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Efficacy and safety of sofosbuvir in the treatment of SARS-CoV-2: an open label phase II trial

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Abstract: **Objective:** Despite the worldwide spread of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an effective specific antiviral treatment for coronavirus disease of 2019 (COVID-19) is yet to be identified .We did this study to investigate the safety and efficacy of sofosbuvir as antiviral therapy among hospitalized adult patients with SARS-CoV-2.

Methods: Patients were randomized into intervention arm receiving sofosbuvir or comparison arm receiving usual antiviral agents in addition to standard of care. The primary end point of the study was clinical recovery as defined by normal body temperature and normal oxygen saturation. The main secondary outcome was all-cause mortality during the admission in hospital or within 14 days after discharge if applicable. Reports of severe adverse events were observed in the intervention arm.

Results: Fifty-seven patients enrolled into either the clinical trial arm (n=27) or the comparison arm (n=30). Primary outcome was achieved by 24 (88.9%) and 10 (33.3%) in the intervention and comparison arms, respectively. Median hospital length of stay was significantly shorter in the intervention arm (10 days [IQR: 5-12] vs. 11.5 days [IQR: 8.5-17.75], P = 0.016). All-cause mortality was two and thirteen in intervention and comparison groups, respectively. No serious adverse events were reported by the patients receiving sofosbuvir during the study.

Conclusion: Among patients hospitalized with SARS-CoV-2, those who received sofosbuvir had more clinical recovery rate and had a shorter hospital length of stay than those who received usual antiviral agents in the study and these differences were statistically significant.

Keywords: Antiviral Agents; COVID-19; SARS-Cov-2; Sofosbuvir

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1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as a public health emergency, has been terribly and quickly spreading to all of the world since December 2019 (1). Despite the worldwide spread of the SARS-CoV-2, an effective specific antiviral treatment for COVID-19 is yet to be identified (2).

Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and SARS-CoV-2 viruses, are similar to hepatitis C virus (HCV) and Flaviviridae; all have positive sense single-strand ribonucleic acid (RNA) viruses, able to share a similar replication mechanism needing a RNA-dependent RNA polymerase (RdRp) (3-5).

Sofosbuvir, a nucleoside analogue that prevents HCV NS5B polymerase, is believed to be a nucleotide prodrug experiencing intracellular metabolism in order to form active uridine analog triphosphate (GS-461203) that can act like a chain terminator by combining to HCV RNA through the NS5B polymerase as RdRp, an essential enzyme for HCV RNA replication (6).

High rate of the therapeutic effect with minimal adverse events, and low risk of genotypic and phenotypic resistance are the fundamental properties of sofosbuvir in the treatment of chronic hepatitis C (7-10). It is assumed that it does not interfere with most drugs that are responsible for the metabolizing enzymes similar to the cytochrome P450 system. Low drug-drug interaction feature of sofosbuvir with other drugs, such as antiretrovirals, can make it a safe profile and a well-reputed drug in clinical trials (11). The effective dose for sofosbuvir in chronic hepatitis C is 400 milligrams (mg) per

day in normal renal function state which can be prescribed in an oral single daily dose, hence the compliance and adherence of drug by the patients are remarkable.

It has been demonstrated that sofosbuvir, in addition to have antiviral effect on Flaviviridae family virus (including Zika and Dengue, and yellow fever), is also able to inhibit chikungunya virus replication 3 times more than other similar drugs and can also induce toxicity in liver 25% less than ribavirin (12-15).

In the study by Abdo A Elfiky, a model for Wuhan COVID-19 RdRp was built using sequence analysis, modeling, and docking. The bioinformatics model in silico showed three dimensional structure of sofosbuvir could perform excellent docking in the active site of RdRp of COVID-19 and proposed as an eligible drug to wipe out the COVID-19 RNA replication (16).

