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Evaluation of Sovodak (sofosbuvir/daclatasvir) treatment outcome in COVID-19 patients compared with Kaletra (lopinavir/ritonavir); a randomized clinical trial

Mahdi Yadollahzadeh[1], Mohana Eskandari[1], Maryam Roham[2], Farhad Zamani[3], Azadeh Laali[2,4], Saeed Kalantari[2], Zeynab Yassin[2], Erfaneh Movahedi[1], Mohsen Farrokhpour[1], Mohamad Taghei Zeiaei[2], Nima Motamed[5], Amirhossein Aliakbar[6], Fatemeh Soleimany[6], Sajad Karampoor[3,7], Gholam Hossein Ashrafi[8], Fahimeh Safarnezhad Tameshkel[3], Mitra Ranjbar[4*], Mahin Jamshidi Makiani[2,4*], Mohammad Hadi Karbalaie Niya[3,7]

[1]Department of Internal Medicine, School of Medicine, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[2]Antimicrobial Resistant Research Center, Iran University of Medical Sciences, Tehran, Iran
[3]Gastrointestinal and Liver Diseases Research Center, Iran University of Medical Sciences, Tehran, IR Iran
[4]Department of Infectious Diseases, Iran university of Medical Sciences,Tehran, Iran
[5]Department of Social Medicine, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[6]Department of Biostatistics, Faculty of Public Health, Iran University of Medical Sciences, Tehran, Iran
[7]Department of Virology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[8]Cancer theme SEC Faculty Penrhyn Road, Kingston University London KT1 2EE, United Kingdom

***Correspondence to**
Prof. Mahin Jamshidi Makiani, Email: jamshidimakiani.m@iums.ac.ir, and Prof. Mitra Ranjbar, Email: ranjbar.m@iums.ac.ir

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection and treatment are significant health organizations' concerns worldwide. Although there is no proven drug license against the virus, a variety of components have under investigation.
Objectives: In this regard, the present study was intended to evaluate the consequences of Sovodak (sofosbuvir/daclatasvir) treatment in COVID-19 patients compared with Kaletra (lopinavir/ritonavir).
Patients and Methods: This study was conducted as a randomized trial using 120 COVID19 confirmed cases between August 19th and September 19th, 2020, in which subjects were classified into two treatment groups, 58 (Sovodak group) and 54 (Kaletra group). Related statistical operations calculated significant outcomes such as survival rate and hazard ratio by SPSS version 16. Sovodak was composed of sofosbuvir 400mg and daclatasvir 60mg, and Kaletra included lopinavir 400 mg and ritonavir 100 mg.
Results: We observed that there was no significant difference concerning the comorbidities, death, intensive care unit admission, remission. Besides, Kaletra had a higher rate of discharge versus Sovodak [HR=1.551 (95% CI=1.008-2.386), P =0.046] and a better outcome was observed in patients receiving.
Conclusion: Sovodak compared to Kaletra by Hazard plot. Sovodak (sofosbuvir/daclatasvir) therapy in COVID19 cases was accompanied by a significantly higher survival rate and better outcome than Kaletra (lopinavir/ritonavir).
Trial Registration: This study has been registered in the Iranian Registry of Clinical Trials (identifier: IRCT20200328046885N1; https://en.irct.ir/trial/47565, Ethical code #IR.IUMS.FMD.REC.1399.407).

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in China and then spread to the rest of other countries. World Health Organization (WHO) announced a global alarm called COVID-19 for the disease (1). The recent Situation Report (14 December 2020) of a total of 71 051 805 confirmed cases, 1 608 648 have died and there are 574 969 new cases per day and 8726 new deaths. Iran reported 1 108 269 confirmed cases and 52 196 deaths with daily new cases of 7451 and deaths of 247 people in which it is ranked the 14th among all countries (2). Currently, there are no licensed drug available acts against SARS-CoV-2. However, there are different candidate components and drugs under clinical trials such as atazanavir, lopinavir/ritonavir, remdesivir, sofosbuvir, favipiravir, Arbidol, chloroquine and hydroxychloroquine, immunomodulators, TNF antagonist, anti-IL6 antibody, intravenous immunoglobulin, corticosteroids, cyclosporine, tacrolimus (3,4). Lopinavir/ritonavir (LPV/RTV) or Kaletra are antiretroviral protease inhibitors that have been used in the treatment of

