negative</li> <li><input type="radio"/> Not done</li> </ul>
<p><b>Which symptoms did you have during the illness?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Fever, chills/ shivering</li> <li><input type="radio"/> Shortness of breath /increased</li> <li><input type="radio"/> Newly developed Cough /increased</li> <li><input type="radio"/> Sore throat</li> <li><input type="radio"/> Funny nose</li> <li><input type="radio"/> Nausea, vomiting, diarrhea</li> <li><input type="radio"/> Generalized body aches, fatigue</li> <li><input type="radio"/> Headache</li> <li><input type="radio"/> Chest pain</li> <li><input type="radio"/> New Inability to taste or smell</li> <li><input type="radio"/> No symptoms</li> <li><input type="radio"/> Others</li> </ul>
<p><b>Have you had radiological evidence of pneumonia chest X-ray or MSCT?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Yes</li> </ul>

<input type="radio"/> No <input type="radio"/> Not done			
<b>Were you admitted to the hospital?</b>			
<input type="radio"/> Yes <input type="radio"/> No			
<b>Were you cared for in the ICU?</b>			
<input type="radio"/> Yes <input type="radio"/> No			
<b>How many days did you stay at the hospital?</b>			
<input type="radio"/> No hospital admission <input type="radio"/> 7 days or less <input type="radio"/> 7-14 days <input type="radio"/> 14-30 days <input type="radio"/> More than 1 month			
<b>Did you need to have a breathing tube or ventilator?</b>			
<input type="radio"/> Yes <input type="radio"/> No			
<b>How long was the period of infection with COVID-19?</b>			
<b>How long did it take to get a negative test?</b>			
<input type="radio"/> > 10 days <input type="radio"/> ≤ 10 days <input type="radio"/> No PCR had been done			
<b>Mention the drug regimen that had been taken during the COVID-19 infection.</b>			
<input type="radio"/> Panadol <input type="radio"/> Vitamin C <input type="radio"/> Zinc <input type="radio"/> Antibiotic <input type="radio"/> Antiviral <input type="radio"/> Clexan <input type="radio"/> Corticosteroid <input type="radio"/> Lactoferrine <input type="radio"/> Chloroquine			
<b>Is there clinical improvement and no limitation of movement after COVID-19 infection?</b>			
<input type="radio"/> Yes <input type="radio"/> No			
<b>Did you need ventilation or high-flow oxygen therapy?</b>			
<input type="radio"/> Yes <input type="radio"/> No			
<b>Did you need intubation and mechanical ventilation?</b>			
<input type="radio"/> Yes <input type="radio"/> No			
<b>What is the fate of the patient after COVID-19 infection?</b>			
<input type="radio"/> Survival <input type="radio"/> Death			
<b>Laboratory investigations that have been done during the illness</b>			
<b>I. Liver enzymes</b>			
<input type="radio"/> Normal <input type="radio"/> Elevated			
<b>II. Inflammatory markers</b>			
<b>LDH</b>	<b>ESR</b>	<b>CRP</b>	<b>S. ferritin</b>
<input type="radio"/> Normal <input type="radio"/> Elevated	<input type="radio"/> Normal <input type="radio"/> Elevated	<input type="radio"/> Normal <input type="radio"/> Elevated	<input type="radio"/> Normal <input type="radio"/> Elevated
<b>III. CBC</b>			
<b>Hemoglobin level</b>	<b>Lymphopenia</b>	<b>Platelet count</b>	
<input type="radio"/> Normal <input type="radio"/> Decreased	<input type="radio"/> Present <input type="radio"/> Absent	<input type="radio"/> Normal <input type="radio"/> Decreased	

**Statistical analysis:**

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Data analysis was accomplished by SPSS software package version 21 (SPSS Inc. Chicago, Illinois, USA). Continuous data were presented as mean and SD, while nominal data were presented as frequencies (percentages). A Chi<sup>2</sup> test was carried out to compare the occurrence of COVID-19 infection and other characteristics between the two patient groups. The statistical significance of the P value was determined at a confidence level of 95%, indicating that a value below 0.05 would be considered significant for the study's purposes.

## RESULTS

### Demographic characteristics of the studied patients (Table 1):

The age of the patients engaged in this study ranged from 20 to 88 years, with a mean age of 53.6 years. Out of those patients, 105 (52.5%) patients were males.

Thirty-eight (19%) patients were smokers.

