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RESEARCH ARTICLE

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# Efficacy and safety of sofosbuvir plus daclatasvir or ravidasvir in patients with COVID-19: A randomized controlled trial

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## Abstract

Only a few treatments are approved for coronavirus disease-2019 (COVID-19) infections, with continuous debate about their clinical impact. Repurposing antiviral treatments might prove the fastest way to identify effective therapy. This trial aimed to evaluate the efficacy and safety of sofosbuvir (SOF) plus daclatasvir (DCV) or ravidasvir (RDV) added to standard care (SOC) for patients with moderate and severe COVID-19 infection. Multicentre parallel randomized controlled open-label trial. One hundred and twenty eligible patients with moderate and severe COVID-19 infection were randomized to one of the study arms. Ten days of treatment with SOF plus DCV or RDV in addition to the standard of care compared to SOC. Follow up in 7 days. Sum of the counted symptoms at 7 and 10 days, mean change in oxygen saturation level, viral negativity, and rate of intensive care unit (ICU) admission. Compared to SOC, the SOF-DCV group experienced a significantly lower sum of the counted symptoms (fever, headache, generalized aches, or respiratory distress) combined with no evidence of deterioration (ICU admission and mechanical ventilation) on Days 7 and 10 of treatment. Oxygen saturation also significantly improved among the SOF-DCV group compared to SOC starting from Day 4. The study also showed positive trends regarding the efficacy of SOF-DCV with a lower incidence of mortality. On the other hand, adding SOF-RDV to SOC did not show significant improvements in endpoints. The results support the efficacy and safety of SOF-DCV as an add-on to SOC for the treatment of moderate to severe COVID-19 infections.

**KEYWORDS**
COVID-19, sofosbuvir, daclatasvir, repurposing antiviral drugs

## 1 | INTRODUCTION

By December 2019, a series of acute pneumonia cases emerged in Wuhan, China, referred to as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

With increasing cases and the vast geographic spread of the disease globally, the WHO declared the coronavirus disease-2019 (COVID-19) a pandemic on March 11, 2020.[1] Since then, rigorous research work and massive international efforts have been ongoing to develop preventive and treatment approaches. To date, there are

  

more than 200 vaccines, 245 antivirals, and 390 treatments in preclinical or clinical development,[2] and the development of effective and safe antiviral treatment agents is eagerly pursued.

Currently, no antiviral medication for COVID-19 treatment has been validated apart from remdesivir, which is the only medication approved by the FDA based on various reports, including randomized clinical trials.[3,4] For this reason, repurposing of drugs approved for other diseases has been attempted. SARS-CoV-2 shares similarities with viral genomic replication mechanisms with other RNA viral families through RNA-dependent RNA polymerase (RdRp).[5] Therefore, existing antivirals targeting the RdRp can potentially be repurposed for treating SARS-CoV-2. The hepatitis C (HCV) and SARS-CoV-2 RNA viruses use similar viral genome replication mechanisms. Direct antiviral agents against hepatitis C have shown laboratory activity against SARS-CoV-2, supported by a molecular docking experiment.[6] Using the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) model, the tight binding of sofosbuvir (SOF) to the coronavirus RdRp was identified.[7] Ledipasvir and velpatasvir were also found by virtual screening to be potential candidates to block another vital target in SARS-CoV-2 replication, the 3-chymotrypsin-like protease (3CLpro), also known as main protease (Mpro).[8] In another molecular docking model, elbasvir and ledipasvir showed similar binding potential against helicase, RdRp, and protease from both viruses.[9] SOF is the backbone of many approved anti-HCV regimens. Data from multiple trials and real-world experience proved that a combination of SOF with an NS5A inhibitor is effective, safe, and well-tolerated in treating patients with HCV.[10] In silico activity of SOF plus daclatasvir (DCV) is reported against SARS-CoV-2.[11–13] Similar to DCV, ravidasvir (RDV) has antiviral activity through NS5a inhibition. DCV and RDV are both safe and effective pan-genotypic NS5a inhibitors.[14]

## 2 | OBJECTIVES

We proposed that SOF plus DCV (SOF-DCV) or RDV (SOF-RDV) could be repurposed antiviral treatments for COVID-19 because they could inhibit two SARS-CoV-2 replication enzymes. This study evaluated the role of adding SOF plus DCV (SOF-DCV) or RDV (SOF-RDV) to standard treatment compared to standard treatment in patients with SARS-CoV-2 infection.

## 3 | METHODS

This study was a randomized, open-label, prospective trial to evaluate the safety and efficacy of SOF plus DCV (SOF-DCV) or RDV (SOF-RDV) in addition to standard treatment compared to standard treatment in Egyptian adults with COVID-19.

### 3.1 | Trial design

This study was a phase III, randomized, open-label, prospective, controlled study. Patients were randomized (1:1:1) into three treatment groups: Group 1 ($n = 40$) received SOF-DCV in addition to the standard of care therapy for 10 days, Group 2 ($n = 40$) received SOF-RDV in addition to the standard of care therapy for 10 days, and Group 3 ($n = 40$) received the standard of care therapy without investigational medications.

The data collected during the screening period included demographic data (age, gender, type of employment, income, level of education, smoking, alcohol intake, and marital status), medical and surgical history, concomitant medications, physical examinations, vital signs, standard 12-lead ECG, reverse-transcription polymerase chain reaction (RT-PCR) for SARS-COV-2 RNA through a nasopharyngeal swab (Genesig® Real-time PCR assay; Primerdesign Ltd.), blood count, creatinine, total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), sodium, potassium, glucose, total protein, albumin, ferritin, fibrinogen, and creatinine clearance (Cockcroft-Gault calculation), C-reactive protein (CRP), lactic dehydrogenase, HIV antibody, D-dimer, troponin, hepatitis C virus (HCV) antibody, and radiological examination (computerized tomography or X-ray of the chest).