Key point

This randomized clinical trial study showed higher survival rate and better outcome by Sovodak compared to Kaletra in COVID19 patients.

human immunodeficiency virus (HIV) since 2000 (5). Kaletra is composed of LPV/RTV (400 mg and 100 mg, respectively). RTV is conjugated to LPV to increase its half-life (6). LPV acts against the viral 3-chymotrypsin-like protease and it has been used against SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) viruses previously (7-9). There have been some Kaletra administration records for COVID-19 (10) operation, and according to guidelines, it is used for severe patients (11). Several investigations have focused on its efficacy in COVID19 patients (12,13). Sofosbuvir is a clinically approved anti-hepatitis C virus (HCV) drug (14). Sofosbuvir is a nucleotide analog that has been approved against HCV polymerase. This drug is also able to suppress positive-strand RNA viruses (15). SARS-CoV-2 has RNA-dependent RNA polymerase (RdRp), which could inhibit by sofosbuvir (16). Some studies have suggested that sofosbuvir may bind strongly to the enzyme SARS-CoV-2 RdRp and inhibit its function (17, 18). Sofosbuvir is a safe drug and has fewer side effects. It can be tolerated at a dose of 400 mg daily over a 24-week course of treatment (19). In Iran, sofosbuvir is available in combination with daclatasvir (Sovodak commercial name; doses of 400 and 60 mg, respectively) (20). It has been used for COVID19 patients and then trials run to evaluate its effects.

Objectives

Given the COVID 19 pandemic and the absence of proven treatment, as well as the high cost of Kaletra combination therapy and its scarcity, evaluating the efficacy of drugs such as second-generation oral antivirals in the treatment of COVID 19 can be valuable. Therefore, we decided to conduct a bicentric randomized clinical trial to compare the two treatment regimens Kaletra (LPV/RTV) and the combination therapy Sovodak (Sof/Dac).

Patients and Methods

Study design

In this parallel 2-arm controlled-randomized, single-center study, a total of 120 patients referred to Firoozgar hospital affiliated to Iran University of Medical Sciences, Tehran, Iran, were taken from August 19th to September 19th, 2020.

All patients with mild to moderate disease admitted to Firoozgar hospital, Tehran, Iran, were recruited based on inclusion criteria included age more than 18, hospitalized patients with respiratory symptom and sao2 >90 and diagnostic chest CT scan (mild to moderate scores), with or without temperature >38, excluded patients were patients have hypersensitivity to the drug, pregnant or breastfeeding, using other COVID-19 related drugs, heart rate <60/min, having organ failure, estimated glomerular filtration rate (eGFR)< 50 mL/min, decreased level of consciousness, blood pressure less than 90/60 mm Hg, hypoxia, blood oxygen saturation less than 90%, allergies to study drugs, prior COVID-19 treatment, organ failure and patients requiring mechanical ventilation at the time of hospitalization or patients with adverse reaction drugs. All medical history of patients obtained from hospital data repositories and routine visits.

Patients with underlying disease and comorbidities were included chronic lung disease, chronic liver disease, Hepatitis, Cancer, kidney disease, cardiovascular disease, congestive heart failure, diabetes mellitus, hypertension, immunosuppression disease, anemia.

