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Assessing the Clinical Improvement in Patients with COVID-19 using Lopinavir-Ritonavir: A Systematic Review

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Systematic Review

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ABSTRACT

Aims: Globally the focus is towards finding an effective treatment for COVID-19 patients in order to suppress the spread of this pandemic disease. An antiviral combination of lopinavir-ritonavir is considered to be effective in treating COVID-19 patients. Therefore, the present study aims to assess the clinical improvements of lopinavir-ritonavir in COVID-19 patients.
Study Design: a systematic review study was conducted and articles published since December 2019 were included. The statistical analysis of quantitative data was performed using Review Manager (RevMan) to generate forest plots.
Results: The study showed that there was no significant difference in COVID-19 patients treated with lopinavir-ritonavir or in combination with anti-viral therapy or other conventional methods.
Conclusion: the use of lopinavir-ritonavir resulted in greater adverse consequences among COVID-19 patients. It further recommends conducting meta-analysis studies with a greater number of studies to highlight the clinical improvement associated with the use of Lopinavir-ritonavir.

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1. INTRODUCTION

For many years, strains of coronavirus have been circulating in the animal and human populations. The viruses of this family cause respiratory tract infections in humans [1]. Recently, an outbreak of severe acute respiratory syndrome occurred in Wuhan, China in December 2019 which is now commonly known as coronavirus disease (COVID-19) [2]. In March 2020, this outbreak was declared a global pandemic by the World Health Organization [3]. The main symptoms of COVID-19 include cough, fever and shortness of breath [2]. Older individuals and those with underlying health conditions are more susceptible to this disease; therefore, the disease mortality rate is higher in these individuals.

In this age of pandemic, there is a dire need for a safe and effective treatment for COVID-19. A combination of protease inhibitor with nucleoside analogue is known as lopinavir-ritonavir (LPVr) and it is used to treat human immunodeficiency virus (HIV) type 1 [4]. Previously, LPVr has been administered to patients suffering from severe acute respiratory syndrome and it produced promising results. The drug considerably reduced the viral load after 48 hours of administration and the incidence of adverse clinical outcomes also decreased after 21 days [5,6]. Therefore, worldwide clinical trials are being conducted to determine the effectiveness of LPVr as a treatment for COVID-19 and the most prominent of them is the SOLIDARITY and RECOVERY trial being conducted by World Health Organization [7]. Monitoring of treatments is important along with the examination of the benefit-risk profile of all medications. However, some countries are using lopinavir-ritonavir as a standard treatment for COVID-19.

The plasma half-life of this drug is increased by inhibiting cytochrome P450. A previous study suggested adding lopinavir–ritonavir (400 mg and 100 mg respectively) to ribavirin for reducing adverse clinical outcomes such as acute respiratory distress syndrome or SARS [6]. It is difficult to assess the effect of lopinavir–ritonavir because of the concomitant use of glucocorticoids and lack of randomization/contemporary control group. The activity of lopinavir has been observed in an animal model [2] and in vitro [8] for Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Previous studies have also shown virologic clearance and survival of patients after administrating a combination of lopinavir–ritonavir with ribavirin and interferon Alfa [9-11]. Clinical trials have shown promising results for MERS [12,13]; however, there is a lack of studies about the efficacy of this approach in humans [11].

The effectiveness of lopinavir-ritonavir has been observed in several international clinical trials; however, it failed to gain the approval of the Food and Drug Administration as a treatment option in the current COVID-19 pandemic. Consequently, only three pharmacologically different therapies, at the time of writing this work, have been approved to treat COVID-19: immunotherapy (convalescent plasma therapy), antibiotic-hydroxychloroquine and antiviral-remdesivir [14,15]. One of the clinical trials conducted for lopinavir-ritonavir showed negative outcomes as severe COVID-19 patients who were treated with lopinavir–ritonavir showed no clinical improvement beyond standard care and reduced mortality rate after 28 days [16]. At present, this medicine is considered as tenable evidence of efficacy because this combination is available in the therapeutic guidelines of countries including the USA [17], Ireland (Health Protection Surveillance Centre Treatment guidelines for COVID-19 in Ireland HPSC 2020) and Saudi Arabia [18]. However, there is a steady emergence of negative and conflicting results about lopinavir/ritonavir combination which highlights the need of assessing its safety and efficacy in treating COVID-19. The current study aims to assess the extent of clinical improvement in COVID-19 patients treated with lopinavir-ritonavir combination by gathering data from published researches.