### Drug therapy for HCV, its duration, and response (Table 2):

Only three patients in this study had liver cirrhosis, and those patients received Sofosbuvir with daclatasvir for 6 months, while the majority (98.5%) of patients had chronic hepatitis and received the same regimen for 3 months. Most patients, 183 (91.5%), attained sustained virological response (SVR).

### Adherence of the patients to precautions against SARS CoV-2 (Table 3):

Thirty-seven (18.5%) patients never attended social gatherings outside the home, while 51 (25.5%), 38 (19%), and 74 (37%) patients attended such activities either a few days, some days, or most days, respectively. Eighty-seven (43.5%) patients never wear facial masks, while 35 (17.5%) patients usually wear them, and only 12 (6%) patients always wear them. There were 48 (24%) patients with a history of contact with confirmed COVID-19 cases.

### Frequency of confirmed COVID-19 infection in the studied patients (Figure 1):

Twelve (out of 200 patients)(6%) had been confirmed to have COVID-19 infection.

### Clinical, laboratory data, and outcome of confirmed COVID-19 cases among the studied patients (Table 4):

All patients had a fever, while the other most frequent symptoms were loss of taste and smell (83.3%), cough (66.7%), and dyspnea (50%). In the majority of COVID-19 patients (75%), COVID-19 was diagnosed after one year from the last dose of DAADs. In only 3 patients, COVID-19 was diagnosed within one year from the last DAAD dose. All patients with COVID-19 in this study were completely improved and survived.

### Demographic data, Comorbidity, HCV treatment, and adherence to protective measures among patients who developed COVID-19 in our study (Table 5):

The mean age of those patients was 55.6 years, the majority (66.7%) were females, and 10 (83.3%) patients came from rural areas. Fifty percent had a chronic disease, mainly HTN (41.7%) and DM (33.3%).

Fifty percent attended social gatherings outside the home, and 8 (66.7%) patients never wear facial masks in daily activities. There were 7 (58.3%) patients who had a history of contact with a positive case of SARS-CoV-2 infection. Most patients (50%) rarely follow the recommended hygienic measures.

### Comparison of patients' characteristics based on the occurrence of COVID-19 (Table 6):

Both groups based on the occurrence of COVID-19 had insignificant differences as regards different characteristics and adherence to the hygienic measures ( $p > 0.05$ ) except for the significantly higher frequency of contact with infect patients (58.3% vs. 21.8%;  $p < 0.001$ ) and HTN (41.7% vs. 16%;  $p = 0.04$ ) among patients with COVID-19 infection.

**Table (1): Demographic characteristics of the studied patients**

Variable	N= 200
<b>Age (years)</b>	53.6 ± 15.3
Range	20-88
<b>Sex</b>	
Male	105 (52.5%)
Female	95 (47.5%)
<b>Residence</b>	
Rural	148 (74%)
Urban	52 (26%)
<b>Social status</b>	
Single	11 (5.5%)
Married	175 (87.5%)
Divorced	2 (1%)
Widow	12 (6%)
<b>Comorbidities (Yes )*</b>	47 (23.5%)
Hypertension	35 (17.5%)
Diabetes mellitus	26 (13%)
Cardiac disease	5 (2.5%)
Chest disease	3 (1.5%)
<b>Smoking</b>	38 (19%)
<b>Education level</b>	
Illiterate	124 (62%)
Primary	4 (2%)
Secondary	31 (15.5%)
University/postgraduate	41 (20.5%)
<b>Occupation</b>	
Farmer	23 (11.5%)
Worker	129 (64.5%)
Employee	48 (24%)

Data were expressed as frequency (percentage), mean (SD), range

\*Some patients had more than one comorbid chronic disease.