Sovodak is composed of sofosbuvir 400 mg and daclatasvir 60 mg. Kaletra contains lopinavir 400 mg and ritonavir 100 mg. Two study groups set in a randomized manner by using the ABAB block was applied for the patients. Patients in block a used Sovodak (SOF/DAC 400/60) (Sovodak, Fanavaran Rojan Mohaghegh Daru Co, Tehran, Iran) one tablet every 24 hours. A group was obtained hydroxychloroquine 400 mg every 12 hours for the first day, then 200 mg every 12 hours for 5 to 7 days. Group B used Kaletra (LPV/RTV 400/100) 2 tablets every 12 hours for seven days and took hydroxychloroquine 400 mg for the first day every 12 hours. The clinical recovery analyzed the main outcome in 5 to 7 days by normalization of fever (≤37.2°C), respiratory rate (≤24/min and oxygen saturation (≥94%). All study medication was discontinued at discharge. If the hospitalized patient's condition deteriorated, drop saturation, increased respiratory rate, we change the drug or admit the patient to intensive care unit (ICU), we define them as the failure of treatment. Abnormal lung CT scan was defined as ground glass, air bronchogram and consolidation findings.

Outcomes and laboratory monitoring

White blood cell count (WBC) and erythrocyte sedimentation rate (ESR) were determined at baseline, at the end of the study and during the study, if needed. Clinical recovery was defined as normalization of body temperature (<37.2°C), respiratory rate (<24/min) and oxygen saturation ≥93% without supplementary oxygen therapy at room temperature. The relative improvement of radiological evidence, lesion progression and no need for new treatment and invasive mechanical ventilation methods were also considered responses to the treatment regimens studied.

Routine hematological analysis (WBC count, platelet count, hemoglobin and complete blood cell count) was conducted by an automated cell counter (Sysmex K-4500, Sysmex, Japan). BS200 Auto Analyzer (Mindray, China) was used for biochemical measurements (alanine aminotransferase [ALT] and aspartate aminotransferase [AST], etc).

Statistical analysis

SPSS version 16 was used for statistical analysis. Variables normality was determined using the Kolmogorov–Smirnov test. The better outcome is defined as a lower hospitalization period and no need for re-health care. Fisher's exact test for categorical outcomes. The Cox proportional-hazards model analysis was carried out for adjustment of baseline characteristics. We used the student *t* test or Mann-Whitney U test to compare means and medians. Values less than 0.05 were considered as statistically significant.

Results

Among all COVID-19 admitted patients, 120 patients followed up to 14 days, 112 were included in the analysis (Figure 1). The rest of the study group was excluded from the analysis due to avoid length-bias and other reasons. Around 54 patients (48.2%) were in the Kaletra group and 58 patients (51.8%) were in the Sovodak group. Demographic characteristics of admitted patients in each group are listed in Table 1.

Underlying disease was found in 88 (78.57%) of all patients included in two groups. No statistically significant difference was detected between the two groups regarding the evaluated characteristics. Table 2 shows comorbidity and other variables of statistical analysis.

Table 3 shows the status of the outcome in patients who obtained Sovodak and Kaletra separately. No significant difference was detected between the two groups concerning the evaluated outcomes. Further details were obtained in Table 3.

Table 4 showed the Cox proportional-hazards model results in which the length stay of hospitalization was considered the outcome, and the type of treatment predictor. Our results showed the patients who administered Kaletra had a higher rate of discharge according to the time of hospitalization (HR=1.551, 95% CI=1.008-2.386, *P*=0.046). The survival function plot was displayed in Figure 2.

The hazard function plot was also drawn up and it demonstrated that the Kaletra hazard line is above of Sovodak hazard line. This result could define the better outcome of using Sovodak compared to Kaletra in both patients with underlying disease and without (Figure 3).

Discussion

Pandemic SARS-CoV2 has no proven specific therapies available other than supportive care. Various nations used different drugs included chloroquine, hydroxychloroquine, azithromycin, lopinavir-ritonavir, favipiravir, remdesivir, ribavirin, interferon, convalescent plasma, steroids and anti–IL-6 inhibitors, due to their antiviral or anti-inflammatory features (4,21).

