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The Safety and Efficacy of the Protease Inhibitors Lopinavir/Ritonavir as Monotherapy or Combined with Interferon in COVID-19 Patients

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Abstract: Enzyme inhibitors are frequently used to treat viral illnesses. Protease inhibitors are a promising class for combating novel and life-threatening viral infections. This research aimed to evaluate the efficacy and safety of lopinavir/ritonavir monotherapy or lopinavir/ritonavir plus interferon for the treatment of COVID-19. The PubMed, Scopus, Web of Science, and Cochrane Library databases were searched for English articles with full texts available online. ReviewManager software was used to conduct a meta-analysis, subgroup analysis, and sensitivity analysis. Following the creation of the protocol, the collected sources were sorted into categories and evaluated for quality. Risk and hazard ratios and the random effects model were implemented, with statistical heterogeneity assigned using the Higgins I^2 statistic. Lopinavir/ritonavir, with or without interferon, was associated with a nonsignificant higher mortality rate (odds ratio [OR] 1.29; 95% confidence interval [CI] 0.95 to 1.761; $p = 0.1$), as was clinical improvement (OR 1.2; 95% CI 0.8 to 1.84; $p = 0.36$). The difference in the length of hospital stay was in favor of the control group but statistically insignificant (standardized mean difference [SMD] 0.07; 95% CI −0.44 to 0.57; $p = 0.79$). The pooled data showed that lopinavir/ritonavir, with or without interferon, was associated with a significantly higher number of adverse events than placebo (OR 1.6; 95% CI 1.09 to 2.34; $p = 0.02$). Serious adverse events were insignificantly increased in the treated group over the control group (OR 1.42; 95% CI 0.96 to 2.12; $p = 0.08$). In the subgroup analysis, it was found that interferon used with lopinavir/ritonavir did not have a statistically significant effect on mortality rates (OR 1.75; 95% CI 0.87 to 3.55; $p = 0.37$), adverse effects (OR 1.20; 95% CI 0.75 to 1.91; $p = 0.27$), or serious adverse effects (OR 1.86; 95% CI 1.17 to 2.96; $p = 0.33$). Treatment with lopinavir/ritonavir alone or in combination with interferon for COVID-19 did not significantly outperform placebo in this study. Large randomized clinical trials are required to evaluate lopinavir/ritonavir in conjunction with interferon for the treatment of COVID-19. Such studies would benefit greatly from being conducted in a double-blind fashion at multiple locations.

Keywords: COVID-19; lopinavir; interferon; meta-analysis; ritonavir

1. Introduction

Over the past two decades, significant health issues have been caused by three members of the betacoronavirus genus: SARS-CoV, MERS-CoV, and SARS-CoV-2 [1]. On 12 March 2020, the World Health Organization (WHO) declared that COVID-19 cases had reached the level of a pandemic and become a global public health emergency. As of 19 December 2022, 647,972,911 verified cases had been registered worldwide and 6,642,832 deaths due to COVID-19 had been recorded [2]. Some of the clinical symptoms of COVID-19 include a high temperature, trouble breathing, dyspnea, fatigue, and coughing [3]. Most people infected with COVID-19 experience mild symptoms or have a rapid recovery, although a small percentage of those infected go on to develop multiorgan failure or severe pneumonia and some die [4,5].

While there have been extensive efforts to find effective treatments for SARS-CoV-2 infections all around the world, only a small number of drugs have been approved for use in an emergency setting and none have garnered universal acceptance as cures. Accordingly, research into potential pharmacological treatments for COVID-19 continues. Antiviral drugs such as remdesivir, favipiravir, ribavirin, chloroquine, interferons, protease inhibitors, neuraminidase inhibitors, fusion and entry inhibitors, and hemagglutinin inhibitors have been repurposed to treat COVID-19 [6–9]. The Food and Drug Administration (FDA) in the United States has given the dual protease inhibitor lopinavir/ritonavir the green light for treating acquired immunodeficiency syndrome (AIDS) [10]. Additionally, the drug has demonstrated antiviral activity against MERS-CoV and SARS-CoV [11,12]. The effective treatment of COVID-19 infection has been demonstrated with purine and pyrimidine derivatives, including acyclovir, ganciclovir, and lopinavir [13,14]. Other promising drugs for COVID-19 are simeprevir [15], paxlovid (nirmatrelvir/ritonavir) [16], and molnupiravir [17].