**Table (2): Drug therapy for HCV, its duration and response**

Variable	N= 200
<b>Liver cirrhosis</b>	3 (1.5%)
<b>Drug regimens</b>	
Sofosbuvir/daclatasvir for 3 months	197 (98.5%)
Sofosbuvir/daclatasvir for 6 months	3 (1.5%)
<b>Sustained virological response</b>	
Yes	183 (91.5%)
No	17 (8.5%)

Data were expressed as frequency (percentage). HCV: hepatitis C virus

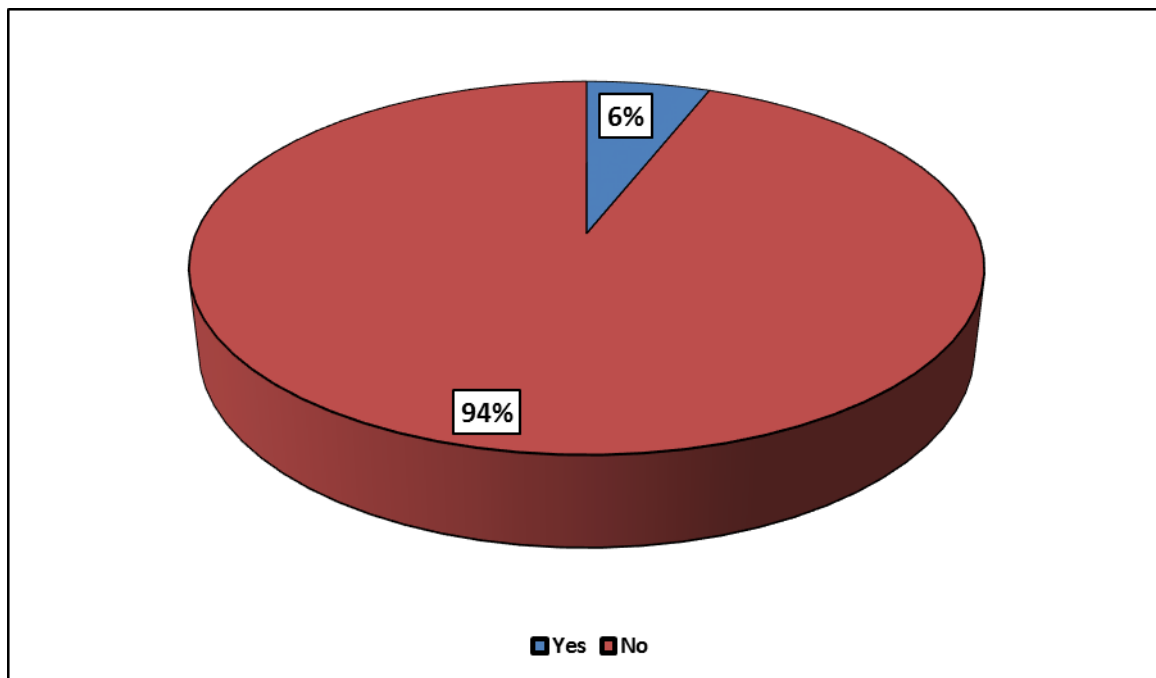
SVR: sustained virological response



**Table (3): Adherence of the patients to precautions against SARS CoV-2**

Variable	N= 200
<b>Attendance social gathering</b>	
No	37 (18.5%)
Few days (< 3 days)	51 (25.5%)
Some days (4-7 days)	38 (19%)
Most days (> 8 days)	74 (37%)
<b>Wear a facial mask in daily activity</b>	
Never	87 (43.5%)
Rare	66 (33%)
Usually	35 (17.5%)
Always	12 (6%)
<b>Contact with infected patients</b>	48 (24%)
<b>How frequently did you follow the recommended hygienic measures</b>	
Rarely (I don't worry about these things)	67 (33.5%)
Sometimes (I do it if I remember it)	90 (45%)
Most of the time (I'm trying to do my best)	31 (15.5%)
All the time (I'm being extra careful)	12 (6%)
<b>Usage of public transport</b>	
No	113 (56.5%)
Few days (< 3 days)	41 (20.5%)
Some days (4-7 days)	20 (10%)
Most days (> 8 days)	26 (13%)

Data were expressed as frequency (percentage). **SARS CoV-2:** Severe acute respiratory syndrome coronavirus 2.