Recent articles have claimed that combination therapy of hydroxychloroquine and Kaletra is unlikely to have any beneficial effects against COVID-19 and might even be harmful to the patients, therefore alternative treatments must be explored and used (22-24). According to the studies (14,16,25,26), there are no specific side effects in people using sofosbuvir, thereby this drug can be used as a suitable alternative for treating patients with COVID-19.

In our study, we have set up a randomized trial on 112 confirmed COVID19 patients (54 were in the Kaletra group and 58 were in the Sovodak group) in a referral hospital in Tehran, Iran. We found that there was no significant difference regarding the comorbidities, death, ICU admission, remission. Additionally, Kaletra had a higher rate of discharge versus Sovodak [HR=1.551, 95% CI: 1.008-2.386, *P*=0.046] and a better outcome was observed in patients using Sovodak compared to Kaletra by hazard plot.

Clinical trials in Iran have been performing on sofosbuvir's efficacy alone or in combination with daclatasvir or other antivirals such as ledipasvir and velpatasvir for the treatment of COVID-19 patients (https://www.irct.ir/). Among these studies, we can

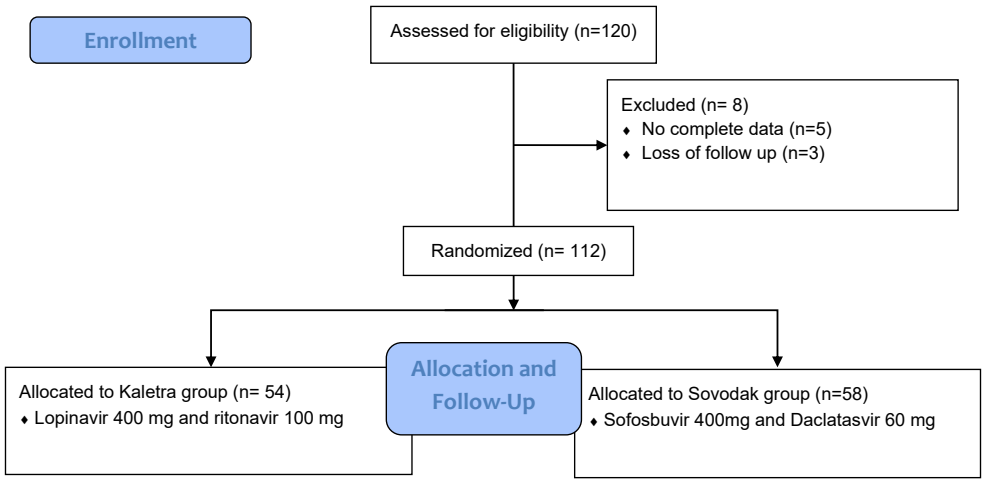

Figure 1. Flow diagram of enrolled patients.

Table 1. The basic characteristics of two treatment groups of our study population