2. METHODS

2.1 Search Strategy and Selection Criteria

A systematic review has been conducted considering the basics of Cochrane Handbook for Systematic Reviews of Interventions. Higgins et al [19] as stated by Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [20,21]. Electronic databases including PubMed, Wiley online library, Medline and Embase were searched for selecting articles published between December 2019 and June 2020. The treatment of COVID-

19 patients with lopinavir/ritonavir was the focus of this review. The primary outcome was related to the efficacy of lopinavir/ritonavir in treating COVID-19 and the secondary outcome focused on the adverse impact of its administration.

The study selected only readily accessible peer-reviewed complete articles, clinical trials and observational cohort studies. There was no age limit for COVID-19 patients to be included in the sample; they just had to be lab-confirmed COVID-19 patients. The keywords used for searching included: COVID-19, novel coronavirus, combination, lopinavir, ritonavir, efficacy, treatment, clinical trial, retrospective, cohort and prospective. The articles including editorials, case reports, duplicate articles, letters to editors and reviews were excluded from the study.

2.2 Data Extraction and Analysis

The authors screened the title and abstracts of all the shortlisted articles separately. Full texts of the relevant articles were reviewed for further evaluation. PRISMA diagram was followed to record the inclusion and exclusion of articles (Fig. 1). The categorization of articles was done on the basis of cohort studies and clinical trials. The data extracted from the selected studies were as follows: author, year of publication, study design and methods, intervention details, control therapies, treatment outcome and adverse events.

2.3 Risk of Bias

To undertake the quality assessment of the included studies, the revised Cochrane Risk of Bias Tool was used for randomized controlled studies [22]. Newcastle Ottawa Scale was used for observational cohort studies [23] and ROBINS-I Tool was used for non-randomized interventional studies [21]. Checking was done for appropriate critical appraisal checklists for each study design. The possibility of the bias of these tools was evaluated by the investigators.