**Figure (1): Frequency of confirmed coronavirus-19 disease in the studied patients**



**Table (4): Clinical, laboratory data, and outcome of confirmed COVID-19 cases among the studied patients**

Variable	N= 12
<b>Clinical manifestations</b>	
Fever	12 (100%)
Loss of taste and smell	10 (83.3%)
Cough	8 (66.7%)
Dyspnea	6 (50%)
Fatigue	4 (33.3%)
Headache	3 (25%)
Nausea/vomiting	2 (16.7%)
Diarrhea	1 (8.3%)
<b>Duration from the last DAAD dose to the emergence of COVID-19 symptoms</b>	
3-6 months	1 (8.3%)
7-9 months	1 (8.3%)
10-12 months	1 (8.3%)
> 12 months	9 (75%)
<b>Pneumonia</b>	3 (25%)
<b>Hospital admission</b>	1 (8.3%)
<b>Hospital stays (days)</b>	< 7
<b>Oxygen therapy</b>	1 (8.3%)
<b>Raised CRP</b>	1 (8.3%)
<b>Raised ESR</b>	1 (8.3%)
<b>Normal hemoglobin</b>	12 (100%)
<b>Normal platelets</b>	12 (100%)
<b>Normal liver enzymes</b>	12 (100%)
<b>Normal ferritin</b>	12 (100%)
<b>Normal LDH</b>	12 (100%)
<b>Duration till seroconversion</b>	
7 days	1 (8.3%)
10 days	9 (75%)
15 days	2 (16.7%)
Survival	12 (100%)

Data were expressed as frequency (percentage). **COVID-19: coronavirus -19 disease; DAAs: direct-acting antiviral agents; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase.**

**Table (5): Demographic data, Comorbidity, HCV treatment, and adherence to protective measures among patients who developed COVID-19 in our study**

Variable	N= 12
<b>Age (years)</b>	55.6 ± 15.3
<b>Sex</b>	
Male	4 (33.3%)
Female	8 (66.7%)
<b>Residence</b>	
Rural	10 (83.3%)
Urban	2 (16.7%)
<b>Married</b>	12 (100%)
<b>Hypertension</b>	5 (41.7%)
<b>Diabetes mellitus</b>	4 (33.3%)
<b>Cardiac disease</b>	1 (8.3%)
<b>Chest disease</b>	1 (8.3%)
<b>Smoking</b>	1 (8.3%)
<b>Education level</b>	
Illiterate	8 (66.7%)
Secondary	3 (25%)
University/postgraduate	1 (8.3%)
<b>Occupation</b>	
Farmer	10 (83.3%)
Employee	2 (16.7%)
<b>Drug regimens</b>	
<b>Sofosbuvir/daclatasvir for 3 months</b>	12 (100%)
<b>Sustained virological response</b>	
Yes	10 (83.3%)
No	2 (16.7%)
<b>Attendance of social gatherings</b>	
None	4 (33.3%)
Some days (4-7 days)	1 (16.7%)
Most days (> 8 days)	6 (50%)
<b>Wear a facial mask in daily activity</b>	
Never	8 (66.7%)
Rare	4 (33.3%)
<b>Contact with infected patients</b>	7 (58.3%)
<b>Follow the recommended hygienic measures</b>	
Rarely (I don't worry about these things)	6 (50%)
Sometimes (I do it if I remember it)	4 (33.3%)
Most of the time (I'm trying to do my best)	2 (16.7%)
<b>Usage of public transport</b>	
None	7 (58.3%)
Few days (< 3 days)	3 (25%)
Some days (4-7 days)	2 (16.7%)

Data were expressed as frequency (percentage), and mean (SD). **COVID-19**: coronavirus infectious disease-19.

**Table (6): Comparison of patients' characteristics based on the occurrence of COVID-19 \***

Variable	Occurrence of COVID-19		P value
	Yes (n= 12)	No (n= 188)	
<b>Gender</b>			0.14
Male	4 (33.3%)	101 (53.7%)	
Female	8 (66.7%)	87 (46.3%)	
<b>Diabetes mellitus</b>	4 (33.3%)	22 (11.7%)	0.06
<b>Hypertension</b>	5 (41.7%)	30 (16%)	<b>0.04</b>
<b>Cardiac disease</b>	1 (8.3%)	4 (2.1%)	0.26
<b>Chest disease</b>	1 (8.3%)	2 (1.1%)	0.17
<b>Residence</b>			0.35
Rural	10 (83.3%)	138 (73.4%)	
Urban	2 (16.7%)	50 (26.6%)	
<b>Education level</b>			0.58
Illiterate	8 (66.7%)	116 (61.7%)	
Primary	0	4 (2.1%)	
Secondary	3 (25%)	28 (14.9%)	
University/postgraduate	1 (8.3%)	40 (21.3%)	
<b>Attendance social gathering</b>			0.27
None	4 (33.3%)	33 (17.6%)	
Few days (< 3 days)	1 (8.3%)	50 (26.6%)	
Some days (4-7 days)	1 (8.3%)	37 (19.7%)	
Most days (> 8 days)	6 (50%)	68 (36.2%)	
<b>Wear a facial mask in daily activity</b>			0.20
Never	8 (66.7%)	79 (42%)	
Rare	4 (33.3%)	62 (33%)	
Usually	0	35 (18.6%)	
Always	0	12 (6.4%)	
<b>Contact with infected patients</b>	7 (58.3%)	41 (21.8%)	<b>&lt; 0.001</b>
<b>How frequently did you follow the recommended hygienic measures</b>			0.53
Rarely	6 (50%)	61 (32.4%)	
Sometimes	4 (33.3%)	86 (45.7%)	
Most of the time	2 (16.7%)	29 (15.4%)	
All the time	0	12 (6.4%)	
<b>Usage of public transport</b>			0.94
None	7 (58.3%)	106 (56.4%)	
Few days (< 3 days)	3 (25%)	38 (20.2%)	
Some days (4-7 days)	1 (8.3%)	19 (10.1%)	
Most days (> 8 days)	1 (8.3%)	25 (13.3%)	