During the treatment period of 10 days, patients were followed up for their vital signs and disease progression daily. RT-PCR for COVID-19 was repeated on Days 7, 10 (end of experimental medication), 17 (7 days after the end of experimental medication) according to the practice of the study centers following the MoH standard procedures, and lab investigations were re-performed on Days 10 and 17.

This study was conducted from September 2020 to March 2021 and followed the guidelines of the Declaration of Helsinki. The clinical sites' institutional review boards and ethics committees, and the Egyptian Ministry of Health approved the study. The trial is registered at the ISRCTN registry with registration number ISRCTN21085622.

### 3.2 | Participants

#### 3.2.1 | Eligibility criteria

*Inclusion criteria*

We included patients aged >18 years with laboratory-confirmed symptomatic COVID-19 as determined by PCR assay in any specimen collected <72 h before randomization, willing and able to provide written informed consent, and had the following disease severity grades: moderate (patients with respiratory rate ≥20 breaths/min, oxygen saturation measured through a pulse oximeter [$SpO_2$] > 90% on room air and heart rate ≥90 beats/min), severe (not critical) (patients with clinical signs indicative of severe systematic illness with COVID-19; such as respiratory rate ≥30/min, heart rate ≥125/min, $SpO_2 \leq 90\%$ on room air or $PaO_2/FiO_2 < 300$). Degrees of severity of COVID-19 were defined according to WHO's COVID-19 disease severity classification.[15]

*Exclusion criteria*

We excluded patients with critically severe COVID-19 requiring invasive mechanical ventilation at screening, patients who have a

severe concomitant illness, patients with hypersensitivity or contraindication to any of the drugs used in the study, patients with liver cirrhosis or elevated ALT, and/or AST above three times the upper limit of normal, patients with cardiac ischemia or clinically symptomatic cardiac abnormalities, patients with a history of any malignancy within the last 5 years, patients with a history of solid organ or bone marrow transplantation, patients who received treatment with any other investigational drug/device or involved in another clinical trial within 6 months before screening, people living with HIV, and pregnant or breastfeeding ladies.

#### 3.2.2 | Sites and of data collection

The study was conducted in four public hospitals dedicated at the time for COVID-19 patients in Egypt: Shebin Fever Hospital, Menouf Fever Hospital, Mahalla Fever Hospital, and the National Liver Institute.

### 3.3 | Interventions

The investigational products were SOF 400 mg tablets (Gratisovir; European Egyptian for Pharmaceutical Industries), RDV 200 mg tablets (European Egyptian for Pharmaceutical Industries), and DCV 60 mg tablets (Daktavira; European Egyptian for Pharmaceutical Industries).

The clinical investigation sites (all in public hospitals) supplied the standard of care therapy received by all patients as per the Egyptian Ministry of Health (MoH) standard protocol for treatment of COVID-19.[16] The standard of care included: acetaminophen 500 mg tablets as needed and multivitamin supplements offered for all patients. Intravenous fluid and oxygen by facemask, nasal cannula, high flow rate, continuous positive airway pressure, and mechanical ventilation were offered promptly as needed per the MoH for critically severe cases. All patients received background therapy according to the treating physician's instructions and in line with the MoH recommendations. These included any of hydroxychloroquine (HCQ), ivermectin, lopinavir/ritonavir, or remdesivir (for the high-risk population with oxygen saturation [$SaO_2$] < 92). Patients with severe dyspnea (respiratory rate [RR] > 24/min or CT scan showing rapid deterioration) received steroids, and antibiotics were added for any patient with a suspected superadded bacterial infection. Severe cases (RR > 30, $SaO_2$ < 92 at room air, arterial oxygen partial pressure to fractional inspired oxygen ratio ($PaO_2/FiO_2$) ratio <300, or chest radiology showing more than 50% lesion or progressive lesion within 24 to 48 h) received two doses of tocilizumab 12 to 24 apart after failure of steroid therapy. Patients with elevated D-dimer (>500 μg/L) received low molecular weight heparin in a low prophylactic dose, while patients with elevated D-dimer >1000 μg/L received a therapeutic dose of the anticoagulant.

### 3.4 | Outcomes

The primary efficacy endpoints were

1- To compare the sum of the counted symptoms (fever, headache, generalized aches [myalgia/arthralgia], respiratory distress combined with no evidence of deterioration [ICU admission and mechanical ventilation]) at Days 7 and 10, controlling for the corresponding count of symptoms at Day 3 for each patient. A Poisson regression model was performed to test the effect of the experimental combinations on the stated outcome.
2- To compare the mean change in oxygen saturation from Day 1 to Day 10 (based on daily recording per CRF).

The secondary endpoints included

1- To compare the percentage of patients with undetectable SARS-CoV-2 RNA by nasopharyngeal swabs on Days 7 and 10.
2- To compare reported AEs/SAEs at any time point from Day 1 to Day 10, and a follow-up visit on Week 1 measured using patient records.
3- To compare the percentage of patients who need ICU admission at any time point from Day 1 to Day 10, and follow up visit on week 1, measured using patient records.