	Drug	Mean	SD	SEM
SBP (mm Hg)	Kaletra	113.69	10.62	1.44
	Sofosbuvir	115.38	10.51	1.38
DBP (mm Hg)	Kaletra	73.43	8.79	1.19
	Sofosbuvir	71.31	7.72	1.01
Temperature (°C)	Kaletra	37.17	0.66	0.09
	Sofosbuvir	37.15	0.64	0.08
WBC	Kaletra	7.05	3.79	0.51
	Sofosbuvir	7.54	6.54	0.85
Lymphocyte count	Kaletra	22.41	12.18	1.65
	Sofosbuvir	24.58	13.87	1.82
PMN	Kaletra	77.58	12.18	1.65
	Sofosbuvir	75.41	13.87	1.82
Hemoglobin (mg/dL)	Kaletra	13.16	1.83	0.25
	Sofosbuvir	13.11	2.09	0.27
Platelet	Kaletra	205.68	83.67	11.38
	Sofosbuvir	202.7	92.14	12.09
ESR (minutes)	Kaletra	39.56	19.78	2.82
	Sofosbuvir	44.3	21.44	2.94
LDH (mg/dL)	Kaletra	541.51	192.57	30.83
	Sofosbuvir	584.42	177.28	25.32
25OH vitD3 (mg/dL)	Kaletra	22.48	9.63	1.62
	Sofosbuvir	22.28	9.32	1.47
Urea (mg/dL)	Kaletra	37.74	21.76	2.96
	Sofosbuvir	42.32	23.19	3.04
ALP (IU/L)	Kaletra	178.75	113.35	15.57
	Sofosbuvir	205.02	218.83	28.73
Bilirubin total (mg/dL)	Kaletra	.95	0.87	0.12
	Sofosbuvir	1.14	1.89	0.25
Bilirubin direct (mg/dL)	Kaletra	0.32	0.21	0.03
	Sofosbuvir	0.32	0.18	0.02
Albumin (mg/dL)	Kaletra	1.40	1.92	0.28
	Sofosbuvir	1.87	1.89	0.26
D-dimer	Kaletra	0.13	0.46	0.06
	Sofosbuvir	0.26	0.7	0.1
Na (mg/dL)	Kaletra	125.19	37.03	5.18
	Sofosbuvir	118.16	46.21	6.28
K (mg/dL)	Kaletra	3.56	1.13	0.15
	Sofosbuvir	3.34	1.51	0.2
Ferritin (mg/dL)	Kaletra	163.32	255.61	37.28
	Sofosbuvir	181.59	226.20	32.31
Days of hospitalization	Kaletra	6.59	3.16	0.43
	Sofosbuvir	9.19	8.43	1.1

SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; PMN, polymorphonuclear; ALP, Alkaline phosphatase; SEM, standard error of mean; SD, standard deviation.

Table 2. The basic characteristics of two treatment groups of study population

Variable	Kaletra (n=54)	Sovodak (n=58)	*P* value
Gender, % (N)			
Male	46.3 (25)	43.1 (25)	0.734[a]
Female	53.7 (29)	56.9 (33)	
Age (y), mean ±SD	56.09 ± 16.51	58.93 ± 14.03	0.328[c]
BMI (kg/m^2), mean ±SD	27.38 ± 2.74	28.08 ± 6.22	0.640[c]
O2 saturation (%), mean ±SD	93.20 ± 2.14	93.47 ± 2.34	0.539[c]
Cr (mg/dL), mean ±SD	1.05 ± 0.52	1.07 ± 0.414	0.800[c]
AST (IU/L), median (IQR)	28.0 (19.0)	34.5 (22.0)	0.427[d]
ALT (IU/L), median (IQR)	26.0 (15.0)	32.5 (32.0)	0.064[d]
PT (s), Mean ±SD	11.99 ± 4.75	11.89 ± 5.39	0.917[c]
Hypertension, % (N)	25.9 (14)	24.1 (14)	0.827[a]
Diabetes mellitus, % (N)	24.1 (13)	19.0 (11)	0.510[a]
Immunosuppressive disease, % (N)	1.9 (1)	5.2 (3)	0.344[a]
Chronic lung disease, % (N)	0.0 (0)	6.9 (4)	0.119[b]
Hepatitis, % (N)	1.9 (1)	1.7 (1)	0.959[a]
Malignancy, % (N)	5.6 (3)	15.5 (9)	0.089[a]
Kidney disease, % (N)	5.6 (3)	6.9 (4)	0.770[a]
Anemia, % (N)	1.9 (1)	6.9 (4)	0.196[a]
Cardiovascular disease, % (N)	16.7 (9)	13.8 (8)	0.672[a]
Dyspnea, % (N)	22.2 (12)	10.3 (6)	0.087[a]
CT scan abnormality, % (N)	40.7 (22)	36.2 (21)	0.622[a]
Comorbidity, % (N)	14.8 (8)	27.6 (16)	0.100[a]
Fever, % (N)	57.1 (20)	42.9 (15)	0.142[a]

ALT, alanine aminotransferase; AST, aspartate Aminotransferase; BMI, body mass index; CT, computerized tomography; Cr, creatinine; IQR, interquartile range; PT, prothrombin time; SD, standard deviation.
[a] Chi-square test; [b] Fisher exact test; [c] Independent *t* test; [d] Mann-Whitney U test.