The date was expressed as frequency (percentage). *P* value was significant if  $< 0.05$ .

\* The Chi-square statistic test ( $\chi^2$ ) was carried out to compare patients' characteristics between the two patient groups.

## DISCUSSION

The replicating process of SARS-CoV-2, a positive-sense RNA virus, is highly dependent on an RdRp. Sofosbuvir plus Daclatasvir has been shown to inhibit HCV replication effectively and can inhibit the replication of SARS-CoV-2. Since other viral families exhibit a similar replication mechanism, there is a possibility of using a specific antiviral regimen interchangeably, particularly during the SARS-CoV-2 pandemic [12].

In this context, we aimed to judge the influence of treating chronic HCV patients by direct-acting antiviral drugs (DAADs) on COVID-19 disease frequency and severity. Two hundred patients who confirmed HCV infection and were eligible for therapy with DAADs were involved. All patients received Sofosbuvir plus Daclatasvir for 3 months except three patients who received the same regimen for 6 months due to liver cirrhosis.

The main findings in this study were: 1) the used regimen was effective in the management of

HCV, where 91.5% of patients achieved SVR, 2) the majority of studied patients did not strictly follow the precautions against SARS-CoV-2 infection, and 74% were coming from rural areas, 3) only 12 (6%) of patients developed COVID-19 and all of them were alive and 4) nine (75%) of those patients with COVID-19 developed their SARS-CoV-2 infection one year since the last dose of DAADs.

Regarding the efficacy of Daclatasvir and Sofosbuvir for treating chronic hepatitis C virus infection, many studies confirmed this point [13-17]. Nouh et al [17] stated that out of 401 patients diagnosed with chronic HCV infection who received Daclatasvir and Sofosbuvir, 385 (96%) patients achieved SVR.

Although the results have been mixed, preclinical trials specify that Sofosbuvir and Daclatasvir have the potential to act on SARS-CoV-2 RdRp. Multiple clinical studies have suggested that Sofosbuvir and Daclatasvir may have potential therapeutic effects for COVID-19 patients [18-20].

The progress of developing nucleoside analogs against respiratory viruses has been evident for coronavirus and influenza viruses but developing such drugs has been slower for Respiratory Syncytial virus (RSV), adenovirus, and mostly rhinovirus. Due to the acute nature of airway infections caused by these viruses, it is essential to initiate antiviral drug treatment promptly after the onset of symptoms [21].

The FDA has expanded its Remdesivir approval to comprise outpatients who are at risk of developing severe COVID-19, in addition to hospitalized patients. Although nucleoside analogs have the potential to restrict the dispersal of respiratory viruses through the community, their effectiveness for this aim has not been fully established. For broader use, orally administered drugs may be more practical compared to those necessitating inhalation or injection [22].

Recently, a meta-analysis indicated that Sofosbuvir and Daclatasvir usage could lessen the mortality rate and requirement for mechanical ventilation in individuals hospitalized with moderate to severe cases of COVID-19. Patients who received Sofosbuvir and Daclatasvir showed a higher overall clinical recovery rate, particularly among those who were hospitalized [23].

A previous study assessed the effectiveness of adding Sofosbuvir and Daclatasvir to the conventional therapy of 174 patients with confirmed COVID-19 infection. The authors found that adding those two drugs had beneficial effects in shortening the hospital stay and rapid seroconversion but had no effect on mortality [24].