Interferons are important components of the immune system in the fight against viruses [18]. Type I, II, and III interferons were recognized in the past, and the type IV interferon was discovered very recently [19]. Type I interferons inhibited SARS-CoV-2 multiplication in vitro utilizing Vero E6 cells in plaque reduction, viral antigen expression, and viral load reduction experiments [20]. When compared with SARS-CoV, SARS-CoV-2 is more susceptible to the effects of type I interferons [21]. Interferon-β has been shown to provide considerable benefits in terms of the time it takes for clinical improvements to occur, but not in terms of reducing mortality rates or shortening hospital stays for COVID-19 patients [22,23]. However, this study's findings were constrained by confounding variables, varying interferon doses, and significant heterogeneity.

The purpose of this research was to examine how effective lopinavir/ritonavir was on its own and in conjunction with interferon in treating patients with COVID-19. Few studies have been performed on the safety and efficacy of lopinavir/ritonavir alone or in combination with interferon. This study evaluated the efficacy of lopinavir/ritonavir with or without interferon versus placebo, standard care, and other antiviral medications, as measured by 28-day mortality rates, clinical response rates, and the length of hospitalization. The number of patients who reported mild or severe adverse effects when taking lopinavir/ritonavir with or without interferon was also compared with the number of people who reported such effects while taking a placebo, receiving normal care, or taking other antiviral medication.

2. Materials and Methods

2.1. Research Question and Guidelines

While conducting this study, the researchers used data from systematic reviews and meta-analyses [24] and relied on the guidelines and recommendations of the Cochrane community [25].

The research question was structured according to the patient/population, intervention, comparison, and outcomes (PICO) model. The population was COVID-19 patients. The intervention was lopinavir/ritonavir with or without interferon. Comparisons were made among patients receiving placebo, standard care, and other antiviral drugs. The primary outcome(s) were mortality rates at day 28 and rates of clinical improvement. The secondary outcomes were the length of hospital stay, adverse events, and serious adverse events. The research question was, "Is the use of lopinavir/ritonavir, with or without interferon, safe and effective compared with placebo, standard care, and other antiviral drugs in managing COVID-19 patients"?

2.2. Inclusion Criteria

The articles that were selected for review for this study were in English and published between 1 January 2020 and 1 December 2022. The length of time it took to finish the study was not relevant. The demographics, research design, and purpose of each article were taken into consideration when determining whether it should be included in the study. An included research article had to satisfy the following conditions: (1) It had to be a randomized clinical trial (RCT). (2) It had to compare laboratory-confirmed COVID-19 patients who were given lopinavir/ritonavir as a single therapy or together with interferon with those who were given placebo, no antiviral agent, or other antiviral agents for COVID-19 treatment. (3) It had to examine at least one of the primary outcomes. The mortality rate on day 28 of treatment was the main safety-linked outcome of concern. After treatment, clinical improvement was the main efficacy-linked outcome of concern. (4) It had to be written in English and published. (5) No specific criteria were used to limit the age of the study population; therefore, all participants were regarded as eligible in terms of age.

2.3. Exclusion Criteria

All non-original publications such as reviews, letters to the editor, conference papers, and comments on published articles were excluded from this study. In addition, articles for which the full text was not available, animal studies, case studies, study protocols, non−peer reviewed journal articles, and studies that could not be sourced in the English language were excluded.

2.4. Search Strategy

To find pertinent articles up to December 2022, a systematic search was performed in PubMed, Scopus, the Cochrane Central Register of Controlled Trials, and the Web of Science. Additional studies cited in the included studies and the reviews' reference lists were searched manually. Only papers having an English abstract or full text were included in the search. The search strategy for pertinent articles on PubMed was (Coronavirus OR COVID-19 OR SARS-CoV-2) AND (lopinavir/ritonavir OR lopinavir/ritonavir AND interferon). A similar strategy was followed while searching other databases.