### 3.5 | Sample size

The rate of SARS-COV-2 viral clearance by PCR on Day 9 of treatment with interferon-α plus lopinavir/ritonavir was 66.70% [17]; while the rate of viral clearance among patients receiving the standard of care was 36.5%.[18] Assuming an α error of 0.05, a two-tail test, and a power of 0.85, a total of 102 patients (34 patients in each group) was appropriate to reject the null hypothesis that the virologic response rates for experimental and control subjects are equal with a probability of 0.85. To account for an expected dropout rate of 10%, a total of 120 patients (40 patients in each group) were randomized in a ratio of 1:1:1. The sample size was calculated using G*Power software version 3.1.9.

### 3.6 | Randomization

Randomization was carried out centrally by a stratified block randomization technique using computer-generated sequences of three balanced treatment groups (each of nearly 40 patients). Patients were stratified by admission to sites. After the delegated person obtained the patients' consent, he telephoned an independent contact for allocation consignment. Investigational products and/or standard of care were dispensed by the delegated pharmacist according to a computer-generated randomization list.

## 3.7 | Statistical methods

Data manipulation, cleaning, and analysis were performed using R software 4.0.0. Criteria for descriptive and comparative analysis are described below.

### 3.7.1 | Descriptive analysis

Mean and *SD* were used for quantitative normally distributed variables, whereas median and interquartile range (IQR) were used for quantitative non-normally distributed variables. Categorical variables were presented as counts and percentages.

### 3.7.2 | Comparative analysis

The Student *t* test and one-way analysis of variance (ANOVA) were utilized to compare continuous variables among the study arms. Mann–Whitney *U* test or Kruskal–Wallis ANOVA test was used to compare two non-parametric continuous independent variables. Paired *t* test and repeated measure ANOVA test were used to compare the paired change in the continuous numerical variables along with the study duration. For unpaired and paired categorical variables, the $\chi^2$ test (or Fisher exact test) and McNemar's test were used, respectively. All tests were performed on the 5% level of significance. The Poisson regression model was applied to compare counts of clinical symptoms for patients among the study groups.[19]

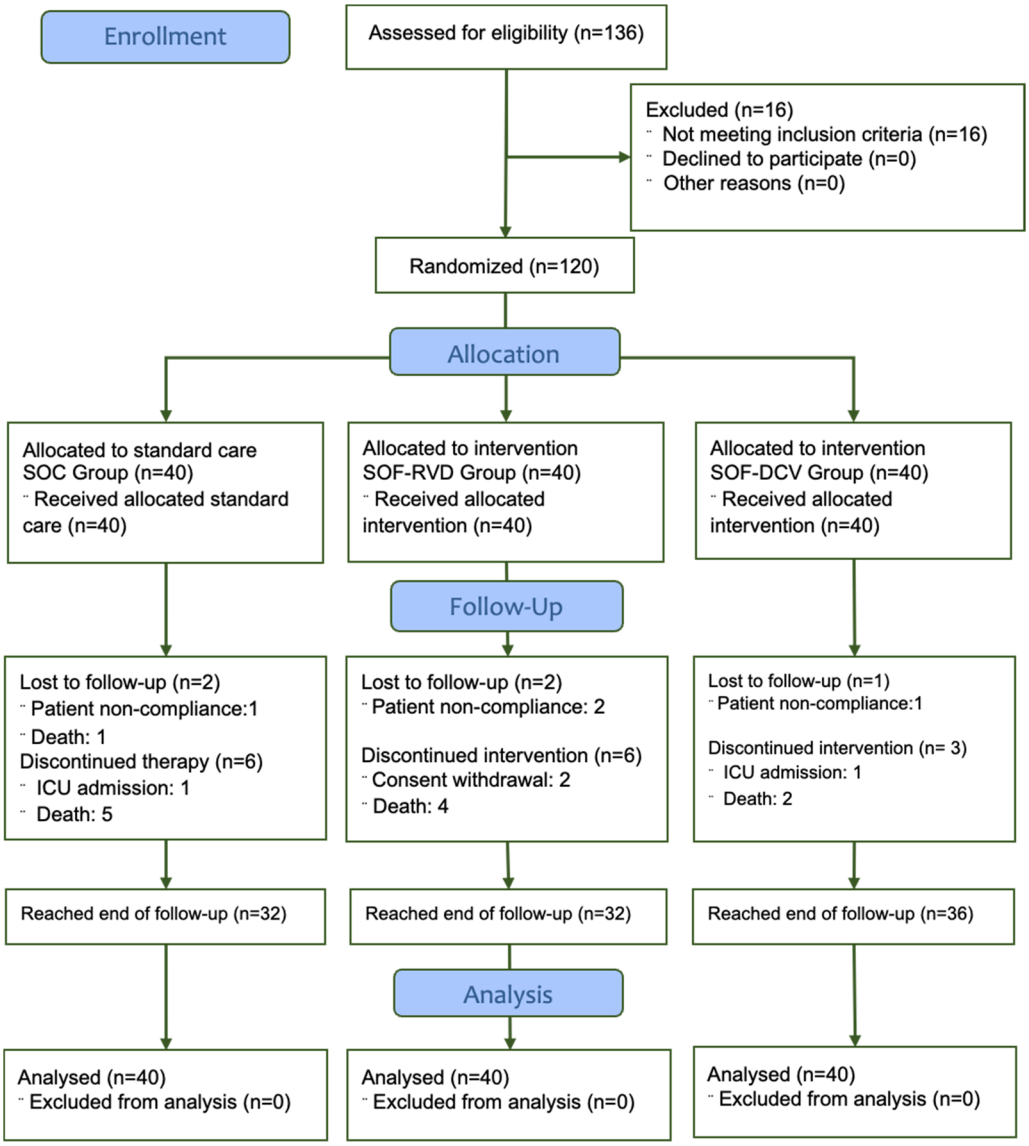


**FIGURE 1** Patient flowchart diagram according to CONSORT standards for reporting controlled randomized clinical trials. DCV, daclatasvir; RDV, ravidasvir; SOC, standard of care; SOF, sofosbuvir

# 4 | RESULTS

## 4.1 | Study population

A total of 136 patients were screened for their eligibility for enrollment in this study between September 2020 to March 2021. Of them, 14 patients were ineligible for enrollment (screen failure), 2 withdrew their consent, and 120 patients were enrolled and randomized. All 120 randomized patients were included in the analysis of stated endpoints. Figure 1 shows the patients' flow diagram in the study according to the consolidated standards for reporting controlled randomized trials (CONSORT).