name a study (26), which was conducted on two groups of patients; a treatment arm receiving sofosbuvir and daclatasvir plus standard care and a control arm receiving standard care alone. This study showed that the addition of sofosbuvir and daclatasvir to standard care significantly reduced the hospitalization duration and mortality rate compared with standard care alone. This study provides timely evidence of the efficacy of Sovodak in the treatment of COVID-19 patients during its rapid pandemic. One of this study's strengths was that all patients were treated with standard medication and the study was not placebo-controlled. In this case, it became possible to compare patients based on the type of treatment of choice, in addition to treatment with hydroxychloroquine. Performing a placebo-controlled trial during a pandemic is a challenge. In addition, due to the higher mortality probability of the present disease, a placebo-controlled trial is not recommended if left untreated.

In a study (13) on 66 COVID19 patients (33 in Kaletra and 33 in Sovodak groups), they have not found any increase in Kaletra's survival rate compared with Sovodak group. Interestingly, we have found significant differences in the two groups' survival rate and Sovodak had a better outcome than Kaletra in both patients with underlying disease and without. These differences may reflect the limitation of Sadeghi et al (13), by the sample size in which our study enrolled more than three times larger sample size versus that study. Additionally, Sadeghi et al (13), reported Sovodak combination with standard care could reduce the hospitalization duration; in the current study, we have found that the Kaletra group had lower ICU admission, disease severity and hospitalization duration compared with the Sovodak group; however, the better outcome was seen in Sovodak group based on hazard function plot.

Table 3. The outcomes status in patients who obtained Sovodak and Kaletra

Outcome	Status	Sovodak % (N)	Kaletra % (N)	*P* value
Death	Yes	5.2 (3)	3.7 (2)	0.707[a]
	No	94.8 (55)	96.3 (52)	
ICU admission	Yes	10.3 (6)	3.7 (2)	0.173[a]
	No	89.7 (52)	96.3 (52)	
Remission	Yes	86.2 (50)	87.0 (47)	0.897[a]
	No	13.8 (8)	13.0 (7)	

ICU: intensive care unit.
[a] Chi square test.

Table 4. The results of Cox regression model

Variable	Wald	HR (Hazard ratio)	*P* value
Drug (Kaletra versus Sovodak)	3.99	1.551 (1.008-2.386)	0.046
Lung disease	0.431	1.504 (0.445-5.086)	0.511
Malignancy	0.561	1.276 (0.674-2.417)	0.454
Anemia	0.182	0.809 (0.306-2.129)	0.669
Dyspnea	0.534	0.806 (0.452-1.437)	0.465
Comorbidity	0.039	1.054 (0.622-1.786)	0.844
ALT	0.173	0.999 (0.996-1.003)	0.678

ALT: Alanine aminotransferase

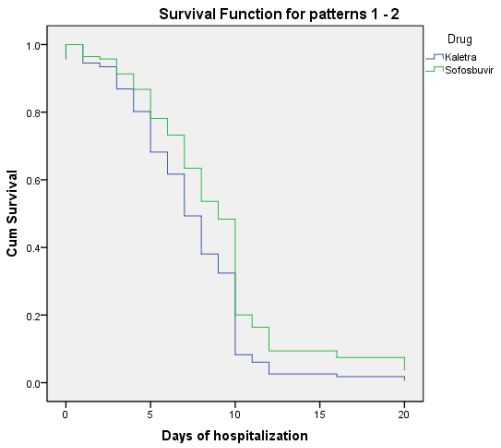

Figure 2. Survival function plot in Cox proportional hazard model.

