Sofosbuvir with daclatasvir and the outcomes of patients with COVID-19: a systematic review and meta-analysis with GRADE assessment

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ABSTRACT

Introduction
COVID-19 remains one of the most prevalent diseases globally despite the best effort to contain them.1 Although most patients have mild–moderate clinical symptoms, a significant proportion of them developed lethal acute complications.2–4 Optimal medications for COVID-19 remained poorly defined, and many completed trials showed negative results.5

SARS-CoV-2 is a positive-sense single-stranded RNA virus that relies on RNA-dependent RNA-polymerase (RdRp) for viral replication.6 Sofosbuvir/daclatasvir (SOF/DCV) is a direct-acting antiviral drug that has been shown to inhibit RdRp of hepatitis C virus (HCV).7 8 Preclinical studies indicate the potential activities of SOF and DCV on SARS-CoV-2 RdRps, although the mixed results.9 10 Several clinical studies indicate the potential benefit of SOF/DCV in patients with COVID-19.9 11 12 These drugs have relatively mild side effects and are affordable. Thus, it can be used as a routine treatment if proven to be effective.9 13 This systematic review and meta-analysis aims to evaluate the effect of SOF/DCV on mortality, the need for intensive care unit (ICU) admission or invasive mechanical ventilation (IMV) and clinical recovery in patients with COVID-19.

Materials and methods
We performed a systematic literature search through the PubMed, Scopus and Embase from the inception of databases until 6 April 2021. The intervention group was SOF/DCV, and the control group was standard of care. The primary outcome was mortality, defined as clinically validated death. The secondary outcomes were (1) the need for ICU admission or IMV and (2) clinical recovery. The pooled effect estimates were reported as risk ratios (RRs).

Results
There were four studies with a total of 231 patients in this meta-analysis. Three studies were randomised controlled trial, and one study was non-randomised. SOF/DCV was associated with lower mortality (RR: 0.31 (0.12, 0.78); p=0.013; I²: 0%) and reduced need for ICU admission or IMV (RR: 0.35 (0.18, 0.69); p=0.002; I²: 0%), Clinical recovery was achieved more frequently in the SOF/DCV (RR: 1.20 (1.04, 1.37); p=0.011; I²: 21.1%). There was a moderate certainty of evidence for mortality and need for ICU/IMV outcome, and a low certainty of evidence for clinical recovery. The absolute risk reductions were 140 fewer per 1000 for mortality and 186 fewer per 1000 for the need for ICU/IMV. The increase in clinical recovery was 146 more per 1000.

Conclusion
SOF/DCV may reduce mortality rate and need for ICU/IMV in patients with COVID-19 while increasing the chance for clinical recovery.

Protocol registration
PROSPERO: CRD42021247510.

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COVID-19 remains one of the most prevalent diseases globally despite the best effort to contain them.1 Although most patients have mild–moderate clinical symptoms, a significant proportion of them developed lethal acute complications.2–4 Optimal medications for COVID-19 remained poorly defined, and many completed trials showed negative results.5

SARS-CoV-2 is a positive-sense single-stranded RNA virus that relies on RNA-dependent RNA-polymerase (RdRp) for viral replication.6 Sofosbuvir/daclatasvir (SOF/DCV) is a direct-acting antiviral drug that has been shown to inhibit RdRp of hepatitis C virus (HCV).7 8 Preclinical studies indicate the potential activities of SOF and DCV on SARS-CoV-2 RdRps, although the mixed results.9 10 Several clinical studies indicate the potential benefit of SOF/DCV in patients with COVID-19.9 11 12 These drugs have relatively mild side effects and are affordable. Thus, it can be used as a routine treatment if proven to be effective.9 13 This systematic review and meta-analysis aims to evaluate the effect of SOF/DCV on mortality, the need for intensive care unit (ICU) admission or invasive mechanical ventilation (IMV) and clinical recovery in patients with COVID-19.

Materials and methods
We performed a systematic literature search through PubMed, Scopus and Embase using the terms ‘(SARS-CoV-2 or 2019-nCoV or COVID-19) and (sofosbuvir or daclatasvir or Sofosbuvir/daclatasvir)’ from the inception of databases until 6 April 2021. Screening of title/abstracts were performed by two independent authors. The eligibility of the articles was assessed based on the inclusion and exclusion criteria. Discrepancies that arose were resolved by discussion.