A study found that severe COVID-19 patients who were treated with hydroxychloroquine (HCQ) along with Sofosbuvir and Daclatasvir (35 patients) or ribavirin (27 patients) had significantly different outcomes. Specifically, the group receiving Sofosbuvir and Daclatasvir had a lower mortality rate (6% vs. 33%) and shorter hospitalization duration (5 days vs. 9 days) compared to the group receiving ribavirin [19].

Another study compared the use of Sofosbuvir and Daclatasvir with hydroxychloroquine (HCQ) to HCQ alone in 55 patients. The study found no significant difference in symptom relief on Day 7 between the two groups [12]. Assessing the efficacy of Sofosbuvir and Daclatasvir after only 7 days may not fully reflect their potential benefits, which becomes more obvious after Day 14 [24].

Generally, Sofosbuvir-based treatment was found to be linked to a substantially higher rate of clinical recovery, reduced rate of necessitating mechanical ventilation, and intensive care unit admission. In addition, patients who received this treatment had shorter hospital stays and recovery times compared to those in the control groups. Moreover, Sofosbuvir-based treatment was consistently observed to provide clinical benefits in hospitalized patients with COVID-19, according to subgroup analyses [25]. Furthermore, the subgroup analysis revealed that patients who received Sofosbuvir and Daclatasvir experienced improved clinical outcomes compared to those who received comparators, consistent with previous studies' findings [23, 26].

We noticed that our study is different from those cited studies, where in the majority of those studies, there was another group used as a control to compare the effect of Sofosbuvir/Daclatasvir on the outcome of patients who were already diagnosed with COVID-19 infection. Nevertheless, our study assessed the frequency of developing COVID-19 infection following the usage of

Sofosbuvir/Daclatasvir in individuals experiencing chronic HCV infection.

In the present work, we discovered that only 12 (6%) HCV patients who received Sofosbuvir/Daclatasvir therapy had confirmed COVID-19 and all of them had mild to moderate disease and were alive. In addition, most of them had COVID-19 after 1 year from the last dose of DAADs.

A retrospective case-control study found that patients who received chronic hepatitis C treatment using Sofosbuvir and Daclatasvir exhibited a reduced SARS-CoV-2 infection rate (2.2%, 11 SARS-CoV-2 infections) relative to cases of the control group (6%, 30 SARS-CoV-2 infections with significant differences regard the severity [27].

In the comparison of our patients' characteristics based on the occurrence of COVID-19, we found a significantly higher frequency of contact with infected patients (58.3% vs. 21.8%;  $p < 0.001$ ) and hypertension (41.7% vs. 16%;  $p = 0.04$ ) among patients with COVID-19 infection versus those without.

Middle-aged individuals are typically infected within the community, whereas older individuals are more susceptible to infections through contact with family members or during hospitalization due to coughing and sneezing from infected individuals [28]. Men appear to be more susceptible to SARS-CoV-2 infection, making the male sex a risk factor for COVID-19. Other risk factors for COVID-19 infection include DM, malignancy, cardiovascular diseases, and other conditions that weaken immunity [29].

Significant risk factors for COVID-19 infection were male gender, age group over 60 years, residing in densely populated areas, being married, having close contact with individuals infected with COVID-19, and underlying health conditions [30].

**Limitation of the study:** The current study has several limitations, including a small sample size, a single-center study, and the absence of a control group.

## CONCLUSION

Previous chronic hepatitis C treatment by Sofosbuvir and Daclatasvir protects against

SARS-CoV-2 infection. If chronic HCV patients who finished treatment with DAADs had COVID-19, their disease course was mild, and they ultimately improved. Larger randomized controlled studies and multi-center Egyptian studies are necessitated to confirm the effectiveness of direct-acting antiviral drugs (DAADs) as a possible SARS-CoV-2 infection therapy.

**Competing interest:** Not applicable.

**Funding:** Not applicable.

**Ethical considerations:** The aim of the study was explained to participants before filling out the questionnaire and written informed consent was obtained.

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## HIGHLIGHTS

- There is still a debate about the gold standard therapy for COVID-19 infection
- Patients who were previously treated with antivirals (DAADs) for chronic hepatitis C virus infection may be protected from COVID-19.
- Future studies are still warranted to draw a firm conclusion

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