Clinical outcomes of sofosbuvir-based antivirals in patients with COVID-19: A systematic review and meta-analysis of randomized trials

Abstract

Background

Few randomized trials evaluated the effect of combination therapy of Sofosbuvir-based direct-acting antivirals on mortality risk in patients with COVID-19. Therefore, we aimed to summarize the overall evidence in the form of a systematic review and meta-analysis.

Methods

A systematic literature search with no language restriction was performed in electronic databases and preprint repositories to identify eligible randomized trials published up to July 8, 2021. A random-effects model was used to estimate the pooled odds ratio (OR) for outcomes of interest using sofosbuvir combined with direct-acting antiviral agents relative to non-use of sofosbuvir-based direct-acting antiviral agents at 95% confidence intervals (CI).

Results

The estimated effect of sofosbuvir-based direct-acting antiviral agents on the mortality risk indicated a significantly reduced risk (pooled odds ratio = 0.59; 95% confidence interval 0.36 to 0.99) with inadequate evidence against our model hypothesis of no significant difference at the current sample size. However, no statistically significant difference in the odds of development of composite endpoint of severe illness (pooled odds ratio = 0.79; 95% confidence interval 0.43 to 1.44), with the administration of a combination of sofosbuvir-based direct-acting antiviral agents among patients with COVID-19, relative to non-administration of sofosbuvir-based direct-acting antiviral agents.

Conclusion

The sofosbuvir-based direct-acting antiviral agents have no protective effects against the development of severe illness in patients with COVID-19 with the current dosing regimen. Whether sofosbuvir-based direct-acting antiviral agents could offer mortality benefits would require further investigations.

Keywords: Antivirals, COVID-19, mortality, SARS-CoV-2, severity, sofosbuvir

1. Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) in late December 2019, morbidity and mortality continue to increase worldwide, with more than 181 million cases have been reported, and over 3 million people lost their lives due to this deadly disease, and even with numerous reports of re-infection [1,2]. The spectrum of COVID-19 ranges from asymptomatic to critical; most cases are of mild-to-moderate severity. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative pathogen for COVID-19; antiviral agents effective against SARS-CoV-2 may be useful across the whole spectrum of severity in COVID-19.

Coronaviruses are nidovirale order members, including alfa, beta, gamma, and delta family with the largest known RNA. SARS-CoV-2 belongs to the family of beta coronaviruses, consisting of other members, including Middle East respiratory syndrome human coronavirus (MERS-CoV) and severe acute respiratory syndrome human coronavirus (SARS-HCoV). SARS-CoV-2 and other beta coronaviruses enter the host cell and assemble a multisubunit RNA-dependent RNA polymerase (RdRp) complex of viral nonstructural proteins such as main protease (Mpro) and helicase that plays an essential role in the transcription and replication of the viral genome. Other viral families such as the hepatitis C virus share similar replication mechanisms, and therefore, the available antivirals may be used to neutralize SARS-CoV-2.

Sofosbuvir-daclatasvir is an effective direct-acting antiviral agent against the hepatitis C virus. Sofosbuvir inhibits NS5B-RdRp, a crucial enzyme in replicating hepatitis C virus, while ledipasvir inhibits NS5A, an essential protein for RdRp function. A study (*in-silico*) reported that sofosbuvir and daclatasvir could have theoretical antiviral activity against SARS-CoV-2 due to their predictive ability to bind to RdRp and Mpro with high energy. Therefore, they are attractive to be repurposed for the treatment of COVID-19 [3,4]. Indeed, in an in vitro study [5], sofosbuvir and daclatasvir demonstrated antiviral activity against SARS-CoV-2-infected Huh-7 and Calu-3 cells. In the same study [5], daclatasvir demonstrated antiviral activity against Vero E6-infected cells but not for sofosbuvir. Sofosbuvir has also exhibited neutralizing activity against SARS-CoV-2-infected brain organoids, suggesting its potential protective effects against COVID-19 related neurological complications [6].

Velpatasvir and ledipasvir, used mainly in combination with sofosbuvir, are also direct-acting antiviral agents against the hepatitis C virus by targeting the NS5A protein. There are reports of inhibitory activity of velpatasvir tailored to A chain and B chain active sites of the coronavirus 3C-like protease (3CLpro) [7]. On the other hand, based on *in silico* experiments with docking, ledipasvir is effective against SARS-CoV-

2 due to its potential to bind tightly to the RdRp and 3CLpro of SARS-CoV-2 and maybe also one of the potential drugs for the treatment of COVID-19 [7,8]. In addition, in a recent in vitro study, ledipasvir exerted antiviral action against SARS-CoV-2-infected Vero E6 cells [8].