## 4.2 | Baseline characteristics

Patients' baseline characteristics are presented in Table 1. The three groups were almost homogenous regarding their demographics, comorbidities, and severity of the disease.

## 4.3 | Analysis set

The analysis was intention-to-treat and involved all patients who were randomly assigned.

## 4.4 | Outcomes

### 4.4.1 | Primary endpoints

*Count of clinical symptoms*

There was a significant decline in the sum of the counted symptoms among the SOF-DCV group on Days 7 and 10. The model coefficients showed that the SOF-DCV combination led to a significant decrease in the count of symptoms at Days 7 and 10 ($p$ 0.041 and 0.0399 respectively). On the other hand, this was not the case for the patients in the SOF-RDV group, who did not experience significant reductions in the sum of the counted symptoms at Day 7 or 10 compared to the SOC group (Table 2).

**TABLE 1** Baseline characteristics of patients

| | SOC | SOF-DCV | SOF-RDV | $p$ value |
|---|---|---|---|---|
| | ($n$ = 40) | ($n$ = 40) | ($n$ = 40) | |
| Baseline demographics | | | | |
| Age, mean (*SD*) | 46 (5.8) | 40 (6.1) | 48 (2.2) | 0.877 |
| Male, *n* (%) | 20 (50.0%) | 22 (55.0%) | 22 (55.0%) | 0.875 |
| Severity of disease at baseline, *n* (%) | | | | |
| Moderate | 13 (32.5%) | 15 (37.5%) | 18 (45%) | 0.512 |
| Severe | 27 (67.5%) | 25 (62.5%) | 22 (55%) | |
| Comorbidities, *n* (%) | | | | |
| Asthma | 2 (5%) | 0 (0%) | 0 (0%) | 0.397 |
| Diabetes | 6 (15%) | 9 (22.5%) | 7 (17.5%) | 0.927 |
| Cardiovascular diseases | 29 (72.5%) | 28 (70%) | 34 (85%) | 0.163 |
| Vital signs at baseline, mean (*SD*) | | | | |
| $O_2$ saturation (%) | 88.7 (4.9) | 88.5 (5.6) | 87.8 (4.9) | 0.715 |
| Temperature (°C) | 37.9 (0.7) | 38.1 (0.7) | 38.0 (0.9) | 0.362 |
| Respiratory rate (breaths/min) | 24.3 (3.3) | 24.1 (3.2) | 23.6 (2.9) | 0.66 |
| Pulse (beats/min) | 83 (10) | 87 (13.8) | 88.5 (10.9) | 0.151 |
| Laboratory findings on admission, mean (*SD*) | | | | |
| Lymphocytes ($\times 10^9$/L) | 1.37 (0.8) | 1.48 (0.6) | 1.44 (0.8) | 0.84 |
| D-dimer (mg/L) | 0.9 (1.15) | 0.92 (1.09) | 0.89 (1.1) | 0.994 |
| CRP (mg/L) | 58.2 (68.0) | 54.6 (64.7) | 52.3 (64.4) | 0.941 |
| LDH (U/L) | 354.4 (155.2) | 349.97 (159.3) | 347.8 (157.5) | 0.98 |
| Ferritin (ng/ml) | 652.5 (617.9) | 599.9 (583.5) | 608.5 (594.4) | 0.93 |

Abbreviations: CRP, C-reactive protein; DCV, daclatasvir; IQR, interquartile range; $O_2$, oxygen; RDV, ravidasvir; *SD*, standard deviation; SOC, standard of care; SOF, sofosbuvir.

**TABLE 2** Change in the count of clinical symptoms in the study groups

| | Day 7 | | | Day 10 | | |
|---|---|---|---|---|---|---|
| | Number of evaluable patients | Change in counts of clinical symptoms: value (*SE*) | *p* versus SOC | Number of evaluable patients | Change in counts of clinical symptoms: value (*SE*) | *p* versus SOC |
| SOF-DCV | 40 | −0.12647 (0.13953) | 0.041 | 40 | −0.031655 (0.174262) | 0.0399 |
| SOF-RDV | 40 | −0.09579 (0.13895) | 0.491 | 40 | +0.071006 (0.166456) | 0.66969 |

Abbreviations: DCV, daclatasvir; RDV, ravidasvir; SOC, standard of care; SOF, sofosbuvir.

*Change in oxygen saturation level*

There was a significant improvement in oxygen saturation level over time for all study groups ($p < 0.000$). The mean oxygen saturation level for the SOF-DCV group significantly improved versus the SOC group starting from Day 4. Sustainable improvement in oxygen saturation occurred starting Day 6 (Table 3).

### 4.4.2 | Secondary endpoints

*Viral negativity*

At the end of treatment on Day 10, the percentage of patients with undetectable SARS-COV-2 RNA on two consecutive nasopharyngeal swabs was higher in the SOF-DCV group versus SOC (46.2% vs. 40.0%, OR = 1.29, $p = 0.581$). On the other hand, the percentage was almost the same for SOF-RDV versus SOC group (41.5% vs. 40.0%, $p = 0.893$).