Inclusion and exclusion criteria
Studies that match the following criteria were included: (1) randomised controlled trials (RCTs) or observational studies in patients with COVID-19, (2) comprise of SOF/DCV arm and a control arm and (3) reporting either (a) mortality or (b) the need for ICU admission or IMV or (c) clinical recovery.

Studies that match one of the following criteria were excluded: (1) conference papers, (2) abstract-only publications, (3) review articles and (4) commentaries. We did not impose any language restriction for this systematic review.

Data extraction
Two authors independently extracted data from the studies for the first author, study design, country of origin, setting of the study (inpatients or outpatients), details and dosing of the intervention group, details and dosing of the control group, sample size,
age, gender, diabetes, chronic obstructive pulmonary disease, chronic kidney diseases, cardiovascular diseases and the laboratory values, including haematology parameters and liver and renal functions. Discrepancies were resolved by discussion.

Risk of bias assessment
We used the Cochrane Risk of Bias Assessment for RCTs and Newcastle-Ottawa Scale (NOS). NOS comprises of selection, comparability and outcome. Cochrane Risk of Bias Assessment assessed the possibility for selection, performance, detection, attrition, selective reporting and other biases. Discrepancies during the process were resolved by discussion. Grading of Recommendations Assessment, Development and Evaluation framework was used to determine the certainty of evidence.

Intervention and outcome
The intervention group was SOF/DCV, defined as 400 mg SOF and 60 mg DCV to treat COVID-19. The control group was the standard of care or placebo set by each trial/studies. The primary outcome was mortality, defined as clinically validated death. The pooled effect estimate was reported as risk ratio (RR). The secondary outcomes were (1) the need for ICU admission or IMV and (2) clinical recovery. Clinical recovery was defined as resolution of fever (≤37.2°C) with a normal respiratory rate (≤24 breaths/min) and oxygen saturation (≥94%) without the need for supplementary oxygen therapy for at least 24 hours or can be discharged from the hospital based on clinical improvement. The pooled effect estimate was reported as RRs.

Statistical analysis
DerSimonian Laird random-effects meta-analysis was used to calculate the pooled RRs for mortality, need for ICU admission/IMV and clinical recovery in the SOF/DCV compared with the control group. P values (two-tailed) of ≤0.05 were considered statistically significant. To evaluate heterogeneity, we used Cochran’s Q test and $I^2$ statistics; $I^2$ values above 50% and p value below 0.10 indicate significant heterogeneity. Sensitivity analysis was performed for outpatient studies. STATA V.16.0 was used to perform the statistical analysis.

RESULTS
Baseline characteristics
There were four studies with a total of 231 patients in this systematic review and meta-analysis (figure 1). Three studies were RCT, and one study was non-randomised (table 1).

SOF/DCV and outcomes
SOF/DCV administration was associated with reduced mortality (RR: 0.31 (0.12, 0.78), p=0.013; $I^2$: 0%, p=0.400) (figure 2). Use of SOF/DCV was associated with reduced need for ICU admission or IMV (RR: 0.35 (0.18, 0.69), p=0.002; $I^2$: 0%, p=0.700) (figure 3). Clinical recovery was achieved more frequently in the SOF/DCV (RR: 1.20 (1.04, 1.37), p=0.011; $I^2$: 21.1%, p=0.284) (figure 4). Sensitivity analysis by removal of outpatient setting (Roozbeh et al 2021) showed that SOF/DCV
use in in-hospital setting was associated with increased clinical recovery (RR: 1.23 (1.08, 1.40), p<0.001; I²: 0.3%, p=0.367).

Risk of bias assessment
The risk of bias assessment of individual studies indicates low–moderate risk of bias (figure 5) (table 1).

Certainty of evidence
There was a moderate certainty of evidence for the mortality and need for ICU/IMV outcome, and a low certainty of evidence for clinical recovery (table 2). The absolute risk reductions were 140 fewer per 1000 (from 178 fewer to 45 fewer) for mortality and 186 fewer per 1000 (from 234 fewer to 89 fewer) for the need for ICU/IMV. The increase in clinical recovery was 146 more per 1000 (from 29 more to 278 more).