Two-component direct-acting antivirals (sofosbuvir-daclatasvir, sofosbuvir-velpatasvir, sofosbuvir-ledipasvir) may be well-favored candidates to be repurposed for the treatment of COVID-19 because they could inhibit two different coronavirus enzymes and thus decreases the development of resistance during antiviral therapy. However, few randomized trials had evaluated the effect of sofosbuvir-based direct-acting antivirals on the risk of mortality and severe illness in patients with COVID-19. Therefore, we aimed to summarize the overall evidence in the form of a systematic review and meta-analysis of the association between the use of sofosbuvir-based direct-acting antivirals and risks of mortality and severe illness in patients with COVID-19.

2. Methods

2.1 Identification and Eligibility of Trials

This study was conducted according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. Two investigators (CSK and SSH) independently conducted systematic literature searching in electronic databases, including PubMed, Cochrane Central Register of Controlled Trials, Google Scholar, and preprint repositories (SSRN, Research Square, and medRxiv), up to July 8, 2021, with the following keywords and their MeSH terms: "COVID-19", "SARS-CoV-2", "novel coronavirus disease", "direct-acting antiviral", "sofosbuvir", "daclatasvir", "ledipasvir", "velpatasvir", "NS5A inhibitor", "nucleotide polymerase inhibitor", "randomized", "controlled trial", and "clinical trial" without language restrictions. The Clinical Trial Registries of the United States (clinicaltrials.gov) were also searched for ongoing registered clinical trials of sofosbuvir-based direct-acting antiviral agents for the treatment of COVID-19, which had released their findings. In addition, we hand-searched the reference lists of relevant articles to identify additional studies. The inclusion criteria of studies for this systematic review and meta-analysis were randomized controlled trials comparing the clinical outcomes between sofosbuvir-based direct-acting antiviral agents (sofosbuvir-daclatasvir, sofosbuvir-velpatasvir, sofosbuvir-ledipasvir, sofosbuvir alone, etc.) and their comparators for the treatment of patients with COVID-19. The single-arm trials, non-randomized trials, and trials that report only virological outcomes were excluded.

2.2 Outcomes and Data Extraction

The outcome of interest was all-cause mortality and the composite endpoint of severe illness (intubation/mechanical ventilation and/or admission into intensive care units). Two investigators (CSK and SSH) independently evaluated each study, who also extracted the study characteristics. Study characteristics extracted included first author's surname, year of publication, trial design, the country where the trial was performed, disease severity of study population, mean/median age of patients, regimen of sofosbuvir-based direct-acting antiviral agents, the regimen of comparative agents, number of deaths in the intervention arm, number of deaths in the control arm, number of patients with severe illness in the intervention arm, and number of patients with severe illness in the control arm.

2.3 Risk of Bias Assessment

Two investigators assessed the risk of bias of the included trials with Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), a standardized method to evaluate potential bias in reports of randomized interventions [10]. RoB 2 is structured into a fixed set of bias domains, which include 'randomization', 'deviations from intervention', 'missing outcome data', 'measurement of the outcome', and 'selection of the reported results'. A proposed judgment about the risk of bias arising from each domain is generated by an algorithm, where judgment can be 'Low' or 'High' risk of bias or express 'Some concerns'. The risk of bias assessments was done independently by two investigators (CSK and SSH), with disagreements resolved through discussion.

2.4 Data Analyses

A random-effects model meta-analysis was used to estimate the pooled odds ratio for outcomes of interest using sofosbuvir-based direct-acting antiviral agents relative to non-use of sofosbuvir-based direct-acting antiviral agents at 95% confidence intervals. In addition, we examined the heterogeneity between studies using the I^2 statistics and the χ^2 test, with substantial heterogeneity at 50% and significance at $p < 0.10$. In the subgroup analyses, associations were estimated that restricted the analyses to trials that administered sofosbuvir-daclatasvir and trials that administered sofosbuvir-based two-component direct-acting antivirals (sofosbuvir-daclatasvir, sofosbuvir-velpatasvir, sofosbuvir-ledipasvir). All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

3. Results

Our systematic literature search retrieved 378 hits, of which 105 were unique. After screening, eleven randomized controlled trials [11-21] were included (**Figure 1**), with a total of 1,110 patients who were

randomized to the intervention arm and received sofosbuvir-based direct-acting antiviral agents and 1,051 patients who were randomized to the control arm and did not receive sofosbuvir-based direct-acting antiviral agents. All the included trials [11-20] assessed and reported mortality outcomes, while nine of the included trials [13-17,21] assessed and reported outcomes on severe illness. In addition, seven of the included trials [11,12,14,15,18-20] were performed in Iran, whereas the remaining four randomized trials [13,16,17,21] were originated from Egypt. Characteristics of the included trials are shown in **Table 1**.