2.5. Quality Assessment

The Cochrane risk-of-bias tool for randomized controlled studies was used to assess the quality of the included studies because only randomized controlled trials were included in this review.

2.6. Data Extraction

Data extraction was performed after studies were chosen from the databases and their methodological quality was evaluated. Microsoft Excel was used to create a consistent

data-collecting format for gathering the following data: author and year of publication, location of the study, number of participants, patient age, participant gender (male), and the study's measured outcome(s). Two researchers independently carried out these steps.

2.7. Data Synthesis

Dichotomous data were converted into pooled odds ratios (ORs) and 95% confidence intervals (CIs). Using the inverse variance approach, the standardized mean difference (SMD) was calculated by pooling the effect sizes for each continuous variable. When they were not reported, the means and standard deviations were computed using ranges, medians, interquartile ranges (IQRs), and sample sizes [26]. Mantel–Haenszel ORs and count data were used to display the results for tolerability (at least one event had to be observed to be included in the analysis). The assumption behind the random effects model was that the disparities between the research populations would result in some fluctuation in the size of the effect between trials [27]. Meta-analysis was performed if there were results from at least two studies on the targeted outcomes.

Heterogeneity was examined using the Cochrane Q test and the I^2 statistic, which evaluated the heterogeneity of the study data. Heterogeneity of less than 25% was categorized as low, between 26% and 74% as moderate, and higher than 75% as high [28]. Sensitivity and subgroup analyses were carried out when appropriate and applicable in order to identify potential sources of heterogeneity. For all statistical analyses, ReviewManager (RevMan) software version 5.4.1 was used.

3. Results

3.1. Study Selection

A total of 680 studies were found in the initial search of the internet databases using the aforementioned keywords. With repetitions removed, we were left with 539 studies. The titles and abstracts of the 539 studies were reviewed to select those that would be included in the meta-analysis. After the initial round of culling, just 34 publications were left; a full-text read led to the elimination of another 25 studies. In the end, 9 articles were found to have effectively met the established eligibility requirements (Table 1). Figure 1 shows the PRISMA diagram for the study selection process.

Table 1. Characteristics of included studies considered in this study.

Study	Study Design	Study Region	Sample Size	Gender, Male	Patients' Age	Intervention (*N*)	Control (*N*)	Outcomes Measured
(Cao et al., 2020)	RCT	China	199	120	≥18 Years	Lopinavir-ritonavir (99)	Placebo (100)	Clinical improvement, mortality, adverse events and serious adverse events
(Arabi et al., 2021)	RCT	Global	617	434	≥ 18 Years	Lopinavir-ritonavir (255)	Placebo (362)	Organ support-free days, mortality, adverse events
(Reis et al., 2021)	RCT	Brazil	471	216	53 (18–94)	Lopinavir-ritonavir (244)	Placebo (227)	Hospitalization, adverse events, serious adverse event, clinical improvement
(Horby et al., 2020)	RCT	UK	5040	3077	66·2 Years (SD 15·9	Lopinavir-ritonavir (1616)	Placebo (3424)	Mortality, discharged from hospital within 28 days
(Ader et al., 2021)	RCT	France and Luxembourg	438	314	63 Years (IQR 54–71)	Lopinavir-ritonavir (145)	Placebo (148)	Mortality, adverse events, serious adverse events
(Ader et al., 2021)	RCT	France and Luxembourg	438	314	63 Years (IQR 54–71)	Lopinavir/ritonavir plus interferon-B-1a (145)	Placebo (148)	Mortality, adverse events, serious adverse events
(Hassaniazad et al., 2022)	RCT	Iran	66	36	18–80 Years	Lopinavir/ritonavir plus interferon-B-1a (33)	Favipiravir plus interferon-B-1a (33)	Clinical improvement, mortality, adverse events
(Li et al., 2020)	RCT	China	86	40	19–79	Lopinavir/ritonavir (34)	Placebo (17)	Clinical improvement, mortality, adverse events and serious adverse events.
(Siami et al., 2022)	RCT	Iran	103	64	20–80 Years	Lopinavir/ritonavir (49)	Atazanavir/ritonavir (54)	Mortality, length of hospital stay, adverse events
(Karolyi et al., 2022)	RCT	Austria	201	135	58.7 Years	Lopinavir/ritonavir (100)	Camostat mesylate (101)	Mortality, adverse events, serious adverse events