As sofosbuvir was proposed as a potential drug against RdRp of the COVID-19 RNA (17,18), here we report the preliminary results of the randomized, controlled, phase II open-label clinical trial of the safety and efficacy of sofosbuvir among hospitalized adult patients with SARS-CoV-2.

2. Methods

2.1. Study design

This study was a randomized, controlled, open label phase II clinical trial in order to assess the safety and efficacy of sofosbuvir as antiviral agent in adult patients hospitalized with SARS-CoV-2. The study was performed at Imam Hossein Medical Center, the referral center for COVID-19, affiliated to Shahid Beheshti University of Medical Sciences, in Tehran, Iran, from April to September 2020. We used primary sample analysis to calculate minimum sample size with the consideration of the 80% power and P-value <0.05.

The study was approved in the institutional review boards of Shahid Beheshti University of Medical Sciences (IR.SBMU.REC.1399.001). Written informed consent was obtained from all patients or their legal representatives, if they were unable to provide consent.

The trial was registered in Iranian Registry of Clinical Trials (IRCT20200328046882N1).

This trial was conducted in accordance with the principles of the declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization (19).

2.2. Study population

We recruited patients between 18-75 years old with chest computerized tomography (CT) scan findings, suggestive of pulmonary infection by COVID-19.

Inclusion criteria were fever (temperature ≥36.6 °C armpit or ≥ 37.2 °C oral or ≥37.8 °C rectal), physical findings concluding of respiratory infection (rales/crackles or decreased respiratory sounds plus egophony or increased tactile fremitus or vocal fremitus) , oxygen saturation (SpO2) ≤ 93% (at room air) , and positive report of reverse transcription polymerase chain reaction (RT-PCR) COVID-19 RNA by a distinguished national diagnostic laboratory.

Exclusion criteria were participation in any other clinical trial, evidence of multi-organ failure, creatinine clearance <30 mL/min, need for mechanical ventilation at screening, pregnant or breast-feeding women, positive human immunodeficiency virus (HIV) or HCV or hepatitis B virus (HBV) tests, and allergy to sofosbuvir.

2.3. Randomization and masking

Once patients passed the inclusion and exclusion criteria and signed the consent form, we used random allocation rule to assign patients into either the clinical trial arm (those who received sofosbuvir) or the control arm (those who received usual antiviral agent). An independent researcher made random allocation cards, using computer-generated random numbers seeling with envelope. The clinicians and patients were not blinded and the principle investigator, outcome assessor, and data analyzer were masked.

2.4. Intervention

Patients in the clinical trial arm received sofosbuvir 400 mg (product of Sobhan Company, Iran) single dose daily orally (as antiviral agent) in addition to standard of care.

Patients in control arm received interferon-beta-1a (ReciGen) (product of CinnaGen Company, Iran) 12 million I.U (44 microgram) on day 1 and then every other day subcutaneously, plus lopinavir/ritonavir 200/50 mg twice a day, two tablets orally (as usual antiviral agent according to the recommendation of national committee of COVID-19 expert panel during the time of study) along with standard treatment. Standard treatment as indicated comprised of oxygen supplementation, noninvasive or invasive ventilation, use of anticoagulants or antibiotic agents, renal-replacement therapy, vasopressor support, use of immunomodulatory agents, and performing extracorporeal membrane oxygenation (ECMO).

The duration of antiviral treatment was determined by the time to clinical recovery in the study population, sustained at least for 72 hours. Standard of care was provided at the time of admission, and antiviral therapy in the clinical trial and comparison groups were prescribed after the clinicians verified the findings of chest CT scan suggestive of pulmonary infection by COVID-19. Nasopharyngeal specimens of patients were collected for RT-PCR COVID-19 RNA upon hospital admission.

Patients were clinically assessed once daily by responsible clinician and twice daily by staff nurses, recording their vital signs and other clinical data using the world health organization (WHO) international severe acute respiratory and emerging infections consortium (ISARIC) case record form. They also monitored the safety of sofosbuvir and asked the patients about any possible adverse events. Clinical data were recorded and kept confidential (Figure 1).