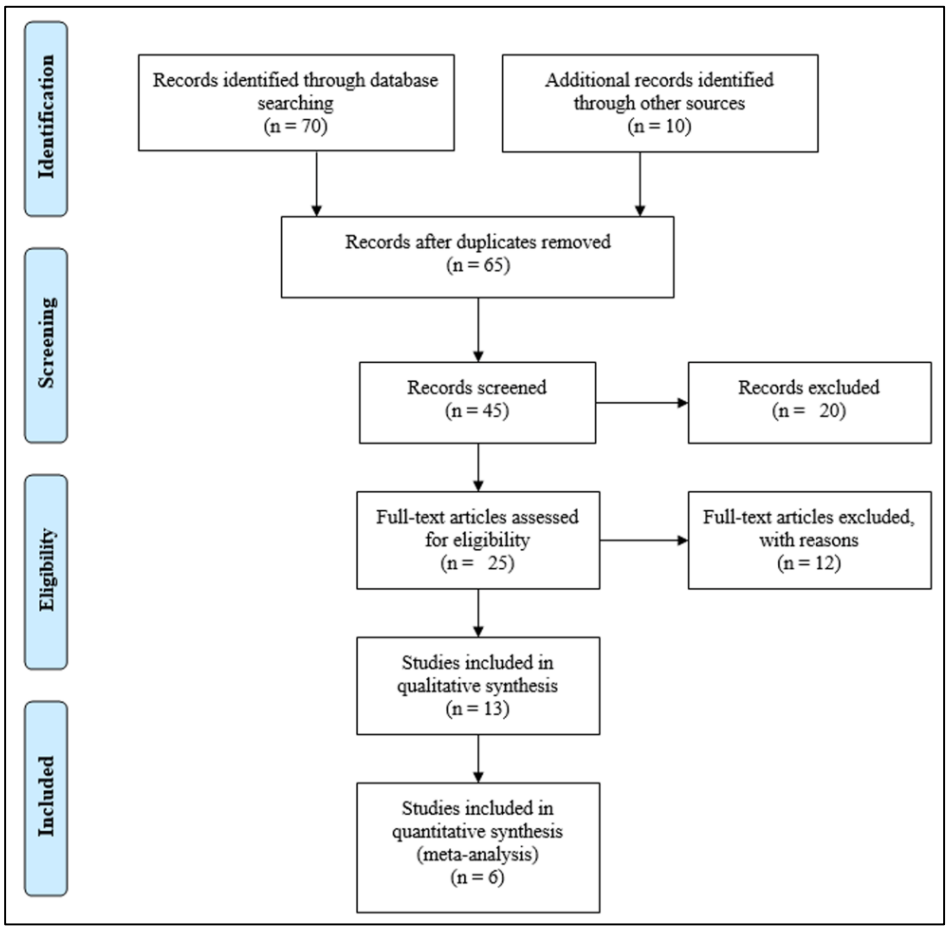

Fig. 1. PRISMA flow chart

2.4 Assessment of Heterogeneity

The study used either mean difference or odds ratio to conduct estimations at 95% confidence interval as all the data were continuous. Meta-analysis was performed by using Mantel Haxel Method for dichotomous data and Inverse Variance Method for continuous data in the absence of significant clinical heterogeneity. A random effect model was utilized and conservative approach was employed to produce wider confidence intervals (See Supplemental Data), as compared to the fixed effect model [19]. The statistical analysis was conducted and forest plots were generated by using the Review Manager (Version 5.3, Oxford, UK; The Cochrane Collaboration 2014).

3. RESULTS AND DISCUSSION

Total 4 literature databases were screened and 65 non-duplicate articles were identified. These articles were further evaluated by screening their titles and abstracts. Among these articles, 25 articles were selected for full-text screening and at the final stage, 11 articles (1192 patients) were chosen for qualitative analysis and six articles (594 patients) were chosen for quantitative analysis (Table 1).

The comparison of lopinavir-ritonavir with no antiviral therapy on the basis of its safety and efficacy has been shown in six studies [6,24-28]. Virologic cure was reported by three studies, with n=117 for no antiviral conventional therapy and n=171 for lopinavir-ritonavir [24,25,28]. A significant mean difference was observed in both the treatment modalities considering the virological cure (mean difference=0.71 day; 95% CI, −4.34 to 2.71; *P* = .006, I2 =70%) (Fig. 2a). The results revealed that administration of lopinavir-ritonavir in comparison with no anti-viral therapy reduced the number of days of the patients' care.

Three of the included studies carried out comparison of lopinavir-ritonavir and umifenovir on day 7 post initiation of the therapy [24,27,28]. Virologic cure was reported by these studies with n=87 for umifenovir and n=127 for lopinavir/ritonavir. A significant mean difference was observed in both the treatment modalities considering the virological cure (mean difference = 0.85 day; 95% CI, −1.01 to 3.00; *P* = .008, I2 = 48%) (Fig. 2b).

Two of the studies on virological cure conducted comparisons between lopinavir/ritonavir and umifenovir along with lopinavir/ritonavir with respect to their efficacies [25,28]. Virologic cure was reported by these studies with n=75 for umifenovir plus lopinavir/ritonavir and n=93 for lopinavir/ritonavir. A significant mean difference was observed in both the treatment modalities considering the virological cure (mean difference = -0.73 day; 95% CI, −2.35 to 0.68; *P* = .56, I2 = 0%) (Fig. 2c).

The current study has also focused on the clinical factors that lead to the improvement of symptoms in the COVID-19 patients including the normalization of body temperature, reduction in cough, and improvement in chest CT. The association between time duration and normalization of body temperature was reported by two studies that compared the efficacies of umifenovir (n=71) and lopinavir/ritonavir (n=93) [24,28]. A significant mean difference was observed in both the treatment modalities considering the virological cure (OR = 0.77 day; 95% CI, 0.32 to 1.68; *P* = .51, I2 = 0%) (Fig. 2d). Similarly, the association between time duration and normalization of body temperature was also reported by two studies that made a comparison between the effects of no antiviral therapy (n=75) and lopinavir/ritonavir (n=93) [24,28]. A significant mean difference was observed in both the treatment modalities considering the virological cure (OR = 0.89 day; 95% CI, 0.39 to 1.89, *P* = .25, I2 = 0%) (Fig. 2e).