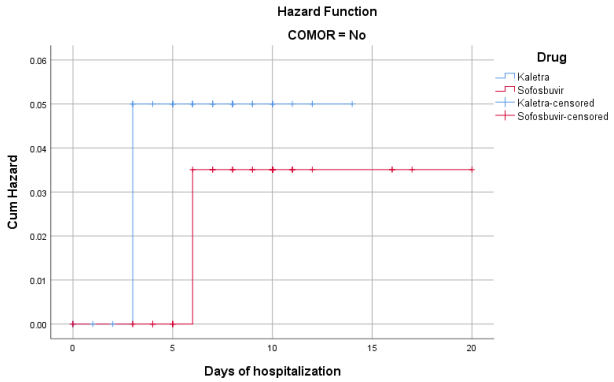

Figure 3. Hazard ratio analysis Sovodak group versus Kaletra group.

Some undesirable events, such as loss of follow-up due to Iran heath policy encourage people to stay at home to follow the treatment until severe symptoms emergence (13) and death, may impact our results. Our study follow-up duration mean was 14 days; however, some of the cases followed 20 or fewer days, like the study by Cao et al (27), which followed the patients for 14 days for more than 85% of their participants.

In a study, the treatment by Kaletra (lopinavir-ritonavir) in COVID19 patients had no associations with acceleration in clinical improvement, reducing mortality and viral load depression (27). Some studies have shown the worse effect of Kaletra+ hydroxychloroquine combination therapy in COVID19 patients (24,27). Compared to our study, we have found more death in the Kaletra group, although it was not significant. Moreover, a worsen outcome was shown in our studied Kaletra group compared with the Sovodak group. However, ICU admission, disease severity and hospitalization duration were lower than those of the Sovodak group due to follow-up loss or death.

In recent study by Chan et al (28), 48 COVID-19 patients divided into two groups as intervention group (24 patients by administration of 400 mg sofosbuvir, 60 mg daclatasvir and 1200 mg ribavirin) and control group (24 subjects as the standard care). They did not find hospitalization stay differences, ICU admission and death rate between the two groups. However, they reported a significantly higher recovery rate in the sofosbuvir/daclatasvir/ribavirin arm (Gray's $P=0.033$). Compared to our study, the differences may be due to the larger sample size, our center setting and enrollment of patients from different provinces referred to the capital of Iran, not just local residents.

Conclusion

In conclusion, this large-scale study proves the administration of Sovodak had priority by little or no side effects versus Kaletra. Sovodak might be useful in reducing the hospitalization duration and mortality rate and increasing patients' remission. These results justify the integration of sofosbuvir/daclatasvir into large-scale trials leading to approval for treatment of coronavirus infection. In this regard, we have found that the overall survival rate and outcome by the Sovodak group were better than those in the Kaletra group. However, our limitations, such as viral load quantitation and long-term follow-ups, need to be considered in further multi-center studies.

Limitations of the study

Our study had some limitations. Viral load quantitation and its follow-up during treatment to calculate the viral shedding period are very important to estimating treatment efficiency; however, total recovery, ICU admission and laboratory tests could illustrate it as well; however, their

association was not clearly understood (27,29). The serum concentration of each drug could help find both drugs' antiviral effect, which contains two components. In this regard, we have failed to calculate their levels due to the high costs of analysis and limited budget. In addition, we have no long-term follow-up after treatment for the participants to estimate the complete drug efficiency. Other limitations include different participant numbers and the difference in CT scan involvement findings at the baseline divided into two groups. Additionally, there was a shortage of SARS-CoV-2 polymerase chain reaction (PCR) tests not to obtain follow-up PCR on the patients.

Authors' contribution

MY, MJM, EM, NM and MR were the principal investigators of the study. SK, ZY, MF, FST, MTZ and MR were included in preparing the concept and design. GHA, FZ, AA, FS, SK, MHKN and AL revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

All authors declare that they have no conflict of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (IR.IUMS.FMD.REC.1399.407). This study has been registered in the Iranian Registry of Clinical Trials (identifier: IRCT20200328046885N1 (https://en.irct.ir/trial/47565). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from the internal medicine resident thesis of Mohana Eskandari at this university. Moreover, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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