2.5. Outcomes

The primary outcome was defined as clinical recovery by normal body temperature (<37.2°C oral, or <36.6°C armpit, or <37.8°C rectal) and normal SpO2 (≥94% on room air), sustained for 72 hours since initiation of antiviral treatment. Secondary outcomes were defined as all-cause mortality during admission in hospital or within 14 days after discharge if applicable, hospital length of stay, rate of intubation and invasive ventilation, and time to clinical recovery. Safety in the study was defined as advent of any adverse events or premature stop of sofosbuvir due to loss of patients' compliance.

2.6. Statistical analysis

Outcomes, general characteristics, baseline laboratory observation and comorbidity variables were summarized by median, interquartile range and percentage. Comparison of categorical variables between two groups was carried out by chi-squared and Fisher's exact test. The independent t-test and the Mann-Whitney U-test were used to compare continuous variables in the two groups. Kolmogorov–Smirnov test was applied to check the data fitness.

A cause-specific competing risk model by adjusting for confounding variables was fitted to time to event variable that a clinical recovery treats as the event of interest, the death as the competing risk and others as the censor. Time to recovery was also compared using graphically plotting the cumulative incidence curve by intervention and control arms. Evaluating difference between two arms in cumulative incidence curve was performed by Gray's test.

P-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using STATA (version 14.2, STATA crop) and SPSS software (version 16, Sep 2007).

3. Results

Finally, 57 patients were enrolled in the study. Among these patients, 27 were assigned to the clinical trial group and 30 patients were categorized as the comparison group. Figure 1 reveals the study flowchart of the study.

The median age of patients in the intervention group was 55 [IQR: 40-67] and in the comparison group was 59.5 [IQR: 49-73]. Thirty eight patients (66.7%) were male and 19 patients (33.3%) were female (Table 1). Among the comorbidities, diabetes, hypertension and cardiovascular diseases were the most common among patients in both groups, respectively (Table 1). Neutrophils, lymphocytes, troponin, lactate dehydrogenase (LDH) and potential of hydrogen (pH) levels were significantly different between the intervention and control groups, but the other baseline characteristics of the patients were not singnificantly different in the two groups (Table 1).

The mean difference of the hospital length of stay for the intervention and the comparison groups was 5.22 and a significant statistically difference was shown (Table 2). The risk of death in the comparison group was 5.8 times higher than the risk of death in the intervention group with a statistically significant difference (Table 2). Rate of intubation and invasive ventilation were not similar between the groups in the study, but this difference was not statistically significant (Table 2). The number of clinical recoveries were 24 (88.9%) in the intervention group and 10 (33.3%) in the comparison group and the difference between the two groups was statistically significant (Table 2).

The median time to clinical recovery was 10 [IQR: 5-12] in the intervention group and 11.5 [IQR: 8.5-16.75] in the comparison group. After checking being homogeneous of the demographic variables (Table 1) and considering death as a competing risk, the incidence of clinical recovery in intervention group was almost 4 times that of the comparison group with a significant statistical difference (Table 2). The cause-specific cumulative incidence was analyzed across both the time and the groups in the study (the intervention and control groups). Accordingly, it was speculated the incidence of clinical recovery in the intervention group was more than comparison group and also the slope curve of clinical recovery in the intervention group was more acute than in the comparison group (Figure 2).

4. Discussion

The results of our study showed the higher clinical recovery rate (mean difference= 0.375, 95% CI: 0.22,0.63, P-value <0.001) and lower hospital length of stay (Risk ratio= 5.22, 95% CI: 1.66,8.78, P-value<0.016) in the patients who received sofosbuvir in addition to standard of care compared to the comparison group. Furthermore, the all-cause mortality in the intervention group (7.4%) was less than the comparison group (43.3%, P<0.002).