Alleviation in cough was reported by two studies that compared the efficacies of umifenovir (n=71) and lopinavir/ritonavir (n=93) [24,28]. The results revealed a significant decrease in the coughing period after using lopinavir/ritonavir by 0.52 (95% CI 0.05 to 5.43, *P* = .01; I2 = 71%) (Fig. 3a). Similarly, alleviation in cough was reported by two studies that compared the effect of no antiviral therapy (n=75) and lopinavir/ritonavir (n=93) [24,28]. No significant difference was observed in both the treatment modalities (OR = 0.7 7 days; 95% CI, 0.00 to 27.06; *P* = .07, I2 = 57%) (Fig. 3b). Decrease in the duration of coughing was, however, observed in comparison with no anti-viral therapy or with umifenovir after the treatment for 7 days.

Table 1. Data gathered from the included studies

Author and Year	Study Design and Setting	Population	Intervention	Control	Outcome	Remarks
Cao *et al.*[5]	Randomized controlled trial	Confirmed cases of COVID-19 with <94% concentration of SaO2	Lopinavir/ritonavir along with standard care was administered to 99 patients.	Only standard care was given to 100 patients.	No significant improvement related to clinical factors in both the groups was observed.	Urgent medical condition was provided to patient with severe symptoms.
Chen *et al.[*6]	Retrospective cohort study	Confirmed cases of COVID-19 with the consideration of laboratory examinations and chest CT	Lopinavir/ritonavir was administered to 52 patients twice daily for 5 days.	Umifenovir or no antiviral therapy was provided in 34 and 45 patients respectively.	The symptoms settled down with antiviral therapy in 4 days; however, groups with lopinavir/ritonavir and umifenovir took 6 days to show stability.	IFN α2b spray therapy was provided to every patient.
Li *et al.*[24]	Randomized controlled trial	Confirmed mild/moderate cases of COVID-19 of patients aged between 8 to 18 years	Lopinavir/ritonavir was administered to 34 patients.	Umifenovir was given to 35 patients and 17 patients received no antiviral therapy.	No difference was observed in cough alleviation, rate of antipyresis, and improvement in chest x-ray.	Standard care was provided to the patients.
Lan *et al.*[25]	Retrospective cohort study	Confirmed COVID-19 cases, who were either given lopinavir/ritonavir alone or in combination with umifenovir	Lopinavir/ritonavir was administered to 34 patients for 14 days.	Lopinavir/ritonavir was administered to 34 patients for 14 days and 39 patients received lopinavir/ritonavir in combination with umifenovir.	No significant difference was observed in outcomes of control and experimental groups.	Standard care was provided to all the eligible patients.
Yan *et al.*[26]	Retrospective cohort study	Confirmed COVID-19 cases with the availability of RNA viral data for the estimation of viral shedding duration	Lopinavir/ritonavir was administered to 78 patients for 10 days or more. (twice a day)	No antiviral therapy was provided to 42 patients.	Viral shedding decreased in the group administered with lopinavir/ritonavir, in comparison with the control group.	Standard care was provided to patients whenever needed.
Zhu *et al.*[27]	Retrospective cohort study	Confirmed COVID-19 case with difference	Lopinavir/ritonavir was given to 34 patients twice daily for 7	Umifenovir was administered to 16	No difference in the duration of fever was observed in both	Standard care was given to patients.