*ICU admission*

Until the end of treatment and follow-up period, the percentage of patients admitted to ICU was lower among SOF-DCV versus SOC group (3 [7.5%] vs. 8 [20.0%], $p = 0.09$). The percentage was lower in the SOF-RDV group with no statistical significance (5 [12.5%] vs. 8 [20.0%], $p = 0.273$).

## 4.5 | Safety

Adverse events (AEs) were significantly less reported among the SOF-DCV group than SOC, while the recorded number was nearly equal between SOC and SOF-RDV groups. Most of the reported events were related to the progression of the disease (death, ICU admission, and need for mechanical ventilation) (Table 4). Death cases were notably less recorded among the SOF-DCV group compared to SOC. All mortalities were due to severe hypoxia leading to respiratory failure. Details of deaths are presented in Table 5.

# 5 | DISCUSSION

There is no approved treatment for COVID-19 until now; there is an increasing list of antiviral agents extensively studied for their potential to be repurposed as a COVID-19 treatment.[20] WHO experts investigated four promising antiviral agents to be repurposed for treatment of COVID-19 infections; however, according to the last interim report published for the WHO Solidarity study, remdesivir, HCQ, lopinavir, and interferon regimens had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[21] Similarly, SOF, ribavirin, umifenovir, oseltamivir, nafamostat, favipiravir, and nitazoxanide were or are being evaluated as treatment options. However, most of these agents still lack established evidence to be appended to the list of approved antiviral agents.[22]

**TABLE 3** Comparison of oxygen saturation level among study groups

| | SOC ($n = 40$) | SOF-DCV ($n = 40$) | $p$ versus SOC | SOF-RDV ($n = 40$) | $p$ versus SOC |
|---|---|---|---|---|---|
| Oxygen saturation level (mean ± *SD*) | | | | | |
| Day 1 | 87.9 (5.8) | 88.7 (4.2) | 0.482 | 87.5 (6.25) | 0.769 |
| Day 2 | 87.3 (7) | 89.4 (4.8) | 0.122 | 88.1 (7.41) | 0.717 |
| Day 3 | 87.3 (10.4) | 90.2 (4.9) | 0.116 | 89.7 (5.13) | 0.141 |
| Day 4 | 87.4 (8.8) | 91.3 (4.7) | 0.016* | 89.8 (5.88) | 0.096 |
| Day 6 | 89.2 (10.5) | 93.1 (3.4) | 0.038* | 91.38 (7.68) | 0.157 |
| Day 7 | 89.9 (10.3) | 94 (3.7) | 0.037* | 92.74 (5.62) | 0.093 |
| Day 10 | 93.4 (3.7) | 95.8 (2.7) | 0.004* | 94.52 (4.58) | 0.054 |

Abbreviations: DCV, daclatasvir; RDV, ravidasvir; SOC, standard of care; SOF, sofosbuvir.
*Significant difference at 5% α error.

**TABLE 4** Reported adverse events among study groups

| | SOC ($N = 40$) | SOF-RDV ($N = 40$) | SOF-DCV ($N = 40$) | $p$ |
|---|---|---|---|---|
| Number of patients | 12 (30%) | 9 (22.5%) | 3 (7.5%) | 0.037 |
| Frequency of events | | | | |
| Number of events | 17 | 15 | 5 | 0.007 |
| SAEs/AEs specification | | | | |
| Death | 6 (15%) | 4 (10%) | 2 (5%) | 0.329 |
| ICU admission | 8 (20%) | 5 (12.5%) | 3 (7.5%) | 0.254 |
| Need for mechanical ventilation | 1 (2.5%) | 2 (5%) | 0 (0) | 0.358 |
| Elevated liver enzyme | 1 (2.5%) | 2 (5%) | 0 (0) | 0.358 |
| Elevated kidney function (creatinine-BUN) | 1 (2.5%) | 0 (0) | 0 (0) | 0.998 |
| Low platelet count | 0 (0) | 1 (2.5%) | 0 (0) | 0.997 |
| High platelet count | 0 (0) | 1 (2.5%) | 0 (0) | 0.997 |

Abbreviations: DCV, daclatasvir; RDV, ravidasvir; SOC, standard of care; SOF, sofosbuvir.

In 2013, SOF was approved for treatment against HCV infection; it is a nucleotide analog that exerts its antiviral activity through nonstructural-5b (NS5b) inhibition. SOF acts as a substrate for HCV RNA-dependant-RNA-polymerase (RdRp), which incorporates into the newly synthesized viral RNA and terminates its synthesis resulting in inhibition of viral replication.[23] At the same time, DCV is an inhibitor for the nonstructural-5a (NS5a) protein which has several roles during the HCV replication cycle, including protein phosphorylation, RNA replication, and cell signaling.[24] Both HCV and SARS-CoV-2 share similarities between NS5a, and NS5b proteins, suggesting that both drugs could be effective antiviral drugs against SARS-CoV-2.[25] The combination of SOF and DCV is used for the treatment of chronic HCV with a high (>90%) sustained virologic response (SVR).[26]

Enzymatic assays showed that SOF could act as a competitive inhibitor and chain terminator for SARS-CoV-2 RdRp,[27,28] while in-vitro studies demonstrated that the combination of SOF-DCV has a cooperative antiviral activity against SARS-CoV-2 in Vero-E6 cells. The study revealed additional inhibitory mechanisms of DCV against SARS-CoV-2 by targeting double-stranded RNA of SARS-CoV-2 and inhibition of viral RNA synthesis, and also through inhibition of the release of interleukin-6, and tumor necrosis factor-α, which are the primary inflammatory mediators of the cytokine storm in COVID-19 patients. The study also showed that the addition of sub-inhibitory concentrations of DCV resulted in increased potency of SOF.[25]