Six of the included trials [11-16] investigated the use of sofosbuvir-daclatasvir for the treatment of COVID-19, which was administered orally at a dose of 400/60 mg once daily across these trials, though the duration of therapy differed across these trials; Sadeghi et al. [11] and El-Bendary et al. [16] administered sofosbuvir-daclatasvir for a duration of 14 days; Mobarak et al. [12] and Yakoot et al. [13] administered sofosbuvir-daclatasvir for a duration of 10 days; Yadollahzadeh et al. [14] administered sofosbuvir-daclatasvir for at least 5-7 days; but Abbaspour Kasgari et al. [15] did not specify the duration of therapy. The trial by Abbass et al. [21] either administered sofosbuvir-daclatasvir orally at a dose of 400/60 mg once daily or sofosbuvir-ravidasvir at a dose of 400/200 mg once daily, for 10 days. On the other hand, two of the included trials investigated the use of sofosbuvir-ledipasvir for the treatment of COVID-19, which was administered orally at a dose of 400/90 mg once daily in these trials; Elgohary et al. [17] administered sofosbuvir-ledipasvir for 15 days, but Nourian et al. [18] administered sofosbuvir-ledipasvir for 10 days. The remaining two trials investigated the use of sofosbuvir-velpatasvir and sofosbuvir alone, respectively, for the treatment of COVID-19; Sayad et al. [19] administered sofosbuvir/velpatasvir at a dose of 400/100 mg once daily for 10 days while Alavi-Moghaddam et al. [20] administered sofosbuvir at a dose of 400 mg once daily until clinical recovery sustained for 3 days.

3.1 Risk of Bias of the Included Trials

The overall risk of bias assessed by RoB 2 is presented in **Table 1**. None of the included trials had a low risk of bias. The trial by Yadollahzadeh et al. [14] is the only trial with an overall high risk of bias; it had a high risk of bias in the domain of missing outcome data since data were not available for about 7% of participants, along with some concerns of bias in the domain of deviations from intervention and the domain of measurement of the outcome due to single-blind design of the trial, and in the domain of selection of the reported results because it was unclear if the trial was analyzed as pre-specified. The remaining 9 trials [11-13,15-20] had some concerns in the overall risk of bias; both the trial by Sadeghi et al. [11] and the trial by Alavi-moghaddam et al. [20] respectively, had some concerns of bias in the domain

of randomization due to a lack of information on allocation concealment and in the domain of deviations from intervention due to open-label design of the trial; the trial by Mobarak et al. [12] had some concerns of bias in the domain of selection of the reported results because it was unclear if the outcome on severe illness (requirement for intubation) was analyzed as pre-specified; the trial by Yakoot et al. [13] had some concerns of bias in the domain of deviations from intervention and in the domain of measurement of the outcome due to open-label design of the trial, as well as in the domain of missing outcome data since there was no evidence that the findings of the trial were not biased by missing outcome data (6%); the trial by Abbaspour Kasgari et al. [15] had some concerns of bias in the domain of deviations from intervention and the domain of measurement of the outcome due to open-label design of the trial, as well as in the domain of selection of the reported results because it was unclear if the mortality outcome was analyzed as pre-specified; the trial by El-Bendary et al. [16] had some concerns of bias in the domain of randomization due to a lack of information on randomization as well as on allocation concealment, in the domain of deviations from intervention due to unclear binding of participants and outcome assessors, and in the domain of selection of the reported results because the protocol and statistical plan were not available; the trial by Elgohary et al. [17] had some concerns of bias in the domain of measurement of the outcome due to single-blind design of the trial and in the domain of selection of the reported results because it was unclear if the trial was analyzed as pre-specified; both the trial by Nourian et al. [18] and the trial by Sayad et al. [19] respectively, had some concerns of bias in the domain of deviations from intervention and the domain of measurement of the outcome due to open-label design of the trial, and in the domain of selection of the reported results because it was unclear if the trial was analyzed as pre-specified. The trial by Abbass etal. [21] had some concerns of bias in the domain of randomization due to a lack of information on allocation concealment and the domain of deviations from intervention and the domain of measurement of the outcome due to the open-label design of the trial.