These results are in line with the results of the study by Sadeghi A et al. and the study by Gholamali Eslam et al. that showed decreased mortality rate (statistically did not reached to a significant level) and reduced hospital stay by adding sofosbuvir and daclatasvir to standard of care (20,21).

Similarly, in another randomized-controlled clinical trial which has been done on moderate to severe COVID-19 patients, it has been demonstrated that adding sofosbuvir/daclatasvir to the standard care (hydroxychloroquine±lopinavir/ritonavir) presumably reduce duration of hospitalization and the time of discharge in comparison to the standard care alone (22).

Khalili et al., in a randomized clinical trial on 82 patients with mild to moderate COVID-19 revealed that time to the clinical response was shorter in patients receiving sofosbuvir/daclatasvir. However, rate of clinical response, duration of hospital and intensive care unit (ICU) stay and 14-day mortality rate were not different (23).

In contrast, in a study by Sayad et al., by addition of sofosbuvir/daclatasvir to standard treatment regimen of 80 subjects with moderate to severe COVID-19, no significant improvement was detected in the clinical status or reduced mortality (24).

Table 1 Baseline characteristics of the study population

Characteristics	Comparison group (n=30)	Intervention group (n=27)	P-value
General			
Age (year), median (IQR)	59.5 (49-73)	55 (40-67)	0.288
Female, n (%)	8 (26.7)	11 (40.7)	0.261
SBP (mmHg), median (IQR)	115 (102-130)	115 (110-130)	0.982
DBP (mmHg), median (IQR)	70 (70-80)	80 (70-80)	0.269
Temperature (°C), median (IQR)	38.2 (37.8-38.6)	38.1 (37.7-38.5)	0.172
RR (breaths/min), median (IQR)	19 (17-21)	18.5 (17.7-21.2)	0.980
PR (beats/min), median (IQR)	82.5 (80-100)	88 (79-102)	0.701
SpO2(%), median (IQR)	87 (84-90.5)	89 (86-92)	0.092
Risk factors, n (%)			
Pulmonary disease	2 (6.7)	2 (7.4)	1.000
Chronic kidney disease	0 (0)	1 (3.7)	0.468
Hypertension	6 (20)	6 (22.2)	0.842
Cardiovascular disease	6 (20)	5 (18.5)	0.877
Use of biologic products	2 (6.7)	2 (7.4)	1.000
Diabetes mellitus	9 (30)	8 (29.6)	0.970
Other diseases	4 (13.3)	9 (33.3)	0.070
Age >60	15 (50)	8 (29.6)	0.123
Body mass index >40	1 (3.3)	0 (0)	1.000
Laboratory findings, median (IQR)			
White blood cells (/mcL)	8900 (6100-13525)	6300 (4800-10100)	0.057
Neutrophil (%)	80 (75.7-88)	67.4 (64.6-75)	0.002*
Lymphocyte (%)	14.15 (6.6-19.6)	24.3 (15-28)	0.001*
Hemoglubin (gr/dL)	13.9 (6.6-19.4)	12 (11.3-13.7)	0.632
Platelet ($\times 10^9$/L)	183 (150.7-270.2)	207 (136-278)	0.649
Alanin transaminase (IU/L)	29.5 (23.5-67.5)	37.5 (23.2-53)	0.942
Aspartate transaminase (IU/L)	43 (26.5-74.5)	40.05 (26.3-58.7)	0.448
Bilirubin (mg/dL)	0.73 (0.59-1.39)	1 (0.72-1.22)	0.401
Pottasium (mmol/L)	4.3 (3.9-4.7)	4.2 (3.8-4.8)	0.530
Calcium (mmol/L)	8.4 (7.7-8.6)	8.4 (7.7-8.85)	0.788
Magnesium (mg/dL)	1.9 (1.7-2.2)	1.9 (1.8-2.15)	0.961
Phosphorus (mg/dL)	2.95 (2.5-3.75)	3.3 (2.15-4.75)	0.720
Creatine phosphokinase (mcg/L)	134 (64.5-499)	82.5 (52-169)	0.059
Ferritin (microgram/L)	732.5 (70.25-1651)	391.8 (145-744.7)	0.426
Troponin (nanogram/mL)	0.64 (0.027-0.64)	0.01 (0.01-0.03)	0.001*
Lactate dehydrogenase (IU/L)	761 (537.7-763)	531 (436-572)	0.041*
Creatinine (mg/dL)	1.15 (0.9-1.6)	1.2 (0.8-1.4)	0.547
Urea (mg/dL)	39 (26.8-67.12)	35.1 (20.5-80)	0.695
pH	7.43 (7.39-7.47)	7.39 (7.37-7.43)	0.011*
PCO2 (mmHg)	42.4 (35.67-46.2)	44.05 (37.55-50.02)	0.173
HCO3 (mmHg)	27.5 (25-29.12)	27.4 (24.45-30.15)	0.571