There is no available result of clinical studies evaluating the efficacy and safety of SOF-RDV among COVID-19 patients. A previous study by Esmat et al.[29] showed that a combination of SOF-RDV in addition to ribavirin was associated with a 95.3% response rate among HCV genotype-4 patients with or without cirrhosis. This is consistent with the STORM-C-1 trial, which reported that SOF-RDV

**TABLE 5** Death cases details

| Treatment group | Event day after randomization (days) | No. of administered doses of IPs |
|---|---|---|
| SOC | 5 | – |
| SOC | 7 | – |
| SOC | 8 | – |
| SOC | 9 | – |
| SOC | 12 | – |
| SOC | 12 | – |
| SOF-DCV | 2 | 3 doses |
| SOF-DCV | 6 | 6 doses |
| SOF-DCV | 2 | 3 doses |
| SOF-DCV | 6 | 1 dose |
| SOF-DCV | 6 | 7 days |
| SOF-DCV | 7 | 7 days |

Abbreviations: DCV, daclatasvir; IPs, investigational products; RDV, ravidasvir; SOC, standard of care; SOF, sofosbuvir.

is efficient and well-tolerated among different populations suffering from chronic HCV infection with or without comorbidities.[30] A recent molecular docking study suggested that RDV could be a potential antiviral drug against SARS-CoV-2 by inhibiting viral 3CLpro.[31] Nevertheless, in our study, we did not observe the superiority of a combination of SOF-RDV versus SOC.

The current study was a randomized, open-label, prospective trial to evaluate the efficacy and safety of adding a combination of SOF plus SOF or RDV to standard medical care for COVID-19 patients.

The results showed that there was a statistically significant reduction in the count of symptoms for the SOF-DCV arm on Days 7 and 10 compared with the SOC group. This statistically significant improvement was not reached in the SOF-RDV arm. By virtue of the natural history of the disease, significant improvement in oxygen saturation was observed over time for all study groups, with a consistently maintained significant benefit with SOF-DCV but not SOF-RDV versus SOC.

In contrast to our findings, Roozbeh and colleagues reported that SOF-DCV plus HCQ was not efficient in reducing COVID-19 symptoms or rate of hospitalization when compared to HCQ alone at Day 7 of follow-up. However, the study included a small sample size of outpatients with mild COVID-19, and the assessment of outcomes was not objective, increasing the risk of bias.[32]

A study by Sadeghi et al.[33] showed that a combination of SOF-DCV in addition to standard care was more efficient in reducing hospital stay, but the study could not assess the correlation between viral load and clinical outcomes among COVID-19 patients to confirm the positive effect of these antiviral drugs used. In our study, RT-PCR for COVID-19 patients was repeated on Days 7 and 17, the proportion of patients with undetectable SARS-COV-2 RNA on two consecutive nasopharyngeal swabs was higher in the SOF-DCV group versus SOC; however, the difference was not statistically significant (46.2% vs. 40.0%, OR = 1.29, $p = 0.581$). A more recent study[34] showed that the combination of SOF-DCV added to standard therapy (compared to standard therapy) was associated with slightly lower mortality, no differences in ICU admission, oxygen therapy, or ventilation. They showed, however, shorter duration of hospital stay, and faster PCR negativity at Day 14 in the group that received SOF-DCV

In our study, ICU admissions were notably less recorded in the SOF-DCV group compared to SOC (3 [7.5%] vs. 8 [20.0%], $p = 0.09$). The difference was statistically significant at 10% α error, revealing an exciting signal of efficacy that needs to be confirmed upon investigating a larger sample size of patients.

ICU admission was also more frequent in the SOF-RDV group than SOF-DCV group (5 [12.5%] vs. 3 [7.5%]), this finding could suggest the DCV alone could be responsible for the positive effect observed in the SOF-DCV arm, this postulation is supported by the findings of the in-vitro studies that showed that SOF is inactive inside the lung cells, and it exerts its inhibitory function inside hepatic cells more than lung cells.[25] Another supporting evidence is the observations of Nourian et al.'s[35] study, which reported that the rate of ICU admission was not different between COVID-19 patients treated with a combination of SOF/ledipasvir in addition to standard of care therapy compared to standard care therapy only. A combination of SOF/velpatasvir was also found ineffective in improving clinical status or reducing mortality rates.[36] So, clinical trials investigating monotherapy versus a combination of antivirals drugs to elucidate this hypothesis are recommended.

Indeed, most of the recorded adverse events were due to SARS-CoV-2 infection itself and not the treatment used, and the reported side effects were less in the SOF-DCV arm than in the SOC and SOF-RDV arms.

These positive trends were observed in a meta-analysis that included four studies investigating SOF-DCV combination to treat moderate to severe COVID-19 infections.[37] Of these four studies, there were 3 RCTs[38–40] and one open-label parallel trial.[41] These studies revealed better clinical improvement rates, lower mortality, fewer ICU admissions, and shorter hospital stays for SOF-DCV groups versus the comparators. However, these outcomes did not reach statistical significance in every single study. Grouping the results in the meta-analysis showed significant improvement in clinical recovery and reduction in ICU admission and mortality for the SOF-DCV group versus comparators.

Our study has several limitations, including the small sample size, the open-label design, and the lack of a placebo group. Larger blinded randomized placebo-controlled trials involving larger and more homogenous populations and measuring more biological parameters for clinical outcomes are required for accurate estimation of efficacy of SOF-DCV among different COVID-19 patients.