3.2 Sofosbuvir-Based Direct-Acting Antiviral Agents and All-Cause Mortality

The meta-analysis of eleven trials (n = 2,161) [11-21] revealed a statistically significant reduction in the odds of mortality with the administration of sofosbuvir-based direct-acting antiviral agents among patients with COVID-19 relative to non-administration of sofosbuvir-based direct-acting antiviral agents; the estimated effect indicated mortality reduction (**Figure 2**; pooled odds ratio = 0.59; 95% confidence interval 0.36 to 0.99) but with inadequate evidence to refute the null hypothesis of 'no significant difference', at the current sample size. However, subgroup analyses with seven trials [11-16,21] that administered sofosbuvir-daclatasvir revealed inconsistent findings with the main analysis, where there

was no statistically significant difference in the odds of mortality with the administration of sofosbuvir-daclatasvir among patients with COVID-19 relative to non-administration of sofosbuvir-daclatasvir (pooled odds ratio = 0.77; 95% confidence interval 0.48 to 1.22). In addition, the subgroup analysis of the ten trials [11-19,21] that administered sofosbuvir-based two-component direct-acting antivirals (pooled odds ratio = 0.80; 95% confidence interval 0.55 to 1.16) also revealed no statistically significant difference in the odds of mortality with the administration of sofosbuvir-based two-component direct-acting antivirals among patients with COVID-19 relative to non-administration of sofosbuvir-based two-component direct-acting antivirals.

3.3 Sofosbuvir-Based Direct-Acting Antiviral Agents and Composite Endpoint of Severe Illness

On the other hand, the meta-analysis of nine trials (n = 1,905) [11-15,17,19-21] revealed no statistically significant difference in the odds of development of composite endpoint of severe illness with the administration of sofosbuvir-based direct-acting antiviral agents among patients with COVID-19 relative to non-administration of sofosbuvir-based direct-acting antiviral agents; the estimated effect indicated a reduced risk of severe illness (**Figure 3**; pooled odds ratio = 0.79; 95% confidence interval 0.43 to 1.44) but is without adequate evidence to refute the null hypothesis of 'no significant difference', at the current sample size. Subgroup analysis with six trials [11-15,21] that administered sofosbuvir-daclatasvir revealed consistent findings with the main analysis, where there is no statistically significant difference in the odds of development of composite endpoint of severe illness with the administration of sofosbuvir-daclatasvir among patients with COVID-19 relative to non-administration of sofosbuvir-daclatasvir (pooled odds ratio = 0.67; 95% confidence interval 0.28 to 1.61). Consistent findings with the main analysis are also observed with subgroup analyses of eight trials [11-15,17,19,21] that administered sofosbuvir-based two-component direct-acting antivirals (pooled odds ratio = 0.76; 95% confidence interval 0.40 to 1.41).

4. Discussion

To the best of the authors' knowledge, this is the first systematic review and meta-analysis of randomized controlled trials investigating sofosbuvir-based direct-acting antiviral agents (sofosbuvir-daclatasvir, sofosbuvir-velpatasvir, sofosbuvir-ledipasvir, sofosbuvir alone, etc.) in patients with COVID-19. It was observed that sofosbuvir-based direct-acting antiviral agents had no beneficial effects on the risk of mortality and the risk of severe illness in this population of patients. We acknowledge the previous attempts [21-23] to systematically review and meta-analyze studies investigating the use of sofosbuvir-based direct-acting antiviral agents investigating the use of sofosbuvir-daclatasvir for the treatment of

COVID-19; these systematic reviews and meta-analyses [21-23] though reported that the use of sofosbuvir-daclatasvir was associated with a significant reduction in mortality as well as severe illness, their analyses were limited by the fact that they included non-randomized trial. Randomized controlled trials, especially systematic reviews and meta-analyses of randomized controlled trials, are the "gold standard" for bringing evidence to the real-world practice about therapeutic interventions.

COVID-19 is widely recognized to cause a two-phase immune response, i.e., viral replication and dysregulated inflammatory phases (cytokine release phase) [24]. SARS-CoV-2 actively replicates in the respiratory epithelium and alveoli during the first phase, and the antiviral response mechanism involving type-I interferon predominates to limit viral replication. However, the first phase antiviral mechanism may be insufficient to contain the infection in certain high-risk patients. Therefore, patients progress to a second phase with a more severe disease course—cell death and local inflammation trigger additional cytokines that attract more immune cells into the lung. The first phase usually corresponds to patients at the asymptomatic or mild stage of illness. In contrast, the second phase usually corresponds to patients at the severe-to-critical stage of illness.

Although our meta-analysis revealed mortality benefits with sofosbuvir-based direct-acting antiviral agents in patients with COVID-19, the significance is lost in subgroup analyses. Hence, the mortality benefits are still uncertain. Thus, in patients with COVID-19 who progress to the cytokine release phase, antivirals such as sofosbuvir-based direct-acting antiviral agents might not be adequate, if not at all useful retard the progression of the disease. Noteworthily, the included trials [11-20] recruited hospitalized participants with mild-to-severe illness, which explains their failure to elicit beneficial effects of sofosbuvir-based direct-acting antiviral agents across these trials. Therefore, to be able to attribute a positive clinical effect to an antiviral, not only that future trials should adopt the same day test and treat approach to ensure that sofosbuvir-based direct-acting antiviral agents can maximize their antiviral efficacy and can suppress the virus as soon as possible, but trials should also restrict the eligibility criteria to include only patients with mild illness. A great example would be the randomized trial [25] investigating the use of SARS-CoV-2 neutralizing antibody (LY-CoV555), which was performed exclusively in outpatients with COVID-19 of whom the majority were with mild illness and reported that the percentage of patients who had a COVID-19 related hospitalization or visit to an emergency department was significantly lower in the LY-CoV555 group (1.6%) as compared to the placebo group (6.3%).