*Statistically significant if P< 0.05; IQR: Interquartile range; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate; PR: Pulse rate; SpO2: Oxygen saturation

Table 2 Primary and secondary outcomes in the study population

Characteristic	Control group (n=30)	Intervention group (n=27)	P-value	Effect size (95% CI)
Primary outcome				
Clinical recovery, n (%)	10 (33.3)	24 (88.9)	<0.001[1]	0.375 (0.22-0.63)[a]
Secondary outcomes				
Hospital length of stay, median (IQR)	11.5 (8.5-17.75)	10 (5-12)	0.016[2]	5.22 (1.66-8.78)[b]
All-cause mortality, n (%)	13 (43.3)	2 (7.4)	0.002[1]	5.85 (1.45-23.6)[a]
Intubation & invasive ventilation, n (%)	6 (20)	2 (7.4)	0.25[3]	2.7 (0.594-12.265)[a]
Time to clinical recovery (days), median (IQR)	11.5 (8.5-16.75)	10 (5-12)	0.002[4]	4.36 (1.703-11.205)[c]

[1]P-values are calculated using chi-squared test; [2]P-value is calculated using the Mann- Whitney U-test;
[3]P-value is calculated using the Fisher's Exact test; [4] P-value is calculated from cause-specific hazard in competing risk model accounting for death as a competing risk.
[a] Risk ratio (binary outcomes); [b] Mean difference (continuous outcomes); [c] Subhazard ratio or SHR (incidence of clinical recovery in intervention to comparison arms); CI: Confidence interval