At the time of writing this manuscript, 12 studies (with nine either ongoing or pending) are registered on clincaltrials. gov evaluating SOF with or without DCV for treatment of patients with COVID-19 of different stages of severity (NCT04530422, NCT04497649, NCT04460443, NCT04498936, NCT04561063, NCT04535869,

NCT04443725, NCT04773756, NCT04532931, NCT04468087, NCT04729153, NCT04757272). Our findings highlight the promising potential of SOF-DCV to offer an effective, safe, cost-effective treatment option COVID-19 management among diverse populations. Although extensive research is ongoing to develop repurposed antiviral agents, the small sample size in this study was a limiting factor, and larger studies are needed.

## 6 | CONCLUSION

This study adds to the existing literature on the efficacy and safety of SOF-DCV combination to treat moderate to severe COVID-19 cases. SOF-DCV addition to the standard of care was found to improve clinical symptoms, oxygen saturation, and decrease ICU admission. The results highlight a potential for the combination to be integrated as an effective and safe antiviral agent to treat such cases.

### REGISTRATION AND EC APPROVAL

The study protocol was approved by the National Liver Institute ethical committee (NLI IRB 00003413) and by The Egyptian MoH IRB (IRB 0000687). Local ethics committees in the other three sites also approved the study protocol. The trial is registered at the ISRCTN registry with registration number ISRCTN21085622.

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### CONFLICT OF INTERESTS

Sherine Helmy and Ola Elrouby are employees of PHARCO, the mother company of the European Egyptian Pharmaceutical Industries (Egypt). Imam Waked received research funding or speaker honoraria from AbbVie, Arena, Eva Pharma, Gilead Sciences, Marcyrl, Novartis, Pharco, and Roche. Other authors declare that there are no conflict of interests.

### AUTHOR CONTRIBUTIONS

Conceptualization: Sherine Helmy and Ola Elrouby; methodology and study design development: Ehab Kamal, Ola Elrouby and Mostafa Salah; project leadership: Mostafa Salah; coordinating investigator: Sherif Abbass; principal investigator at National Liver Institute: Imam Waked; sub-investigators at National Liver Institute: Mohsen Salama, Tary Salman, and Alyaa Sabry; principal investigator at Mahalla Fever Hospital: Mohamed Einar; principal investigator at Menouf Fever Hospital: Ismail Shehab; sub-investigators at Menouf Fever Hospital: Mounir Saif; principal investigator at Shebin Fever Hospital: Mahmoud Farouk; DATA entry: Wael Abdel-Razek, Ahmed Abdelgwad, Neamt Sakr, Mohamed Elgazzar, Eman El-hosieny, Mai Mansour, Doaa Mahdi, and El-Sayed Tharwa; manuscript reviewing and editing: Imam Waked. All authors have read and agreed to the published version of the manuscript.

### DATA AVAILABILITY STATEMENT

The protocol and data that support the findings of this study are available on request from the corresponding author.

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### REFERENCES

1. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. *WHO Director General's speeches* 4; 2020.
2. BioCentury - COVID-19 Resource Center. https://www.biocentury.com/coronavirus
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020;383:1813-1826.
4. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet Lond Engl*. 2020;395:1569-1578.
5. Venkataraman S, Prasad BVLS, Selvarajan R. RNA dependent RNA polymerases: insights from structure, function and evolution. *Viruses*. 2018;10:76.
6. Morse JS, Lalonde T, Xu S, Liu WR. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem Eur J Chem Biol*. 2020;21:730-738.
7. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci*. 2020;248:117477.
8. Chen YW, Yiu C-PB, Wong K-Y. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL (pro)) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. *F1000 Research*. 2020;9:129.
9. Mevada V, Dudhagara P, Gandhi H, Vaghamshi N, Beladiya U, Patel R. Drug repurposing of approved drugs elbasvir, ledipasvir, paritaprevir, velpatasvir, antrafenine and ergotamine for combating COVID19. *ChemRxiv*. 2020. https://doi.org/10.26434/chemrxiv.12115251.v2
10. Omar H, El Akel W, Elbaz T, et al. Generic daclatasvir plus sofosbuvir, with or without ribavirin, in treatment of chronic hepatitis C: real-world results from 18 378 patients in Egypt. *Aliment Pharmacol Ther*. 2018;47:421-431.
11. Jácome R, Campillo-Balderas JA, Ponce de León S, Becerra A, Lazczno A. Sofosbuvir as a potential alternative to treat the SARS-CoV-2 epidemic. *Sci Rep*. 2020;10:9294.
12. Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug–target interaction deep learning model. *Comput Struct Biotechnol J*. 2020;18:784-790.
13. Abbaspour Kasgari H, Moradi S, Shabani AM, et al. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. *J Antimicrob Chemother*. 2020;75:3373-3378.
14. Merat S. SD1000: high sustained viral response rate in 1361 patients with hepatitis c genotypes 1, 2, 3, and 4 using a low-cost, fixed-dose combination tablet of generic sofosbuvir and daclatasvir: a multicenter, phase III clinical trial. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2020;70:2206-2212.