Another potential reason for the failure of sofosbuvir-based direct-acting antiviral agents may be due to inadequate serum and/or pulmonary concentration achieved with the current dosing regimen. Although sofosbuvir-daclatasvir has shown *in vitro* antiviral effects [5], as mentioned beforehand, the EC50 for sofosbuvir and ledipasvir [26] is not within pharmacokinetic exposures, while for daclatasvir [27], the EC50 is at borderline of pharmacokinetic exposures. In addition, with the approved dosing regimen, the fixed-dose combination of sofosbuvir-based direct-acting antiviral agents (sofosbuvir-daclatasvir, sofosbuvir-velpatasvir, sofosbuvir-ledipasvir) has been designed/developed for optimal intracellular penetration in hepatic tissue for the treatment of hepatitis C. Still, there is a lack of data on the uptake and intracellular activation of sofosbuvir in pulmonary tissues [28]. Also, the hepatic cells strongly express carboxylesterase 1, which is required to convert sofosbuvir into its active triphosphate metabolites, while the pulmonary cells had lower enzyme expression levels [29,30]. Therefore, future trials should investigate the clinical efficacy of sofosbuvir-based direct-acting antiviral agents since higher treatment doses against SARS-CoV-2 in pulmonary epithelial cells may be needed than those recommended for hepatitis C.

The present systematic review and meta-analysis have their limitations. Firstly, the sample size of the included trials is relatively small, and it is possible that these trials were underpowered to detect mortality and other clinical benefits. Secondly, all the included trials originated from Egypt or Iran; hence, it is unknown whether the findings can be generalized to patients from other parts of the world. Thirdly, the included trials had at least some concerns in the risk of bias, which affects the certainty of the evidence.

5. Conclusion

The sofosbuvir-based direct-acting antiviral agents have no protective effects against the development of severe illness in patients with COVID-19 with the current dosing regimen. Whether sofosbuvir-based direct-acting antiviral agents could offer mortality benefits would require further investigations. Future trials, preferably with a larger scale, should aim to investigate the use of higher dose sofosbuvir-based direct-acting antiviral agents and restricted the participation to patients with COVID-19 who present early in the symptomatic phase.

Conflict of Interest

The authors declare that they have no competing interests.

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Ethical approval

Not required

Authors' contributions

CSK and SSH drafted the manuscript, and CSK, AJ, DR, and SSH equally contributed to the revision of the manuscript in its final form. All authors read and approved the final manuscript.