**DISCUSSION**
This meta-analysis indicates that SOF/DCV use may reduce the mortality rate and need for ICU/IMV in patients hospitalised with moderate–severe COVID-19. The overall clinical recovery rate was also achieved more frequently in patients receiving SOF/DCV, especially in hospitalised patients. This pooled analysis has low heterogeneity, which indicates small risk of inconsistency. The CI does not cross the imprecision threshold. Large study effects were demonstrated for mortality and the need for ICU/IMV outcomes. However, all included studies originated from a single country (Iran). Additionally, all studies have small sample size and positive results except for one in ‘clinical recovery’ outcome. One of the study that was excluded during the systematic literature search, uses a combination of SOF/ledipasvir, the open-label randomised clinical trial on 82 patients with mild–moderate COVID-19 indicates no

| Table 1 | Baseline characteristics of the included studies |
|---------|-----------------------------------------------|
| Study   | Eslami et al 2020 | Abbaspour Kasgari et al 2020 | Roozbeh et al 2021 | Sadeghi et al 2020 |
| Trial registration number | IRCT2020032404685N2 | IRCT20200328046886N1 | IRCT2020040304962N1 | IRCT20200128046294N2 |
| Country of origin | Iran | Iran | Iran | Iran |
| Setting | Inpatients | Inpatients | Outpatients | Inpatients |
| COVID-19 severity | Severe | Moderate | Unclear | Moderate/severe |
| Sample size | 35 vs 27 | 24 vs 24 | 27 vs 28 | 33 vs 33 |
| Intervention | 400 mg SOF and 60 mg DCV | 400 mg SOF and 60 mg DCV+60 mg ribavirin | 400 mg SOF and 60 mg DCV+HCQ | 400 mg SOF and 60 mg DCV+SOC |
| Control | 600 mg ribavirin | 600 mg ribavirin+HCQ+400 mg lopinavir and 100 mg ritonavir two times per day | HCQ | SOC |
| Age (years) | 61 | 53 | 45 | 60 |
| Male (%) | 51 | 37 | 47.3 | 51.5 |
| Diabetes (%) | 27.4 | 29.2 | – | 42.4 |
| COPD (%) | 9.6 | 2.1 | – | – |
| CKD (%) | 3.8 | – | – | – |
| CVD (%) | 23.1 | 23 | – | – |
| Haemoglobin (g/L) | 120 | 120 | – | 120 |
| WBC (×10⁹/L) | 7.6 | 6.3 | – | 8.5 |
| Lymphocyte (×10⁹/L) | 1.2 | – | – | 1.3 |
| AST (IU/L) | 30 | 26 | – | 35 |
| ALT (IU/L) | 23 | 22 | – | 32 |
| Creatinine (mg/dL) | 1.1 | 0.9 | – | 1 |
| Risk of bias | NOS: 7 out of 9 | Low–moderate | Low–moderate | Low–moderate |
| Funding | Abadan Faculty of Medical Sciences | Mazandaran University of Medical Sciences | Vice-Chancellor for Research | Digestive Disease Research Institute of Tehran |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DCV, daclatasvir; HCQ, hydroxychloroquine; NOS, Newcastle-Ottawa Scale; RCT, randomised controlled trial; SOC, standard of care; SDF, sofosbuvir; WBC, white blood cells.

**Figure 2** Sofosbuvir/daclatasvir (SOF/DCV) and mortality.

**Figure 3** Sofosbuvir/daclatasvir (SOF/DCV) and the need for intensive care unit admission (ICU) or invasive mechanical ventilation (IMV).

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SARS-CoV-2 is a positive-sense RNA virus that highly relies on an RdRp for its replicating process. SOF/DCV has proven to inhibit the HCV replication effectively and potentially inhibit SARS-CoV-2 replication. Similar replication mechanism is demonstrated by other viral families, therefore, raising the possibility of using a particular antiviral regimen interchangeably, especially in the context of SARS-CoV-2 infections.

Several key proteins have been identified in the replication of HCV, such as non-structural protein 5A (NS5A) and NS5B, which become a target of direct-acting anti-viral activity of the SOF. Both HCV proteins NS5A and NS5B might share several similarities with SARS-CoV-2 proteins.

Table 2: GRADE assessment

| Certainty assessment | Number of patients | Effect | Certainty | Importance |
|----------------------|-------------------|--------|-----------|------------|
| Number of studies    | Study design      | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Sofosbuvir/daclatasvir | Control | Relative (95% CI) | Absolute (95% CI) | 95 fewer per 1000 (from 178 fewer to 45 fewer) | 146 more per 1000 (from 29 more to 278 more) | GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICU, intensive care unit; IMV, invasive mechanical ventilation; RR, Risk ratio.