Author and Year	Study Design and Setting	Population	Intervention	Control	Outcome	Remarks
		in age and sex between the two groups	days.	patients 3 times daily.	the groups. No viral load was detected in the umifenovir group.	
Wen *et al.*[28]	Retrospective cohort study	Confirmed COVID-19 cases aged >18 years with no longer than 14 days of hospital stay	Lopinavir/ritonavir was administered to 59 patients for 7 days twice daily.	Umifenovir or combined antiviral therapies were provided to 36 and 25 patients respectively.	There was no significant difference in the overall clinical improvement and lung infection in all the groups.	Standard care was provided to all patients.
Hung *et al.*[32]	Randomized open labeled trial	Confirmed patients of COVID-19 with duration of <14 days and of age >18 years	Lopinavir/ritonavir was administered to 41 patients twice a day for 14 days.	86 patients received lopinavir/ritonavir along with ribavirin, and IFN - beta - 1b (SCI).	Median time was shortened in the control group from the start of study treatment to obtain negative nasopharyngeal swab.	Mortality rate was zero.
Ye *et al.*[33]	Retrospective cohort study	Confirmed cases of COVID-19 treated with lopinavir/ritonavir or not during hospitalization	Lopinavir/ritonavir was administered to 42 patients, along with umifenovir and IFN-α1b	Umifenovir with FN -α1b was administered to 5 patients only.	Normal body temperature was restored in the patients given the combination of lopinavir/ritonavir, Umifenovir, and IFN-α1b	Standard care was provided to the patients, who were in dire need of medical assistance.
Yuan *et al.*[34]	Retrospective cohort study	Confirmed cases of COVID-19 presented with fever, diarrhea, and fatigue	IFN -α + Lopinavir/ritonavir was given to 46 patients.	IFN -α + Lopinavir/ritonavir along with ribavirin was administered to 94 patients.	No significant differences observed between different treatment groups.	Majority of the patients were <40 years of age.
Cai *et al.*[35]	Non-randomized controlled trial	Confirmed moderate cases of COVID-19 of age ranging between 16 and 75 years	Lopinavir/ritonavir was administered to 45 patients twice a day for 14 days.	Favipiravir was administered to 35 patients twice a day for 14 days.	Shorter viral clearance was observed for favipiravir, whereas improvement was observed in chest CT.	All the patients in lopinavir/ritonavir group showed negative detection within 27 days, while only 2 patients taking favipiravir recovered between the time duration of 18 to 21 days.