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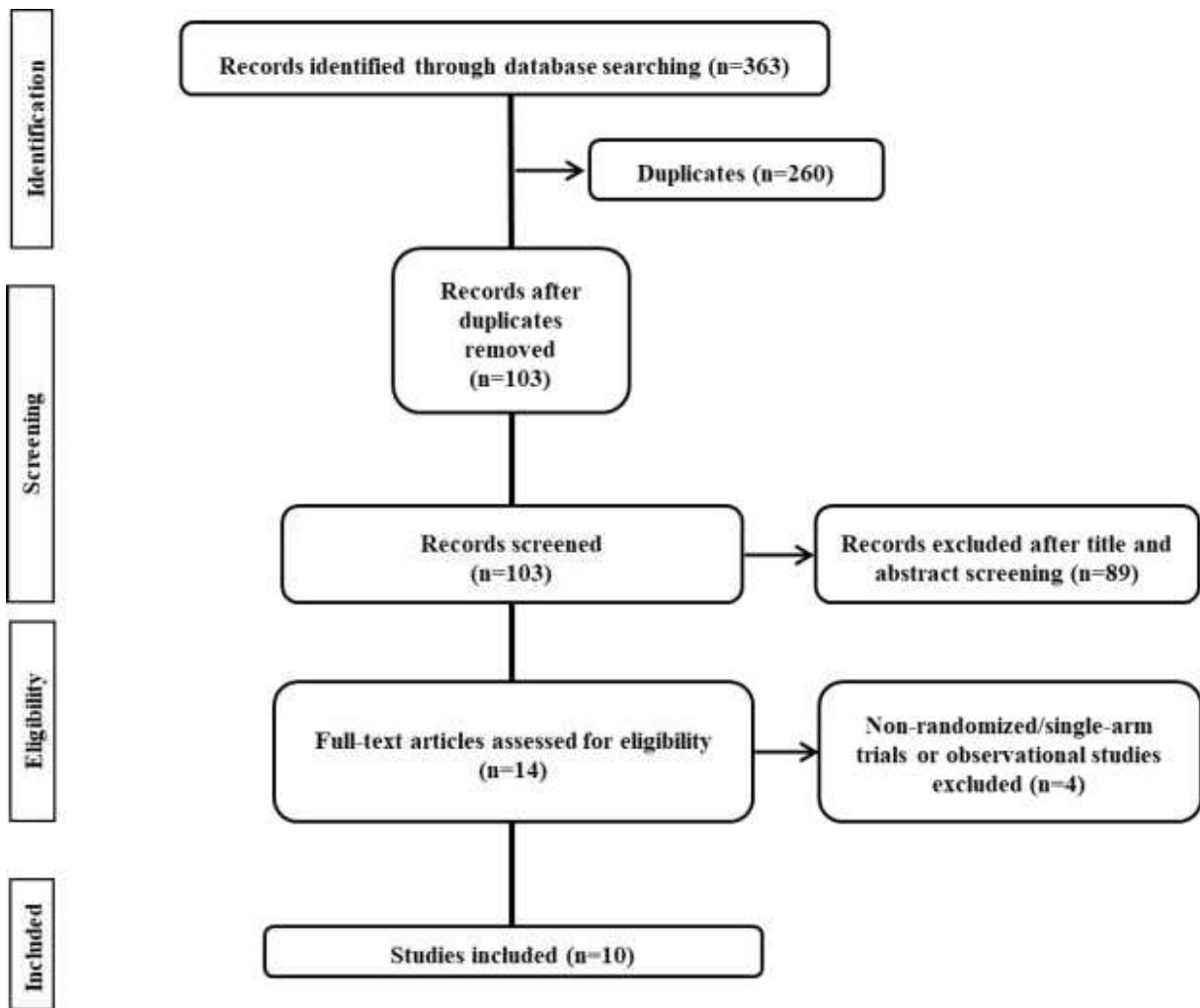
Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of process of study selection
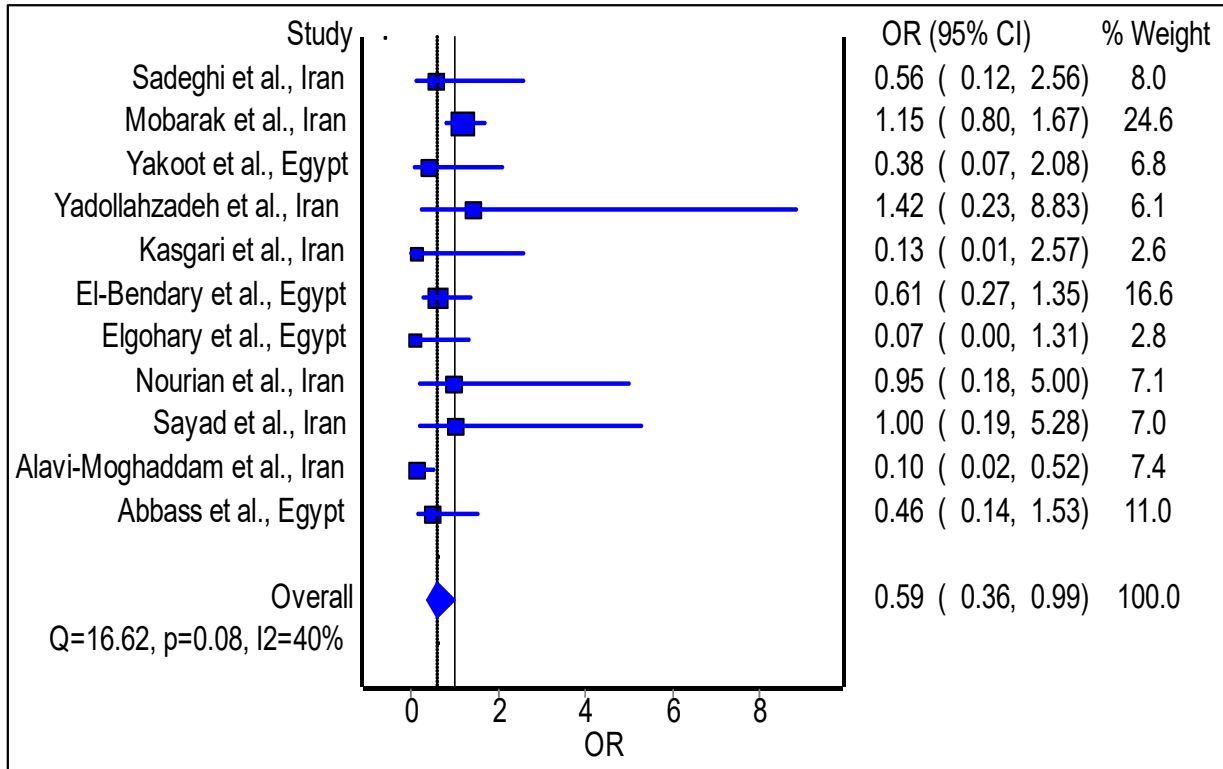
Figure 2: Pooled odds ratio for mortality with the administration of sofosbuvir-based direct-acting antiviral agents relative to non-administration of sofosbuvir-based direct-acting antiviral agents in patients with COVID-19