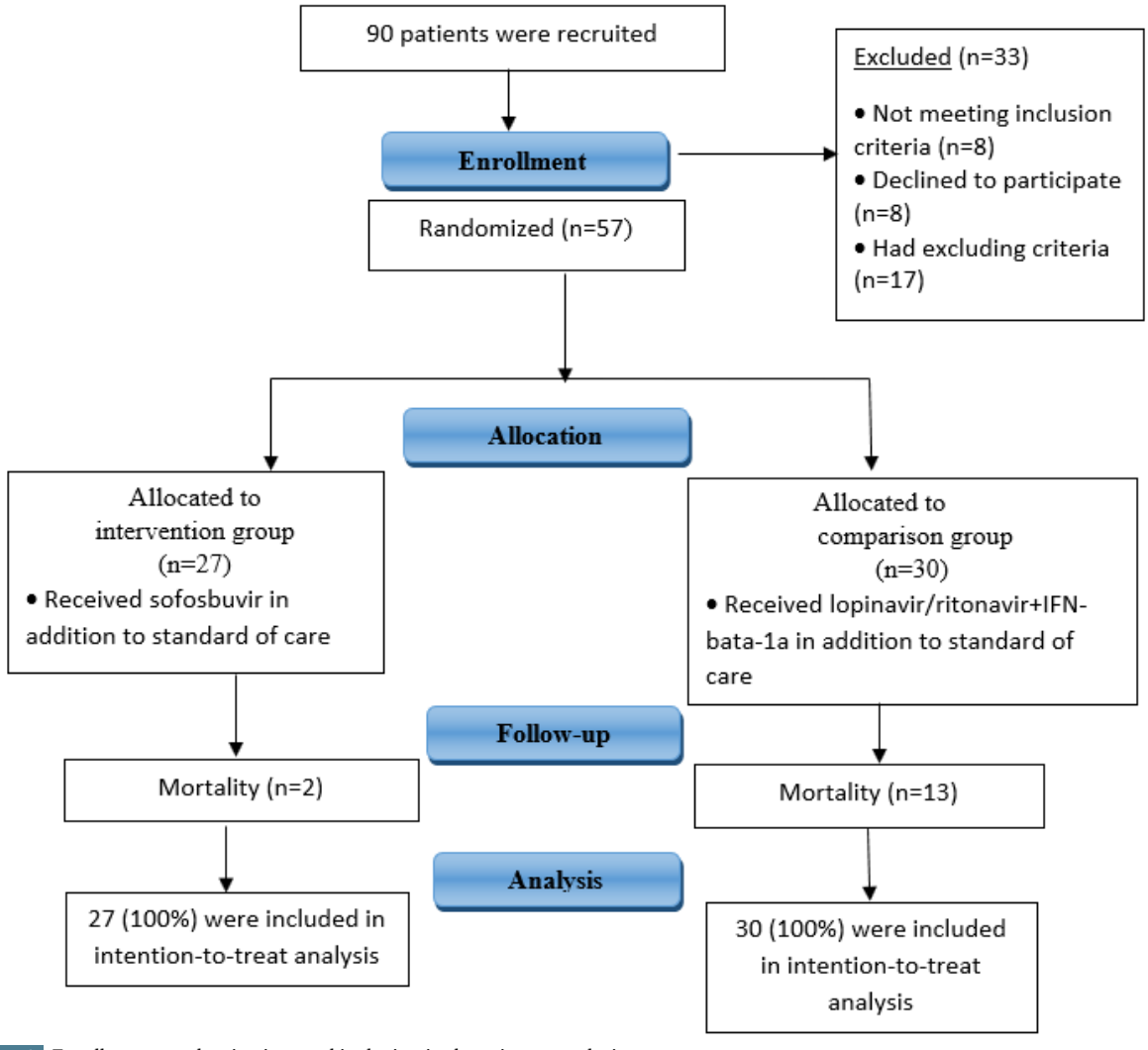

Figure 1 Enrollment, randomization, and inclusion in the primary analysis

A meta-analysis by Bryony Simmons et al., showed significant differences in clinical recovery and all-cause mortality in favor of sofosbuvir/daclatasvir regimens over the three trials included. This meta-analysis included a non-randomized study. Furthermore, the comparison arms across the included studies varied, due to the change in national guidelines in Iran during the progression of the trials (25).

Comparatively, in our study those who received sofosbuvir (without daclatasvir) showed the similar outcome with those who received both sofosbuvir and daclatasvir in the above mentioned studies. Thus, it seems the favorable outcome in these studies are related to sofosbuvir by itself and adding daclatasvir to sofosbuvir did not improve the beneficial outcome.

Many antiviral agents were proposed to treat hospitalized SARS-CoV-2 patients based on in vitro studies in animals, or trials with interventions in infections with other viruses, whether similar to SARS- CoV-2 (e.g., SARS-CoV-1 or MERS) or not (HIV or HCV) (26). The interim results of Solidarity trial were published on 15 October 2020 and revealed little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients in none of the study arms receiving remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon (27).

In the RECOVERY trial, the authors could not detect any beneficial effect for hydroxychloroquine in hospitalized patients with COVID-19. Conversely, the results of RECOVERY trial documented a longer duration of hospitalization and higher need to invasive mechanical ventilation or death in subjects receiving hydroxychloroquine (28).