15. WHOWHO's COVID-19 Clinical management Living guidance. - Section 6: COVID-19 disease severity: In: Screening, triage and clinical assessment: early recognition of patients with COVID 19, Table 6.3: disease severity. 2021. Accessed July 18, 2021. https://apps.who.int/iris/rest/bitstreams/1328457/retrieve
16. Masoud H, Elassal G & Hassany M et al. Management Protocol for COVID-19 patients MoHP Protocol for COVID19. November 2020.
17. Yuan J, Zou R, Zeng L, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. *Inflamm Res Off J Eur Histamine Res Soc A*. 2020;69:599-606.
18. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA*. 2020; 323:2052-2059.
19. Ozga A-K, Kieser M, Rauch G. A systematic comparison of recurrent event models for application to composite endpoints. *BMC Med Res Methodol*. 2018;18:2.
20. Milken. Milken Institute's COVID-19Treatment and Vaccine Tracker tracks the development of treatments and vaccines for COVID-19 at covid-19tracker.milkeninstitute.org #COVID19 #coronavirus #COVID19treatment #COVID19vaccine @MilkenInstitute @FirstPersonSF. 2020. https://covid-19tracker.milkeninstitute.org/
21. WHO Solidarity Trial C, Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19—Interim WHO solidarity trial results. *N Engl J Med*. 2021;384:497-511.
22. Tu H, Tu S, Gao S, Shao A, Sheng J. Current epidemiological and clinical features of COVID-19; a global perspective from China. *J Infect*. 2020;81:1-9.
23. Nourian A, Khalili H. Sofosbuvir as a potential option for the treatment of COVID-19. *Acta Bio Medica Atenei Parm*. 2020;91:239-241.
24. Smith MA, Regal RE, Mohammad RA. Daclatasvir: a NS5A replication complex inhibitor for hepatitis C infection. *Ann Pharmacother*. 2016; 50:39-46.
25. Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, et al. In vitro antiviral activity of the anti-HCV drugs daclatasvir and sofosbuvir against SARS-CoV-2, the aetiological agent of COVID-19. *J Antimicrob Chemother. dkab072*. 2021;76:1874-1885. https://doi.org/10.1093/jac/dkab072
26. Pol S, Vallet-Pichard A, Corouge M. Daclatasvir–sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the clinical trials to real life. *Hepatic Med Evid Res*. 2016; 8(1):21-26. http://doi.org/10.2147/hmer.s62014
27. Chien M, Anderson TK, Jockusch S, et al. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. *J Proteome Res*. 2020;19:4690-4697.
28. Ju J, Kumar S, Li X, Jockusch S, Russo JJ. Nucleotide analogues as inhibitors of viral polymerases. *bioRxiv*. 2020.01.30.927574 2020. https://doi.org/10.1101/2020.01.30.927574
29. Esmat G, Elbaz T, El Raziky M, et al. Effectiveness of ravidasvir plus sofosbuvir in interferon-naïve and treated patients with chronic hepatitis C genotype-4. *J Hepatol*. 2017. S0168-8278(17):32286-32289. https://doi.org/10.1016/j.jhep.2017.09.006
30. Andrieux-Meyer I, Tan SS, Thanprasertsuk S, et al. Efficacy and safety of ravidasvir plus sofosbuvir in patients with chronic hepatitis C infection without cirrhosis or with compensated cirrhosis (STORM-C-1): interim analysis of a two-stage, open-label, multicentre, single arm, phase 2/3 trial. *Lancet Gastroenterol. Hepatol*. 2021;6:448-458.
31. Bera K. Binding and inhibitory effect of ravidasvir on 3CLpro of SARS-CoV-2: a molecular docking, molecular dynamics and MM/PBSA approach. *J Biomol Struct Dyn*. 2021:1-8. https://doi.org/10.1080/07391102.2021.1896388
32. Roozbeh F, Saeedi M, Alizadeh-Navaei R, et al. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. *J Antimicrob Chemother*. 2020;76: 753-757. https://doi.org/10.1093/jac/dkaa501
33. Sadeghi A, Ali Asgari A, Norouzi A, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. *J Antimicrob Chemother dkaa334*. 2020;75:3379-3385. https://doi.org/10.1093/jac/dkaa334
34. El-Bendary M, Abd-Elsalam S, Elbaz T, et al. Efficacy of combined Sofosbuvir and Daclatasvir in the treatment of COVID-19 patients with pneumonia: a multicenter Egyptian study. *Expert Rev Anti Infect Ther*. 2021:1-5. https://doi.org/10.1080/14787210.2021.1950532
35. Khalili H, Nourian A, Ahmadinejad Z, et al. Efficacy and safety of sofosbuvir/ledipasvir in treatment of patients with COVID-19; a randomized clinical trial. *Acta Bio Medica Atenei Parm*. 2020;91:e2020102.
36. Sayad B, Khodarahmi R, Najafi F, et al. Efficacy and safety of sofosbuvir/velpatasvir versus the standard of care in adults hospitalized with COVID-19: a single-centre, randomized controlled trial. *J Antimicrob Chemother*. 2021;76:2158-2167. https://doi.org/10.1093/jac/dkab152
37. Chan HT, Chao CM, Lai CC. Sofosbuvir/daclatasvir in the treatment of COVID-19 infection: A meta-analysis. *J Infect*. 2021;82:e34-e35. Sofosbuvir/daclatasvir in the treatment of COVID-19 infection: A meta-analysis.
38. Abbaspour Kasgari H, Moradi S, Shabani AM, et al. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. *J Antimicrob Chemother*. 2020;75:3373-3378. https://doi.org/10.1093/jac/dkaa332
39. Sadeghi A, Ali Asgari A, Norouzi A, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. *J Antimicrob Chemother*. 2020;75:3379-3385.
40. Roozbeh F, Saeedi M, Alizadeh-Navaei R, et al. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. *J Antimicrob Chemother*. 2021;76:753-757.
41. Eslami G, Mousaviasl S, Radmanesh E, et al. The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. *J Antimicrob Chemother*. 2020;75:3366-3372.

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