Figure 3: Pooled odds ratio for disease severity with the administration of sofosbuvir-based direct-acting antiviral agents relative to non-administration of sofosbuvir-based direct-acting antiviral agents in patients with COVID-19
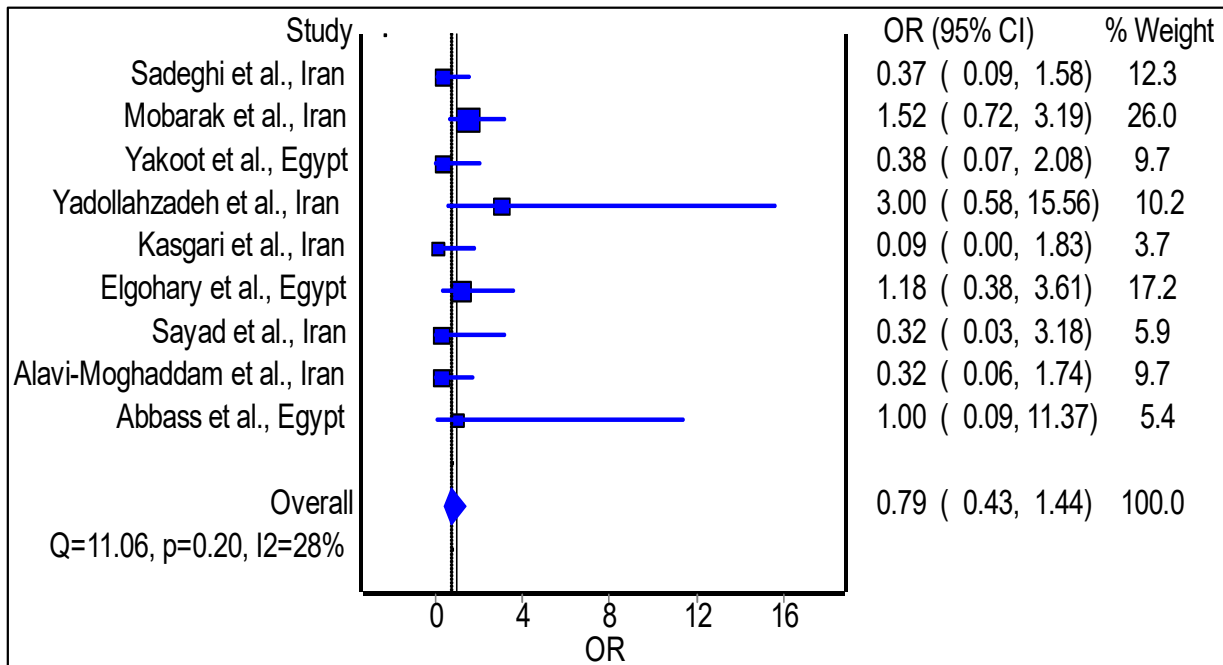
Table 1: Characteristic of included studies