A trial of lopinavir/ritonavir in adult hospitalized patients with SARS-CoV-2 showed that clinical recovery rate or mortality in patients received lopinavir/ritonavir added to the standard care were not different from those who received standard care alone (29). On 4 July 2020, the recommendation of Solidarity trial's international steering committee was accepted by WHO and the hydroxychloroquine and lopinavir/ritonavir arms of the trials were withheld (30). In a randomized clinical trial, add-on therapy by interferon beta-1b (IFN β-1b) significantly reduced the time to clinical recov-

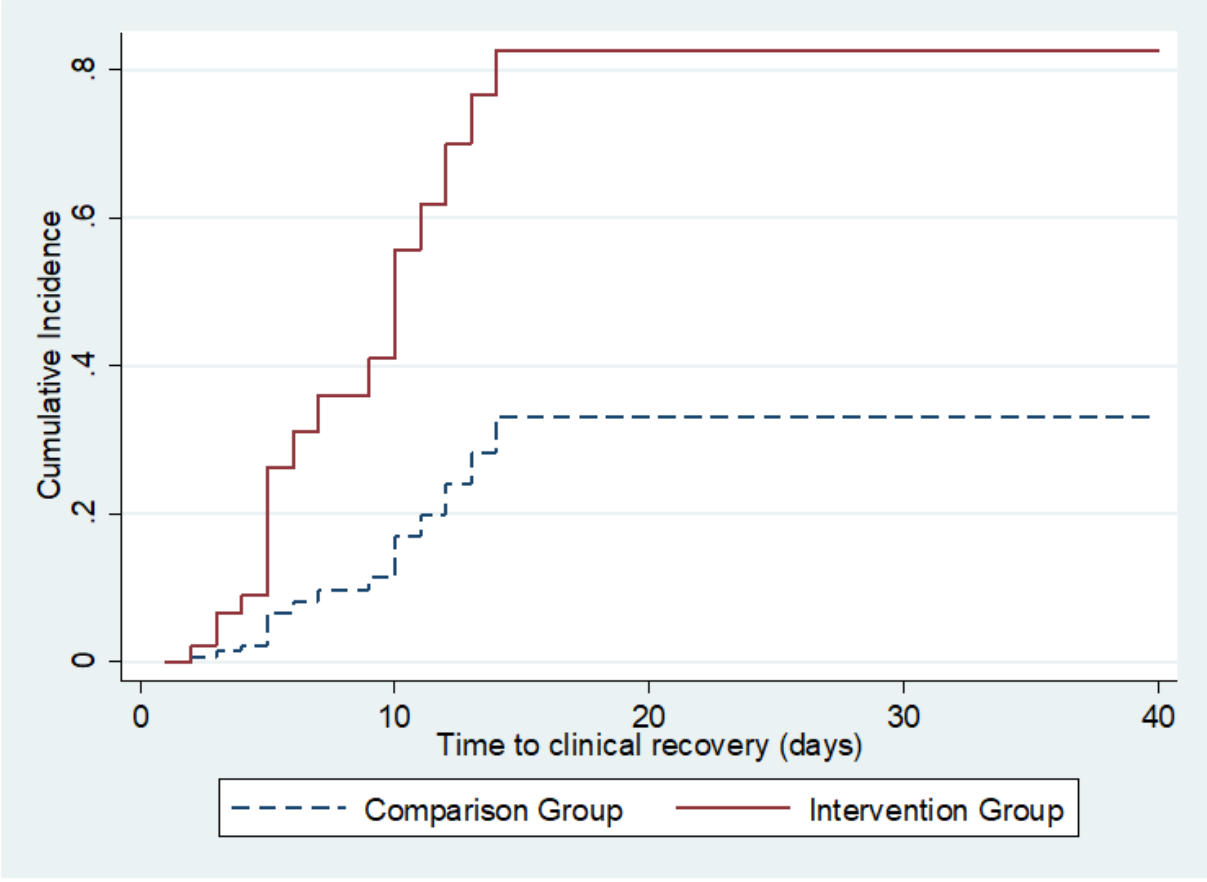

Figure 2 Cause-specific cumulative incidence curve by intervention and comparison arms