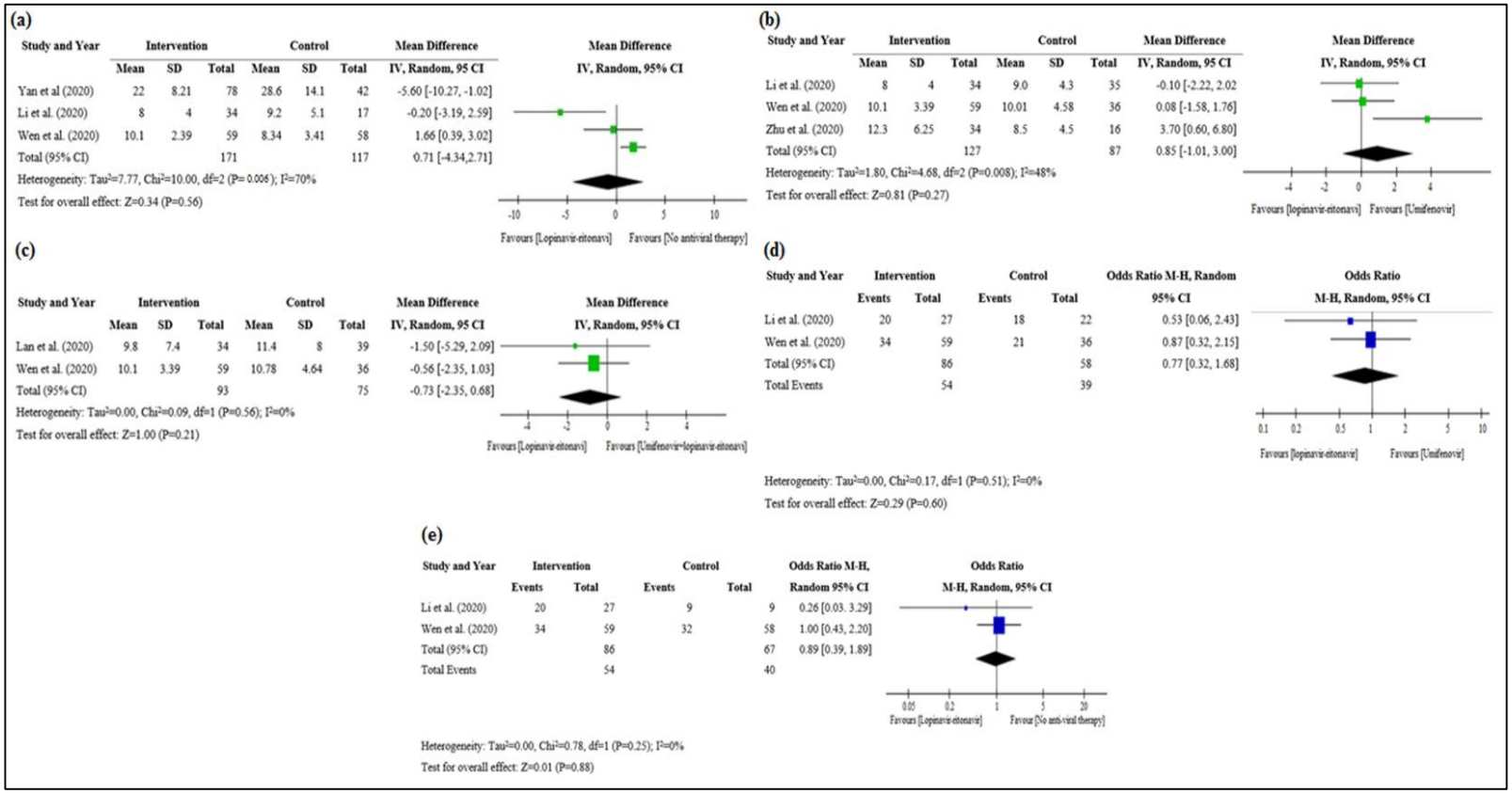

Fig. 2. Time duration of change in result; (a) from positive to negative (Lopinavir-ritonavir vs no antiviral therapy); (b) from positive to negative (Lopinavir-ritonavir vs umifenovir); (c) from positive to negative (Lopinavir-ritonavir vs lopinavir-ritonavir + umifenovir); (d) for body temperature normalization (Lopinavir-ritonavir vs umifenovir); (e) of body temperature normalization (Lopinavir-ritonavir vs no anti-viral therapy)