Mortality

- 3 Randomised trials
- Serious*: Not serious; Not serious; Not serious
- Publication bias strongly suspected strong association†
- 5/92 (5.4%)
- 1784 (20.2%)
- RR: 0.31 (0.12 to 0.78)
- Moderate

Need for ICU/IMV

- 3 Randomised trials
- Serious*: Not serious; Not serious; Not serious
- Publication bias strongly suspected strong association†
- 9/92 (9.8%)
- 2484 (28.6%)
- RR: 0.35 (0.18 to 0.69)
- Moderate

Clinical recovery

- 4 Randomised trials
- Serious*: Not serious; Not serious; Not serious
- Publication bias strongly suspected‡
- 105/118 (89.0%)
- 82/112 (73.2%)
- RR: 1.20 (1.04 to 1.38)
- Low

*One study is not a randomised trial; two studies are open label.
†All studies originated from a single country. Small-sample size with all positive studies.
‡All studies originated from a single country. Small-sample size with all positive studies except for one.

SOF/DCV and clinical recovery.

Figure 4: Sofosbuvir/daclatasvir (SOF/DCV) and clinical recovery.

Figure 5: Risk of bias assessment for randomised controlled trials.
For instance, HCV NS5A is a multifunctional protein involved in HCV replication process and interferon signalling pathway. This protein resembles the non-structural proteins (nsp) 1–14 in SARS-CoV-2. HCV NS5B RNA polymerase might resemble RdRp of SARS-CoV-2, which is also known as nsp12. The SARS-CoV-2 nsp12 along with nsp7 and nsp8, which serve as its cofactor, catalyse the synthesis of viral RNA and thus playing an integral role in the replication of SARS-CoV-2. DCV binds to HCV NS5A and interferes with viral RNA replication and assembly and the production of inflammatory cytokines. In SARS-CoV-2, DCV shows an inhibition of viral replication and induction of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha), which play a significant role in cytokine storm.

SOF is a nucleotide analogue that targets HCV RNA polymerase NS5B, therefore, preventing the addition of the next nucleotide and inhibiting RNA elongation. The action of SOF is also extended beyond HCV as it also demonstrates similar antiviral activity against other viruses. In SARS-CoV-2, SOF serves as a competitive inhibitor and chain terminator of the SARS-CoV-2 RNA polymerase, which is well shown in an enzymatic assay. Structural superposition of the SARS-CoV-2 nsp12 with HCV NS5B was found to bind with SOF, therefore, showing its inhibitory effect. This antiviral activity is retained possibly due to the preservation of RdRp structure among RNA viruses.

In silico, the potential activities of SOF/DCV against SARS-CoV-2 are well demonstrated. This discovery is reinforced by the finding of in vitro activity against SARS-CoV-2 demonstrated by SOF/DCV in Huh-7 and Calu-3 cells. Although current evidence is still lacking, to date, SOF/DCV is known for its good safety profile in treating HCV and shows a promising result against SARS-CoV-2. Therefore, further study is needed to elucidate the use of SOF/DCV in the treatment of COVID-19.

The limitations of this systematic review and meta-analysis were due to a small number and sample size of the studies.

Main messages

- Sofosbuvir/daclatasvir (SOF/DCV) may lower mortality in patients with COVID-19.
- SOF/DCV was associated with significant reduction in the need for intensive care unit/invasive mechanical ventilation.
- SOF/DCV was associated with higher chance of clinical recovery.

Current research questions

1. Additional high-quality randomised controlled trials are required for definite conclusion.
2. Studies originating from other countries are required to increase the certainty of evidence.

What is already known on the subject

- SARS-CoV-2 relies on RNA-dependent RNA-polymerase (RdRp) for viral replication.
- Sofosbuvir/daclatasvir are direct acting antiviral drugs that have been shown to inhibit RdRp of hepatitis C virus.

Moreover, all studies originated from Iran, and it is not known whether it will be applicable to patients from other countries. Further investigation is needed to obtain a higher certainty of evidence.

CONCLUSION

SOF/DCV use may reduce mortality rate and need for ICU/IMV in patients with COVID-19 while increasing the chance for clinical recovery.

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