ery, increased the discharge proportion at 14th day of study and decreased need for ICU admission. However, using IFN β-1b could not affect intubation rate, duration of hospitalization, length of ICU stay and 28-day all-cause mortality (31). In a multicenter randomized open-label phase 2 trial in patients with COVID-19, the authors indicated that, compared with lopinavir/ritonavir alone, adding IFN β-1b and ribavirin to lopinavir/ritonavir (a triple combination) is effective in suppressing virus shedding, not just in a nasopharyngeal swab, but in all clinical specimens, when given during 7 days of symptom onset (32). In our study, those who received lopinavir/ritonavir plus IFN β-1a (as usual antiviral agents) had unfavorable outcome compared to the intervention group and this is contrary to the results in the above mentioned study. Ribavirin in the mentioned study was added to lopinavir/ritonavir and IFN β-1a , and that may be lead to the difference between these two results. Nevertheless, the study by Song Tong et al. showed patients who received ribavirin did not have a survival benefit compared to those who received only supportive therapy (33). In a randomized, double-blind clinical trial, remdesivir for 10 days significantly decreased time to recovery in patients with severe COVID-19 compared to placebo (11 days vs 15 days) (34). Subsequently, a randomized, open-label trial showed that in non-intubated COVID-19 patients who have relative hypoxia or requiring oxygen support, there is no difference in time to recovery with 5-day and 10-day courses of remdesivir (35). In an open-label clinical trial, remdesivir for 10 days did not have a statistically significant effect in clinical status of patients with moderate COVID-19 compared with standard care at 11th day after initiation of treatment (36); similarly, among adult patients hospitalized with SARS-CoV-2, our trial showed favorable clinical outcomes in the intervention arm. As we enrolled patients with severe COVID-19 (those with SpO2 <94% at room air and pulmonary infiltration) in our trial, the results did not pertinent to the patients with moderate COVID-19 (those with SpO2 ≥94% at room air and pulmonary infiltration) and we could not conclude any inference regarding the treatment outcome with sofosbuvir among patients hospitalized with moderate COVID-19. Our study suffers from three limitations. First, the time lapse between the symptoms onset and the date of admission were not determined among patients in the study. The earlier the beginning of the antiviral agent therapy in hospitalized patients after their symptom onset, the more beneficial effect would be expected and this limitation may affect the results of our study. Second, we did not give steroids to the hypoxemic patients in the study because up to the

time of study the efficacy of dexamethasone was not evaluated in hospitalized patients with COVID-19, however, at the time of the submission of the manuscript, robust data recommend that oral or intravenous corticosteroids (i.e. dexamethasone, hydrocortisone or prednisone) for the treatment of severe COVID-19 patients with hypoxemia and that might have some effect on our results in hypoxemic patients (37) and finally, the clinical and laboratory manifestations of secondary hemophagocytic lymphohistiocytosis (HLH) due to cytokine storm among patients in our study were assessed and in those who need to treat HLH by immunomodulatory agents such as high dose steroid, intravenous immune globuline (IVIG) or tocilizumab, the outcomes may be affected.

5. Conclusion

In summary, currently there is no consensus for choosing an effective antiviral agent to treat patients hospitalized with SARS-CoV-2. Our preliminary results indicate that sofosbuvir could be used as a potential antiviral agent for adult hospitalized patients with SARS-CoV-2. More multi-centered randomized controlled clinical trials are needed to be done for extrapolation of the results of the study into the clinical practice.

6. Declarations

6.1. Acknowledgment

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6.2. Funding

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6.3. Conflict of interest

There is nothing to declare.

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