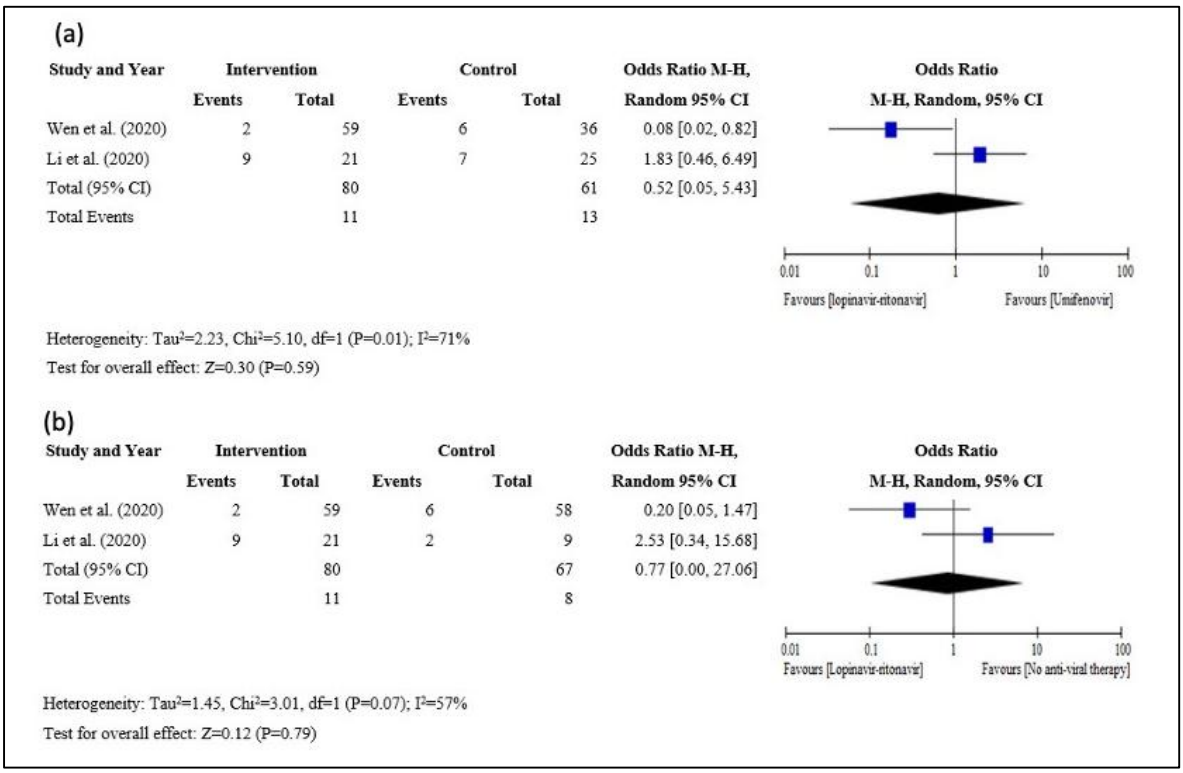

Fig. 3. Rate of alleviation in cough; (a) Lopinavir-ritonavir vs umifenovir; (b) Lopinavir-ritonavir vs no anti-viral therapy

No significant difference was observed between the treatment with lopinavir-ritonavir alone and the treatment with umifenovir plus lopinavir-ritonavir considering the cure from the viral infection after 7 days. However, a study conducted on a small cohort sample showed promising results when a combination of lopinavir-ritonavir and umifenovir was administered [29]. Another study conducted by Lian et al. [30] showed that the duration of the hospital stays increased in patients treated with umifenovir in comparison with other patients. It is known that umifenovir, which is currently used in the treatment of COVID-19 patients, was initially used to treat MERS-CoV and SARS-CoV infections [31].

Considering the improvement in chest CT, the main observation was regarding the progression of lung damage/pneumonia (n=71 for umifenovir and n=59 for lopinavir-ritonavi) [24,28]. The results clearly depicted no significant difference in the radiological progression after using lopinavir/ritonavi (OR = 0.70; 95% CI, 0.32 to 1.44; *P* = .49, I2 = 0%) (Fig. 4a). Similar results were concluded by comparing the effects of no antiviral therapy (n=75) and lopinavir/ritonavir (n=71) [24,28]. The study reported no significant difference in the radiological progression after using lopinavir/ritonavir (OR = 0.59; 95% CI, 0.26 to 1.21; *P* = .32, I2 = 0%) (Fig. 4b).

Radiological progression after the treatment with lopinavir-ritonavir was evident; however, a few patients also showed radiological progression after being treated with umifenovir or anti-viral therapy for 7 days. These results showed no significant difference in all the treatments that include lopinavir-ritonavir, umifenovir, and anti-viral therapy. Further, the current study showed that administration of lopinavir-ritonavir in COVID-19 patients caused some adverse effects in them, which were not reported in patients receiving umifenovir or anti-viral treatment. The adverse events associated with the use of lopinavir-ritonavir included vomiting, nausea, acute gastritis, diarrhea, acute kidney injury, and bleeding in gastrointestinal tract [28].

The efficacy of a combination of lopinavir-ritonavir and IFN-α1b was assessed to test the clinical improvements in COVID-19 patient and the result revealed that inclusion of ribavirin was much safer as compared to the administration of lopinavir-ritonavir alone [32]. Rapid body temperature normalization was observed in