Study (year)	Study design	Country	Age (median/mean)	Proportion of participants with different baseline severity of COVID-19 (%)	Regimen of DAA in the intervention group	Regimen of comparator intervention in the control group	Mortality DAA users (n/N; %)	Mortality Non-DAA users (n/N; %)	Composite endpoint of severe illness[1] DAA users (n/N; %)	Composite endpoint of severe illness[1] Non-DAA users (n/N; %)	Risk of bias[2]
Sadeghi et al [11] (2020)	Open label, randomized controlled trial	Iran	DAA users=58.0 Non-DAA users=62.0	Severe=100	Sofosbuvir/daclatasvir 400/60 mg once daily for 14 days + standard care	Standard care (hydroxychloroquine, lopinavir/ritonavir)	3/33; 9.1	5/33; 15.2	3/33; 9.1	7/33; 21.2	Some concerns
Mobarak et al [12] (2021)	Randomized, double-blind, placebo-controlled trial	Iran	DAA users=57.0 Non-DAA users=59.0	Moderate=68.2 Severe=31.8	Sofosbuvir/daclatasvir 400/60 mg once daily for 10 days + standard care	Placebo + standard care (interferon beta, systemic corticosteroids, other antivirals)	68/541; 12.6	60/542; 11.1	18/541; 3.3	12/542; 2.2	Some concerns
Yakoot et al [13] (2021)	Open label, randomized controlled trial	Egypt	DAA users=48.0 Non-DAA users=50.0	Mild=13.5 Moderate=68.5 Severe=18.0	Sofosbuvir/daclatasvir 400/60 mg once daily for 10 days + standard care	Standard care (hydroxychloroquine, azithromycin, zinc, vitamin C, vitamin D)	2/44; 4.5	5/45; 11.1	2/44; 4.5	5/45; 11.1	Some concerns
Yadollahzadeh et al [14] (2021)	Randomized, single-blind, controlled trial	Iran	DAA users=58.9 Non-DAA users=56.1	Mild=61.6 Moderate=38.4	Sofosbuvir/daclatasvir 400/60 mg once daily for at least 5 to 7 days + hydroxychloroquine	Lopinavir/ritonavir + hydroxychloroquine	3/58; 5.2	2/54;3.7	6/58; 10.3	2/54;3.7	High
Abbaspour Kasgari et al [15] (2020)	Open label, randomized controlled trial	Iran	DAA users=45.0 Non-DAA users=60.0	Moderate=100	Sofosbuvir/daclatasvir 400/60mg once daily + ribavirin	Lopinavir/ritonavir + hydroxychloroquine ± ribavirin	0/24; 0	3/24; 12.5	0/24; 0	4/24; 16.7	Some concerns
El-Bendary et al [16] (2021)	Randomized controlled trial	Egypt	DAA users=52.0 Non-DAA users=54.0	Moderate=77.6 Severe=22.4	Sofosbuvir/daclatasvir 400/60 mg once daily for 14 days + hydroxychloroquine	Hydroxychloroquine	13/96; 13.5	16/78; 20.5	-	-	Some concerns
Elgohary et al [17] (2021)	Randomized, single-blind, controlled trial	Egypt	DAA users=46.8 Non-DAA users=40.2	Moderate=100	Sofosbuvir/ledipasvir 400/90 mg once daily for 15 days + ceftriaxone + methylprednisolone + enoxaparin	Oseltamivir + hydroxychloroquine + azithromycin + ceftriaxone + methylprednisolone + enoxaparin	0/125; 0	6/125; 4.8	7/125; 5.6	6/125; 4.8	Some concerns
Nourian et al [18] (2020)	Open label, randomized controlled trial	Iran	DAA users=61.5 Non-DAA users=63.0	Mild=56.1 Moderate=43.9	Sofosbuvir/ledipasvir 400/90 mg once daily for 10 days + standard care	Standard care (hydroxychloroquine, atazanavir/ritonavir)	3/42; 7.1	3/40; 7.5	-	-	Some concerns
Sayad et al [19] (2021)	Open label, randomized controlled trial	Iran	DAA users=53.6 Non-DAA users=54.6	Moderate-to-severe; no breakdown on the proportion of moderate versus severe cases	Sofosbuvir/velpatasvir 400/100 mg once daily for 10 days + standard care	Standard care (hydroxychloroquine, lopinavir/ritonavir)	3/40; 8.1	3/40; 8.1	1/40; 2.4	3/40; 8.1	Some concerns

Study	Design	Country	Age (mean)	Severity	Intervention	Comparator				Risk of bias
Alavi-moghadd am et al [20] (2021)	Open label, randomized controlled trial	Iran	DAA users=55.0 Non-DAA users=59.5	Severe=100	Sofosbuvir 400 mg once daily until clinical recovery sustained for 3 days + standard care	Interferon beta-1a + lopinavir/ritonavir + standard care (anticoagulants, antibiotics, immunomodulatory agents)	2/27; 7.4	13/30; 43.3	2/27; 7.4	6/30; 20.0	Some concerns
Abbass et al. [21] (2021)	Open label, randomized controlled trial	Egypt	DAA users (sofosbuvir-daclatasvir)=40.0 DAA users (sofosbuvir-ravidasvir)=48.0 Non-DAA users=46.0	Moderate=38.3 Severe=61.7	Sofosbuvir/daclatasvir 400/60 mg once daily or sofosbuvir/ravidasvir 400/200 mg once daily for 10 days + standard care	Standard care (acetaminophen 500 mg as needed and multivitamin supplements)	6/80; 7.5	6/40; 15.0	2/80; 2.5	1/40; 2.5	Some concerns

[1]Risk of bias of included trials was assessed with Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).

[2]Intubation/mechanical ventilation and/or admission into intensive care units

COVID-19 coronavirus disease 2019; DAA direct-acting antivirals