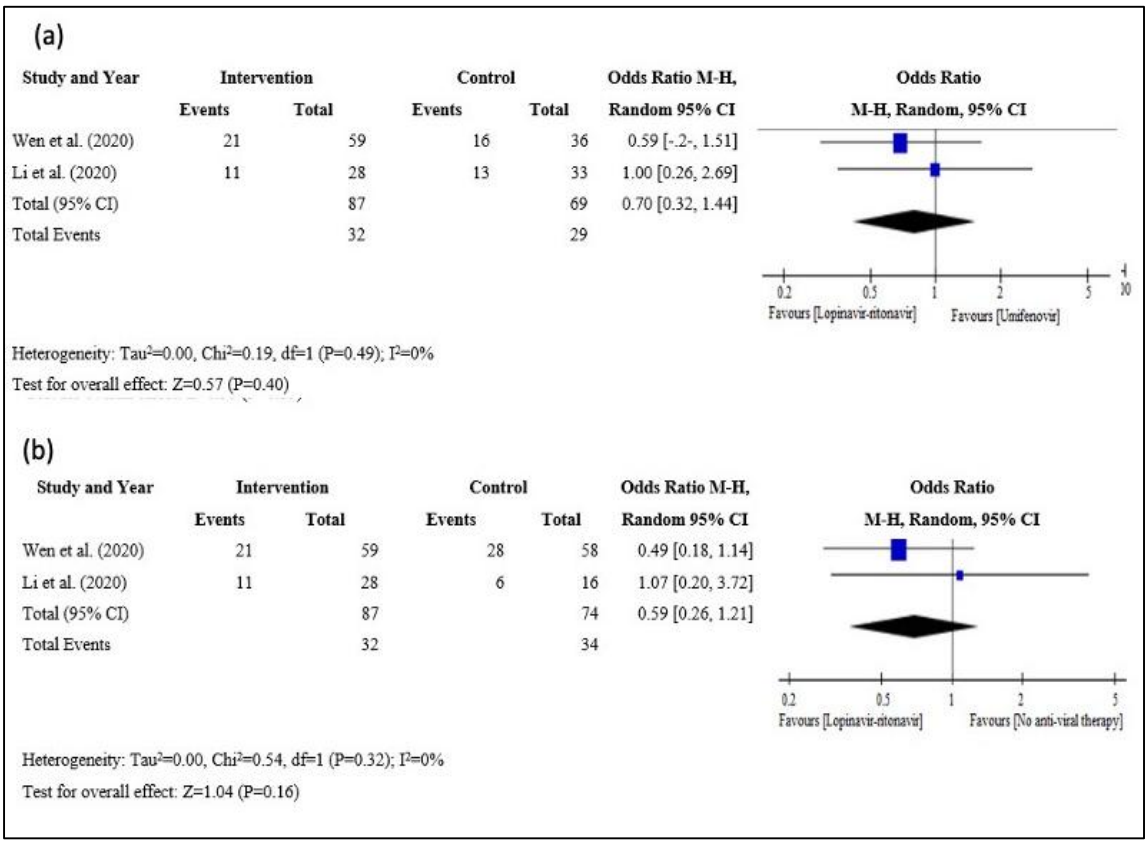

Fig. 4. Improvement in chest CT; (a) Lopinavir-ritonavir vs Umifenovir; (b) Lopinavir-ritonavir vs No anti-viral therapy

patients after the administration of a combination of lopinavir-ritonavir umifenovir and IFN-α1b [33]. However, a decrease in the therapeutic responses was reported in COVID-19 patients in terms of viral clearance after the administration of lopinavir-ritonavir in combination with IFN-α1b. The study conducted by Yuan et al [34] showed that there was no significant difference in IFN-α1b combined with lopinavir-ritonavir or IFN-α1b combined with lopinavir-ritonavir and ribavirin with respect to the average negative conversion time of polymerase chain reaction.

The findings of this study are limited since it included and reviewed only a few studies that investigated clinical improvement in COVID-19 patients. Moreover, on account of large methodological differences, the study failed to assess clinical improvement with respect to the use of lopinavir/ritonavir in combination with other agents or no antiviral therapy or control.

4. CONCLUSION

The current study revealed no significant clinical improvement in COVID-19 patients after their treatment with lopinavir-ritonavir or other antiviral or conventional treatments. However, this systematic review revealed much greater adverse effects associated with the administration of lopinavir-ritonavir in COVID-19 patients. Considering the study limitation, it is suggested that future studies need to include a greater number of studies with large randomized clinical trials to evaluate clinical improvements in COVID-19 patients after their treatment with lopinavir-ritonavir.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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