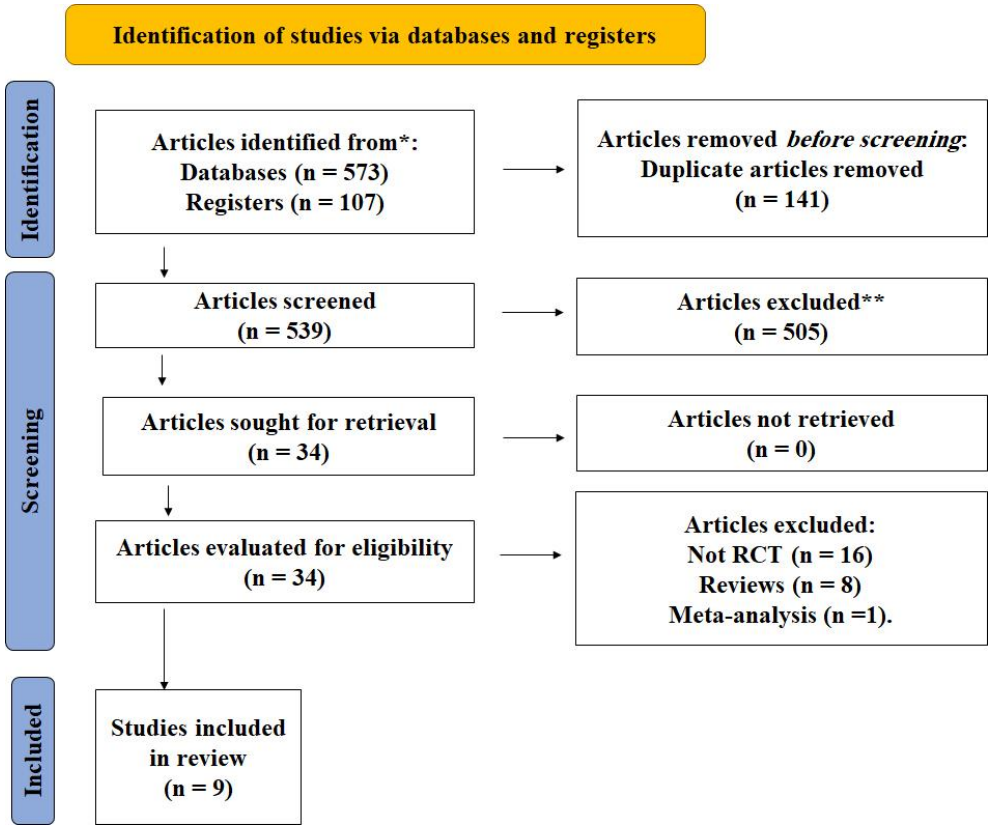


Figure 1. PRISMA flow diagram. * According to the inclusion criteria of articles in the study. ** The articles were excluded according to the exclusion criteria described in the methods section.

3.2. Quality Assessment Results

According to the Cochrane risk-of-bias tool (Figure 2), seven studies had a high risk of performance bias [29–35], five studies had a high risk of detection bias [30–32,34,35], and one study had an unclear risk of detection bias [29]. One study had a high risk of other biases [35], and three studies had an unclear risk of other biases [31,32,34].

3.3. Measured Outcomes

3.3.1. Mortality Rate on Day 28

Seven randomized trials were combined for this meta-analysis [29–34,36]. The control group consisted of 4360 patients, while the intervention group had 2434 individuals. The findings of the I^2 statistic, at 50%, showed that the heterogeneity of the seven studies pooled in this analysis was moderate.

According to the combined data, the groups that took lopinavir/ritonavir with or without interferon had a higher mortality rate (22.1%) than the control group (21.2%). When the lopinavir/ritonavir groups with or without interferon were compared with the control group, the difference in mortality incidence was an OR of 1.29, with a 95% CI of 0.95 to 1.76, favoring the control group. However, because the *p*-value was higher than the established threshold ($p = 0.10$), these findings were not statistically significant. A forest plot of the analysis is presented in Figure 3.

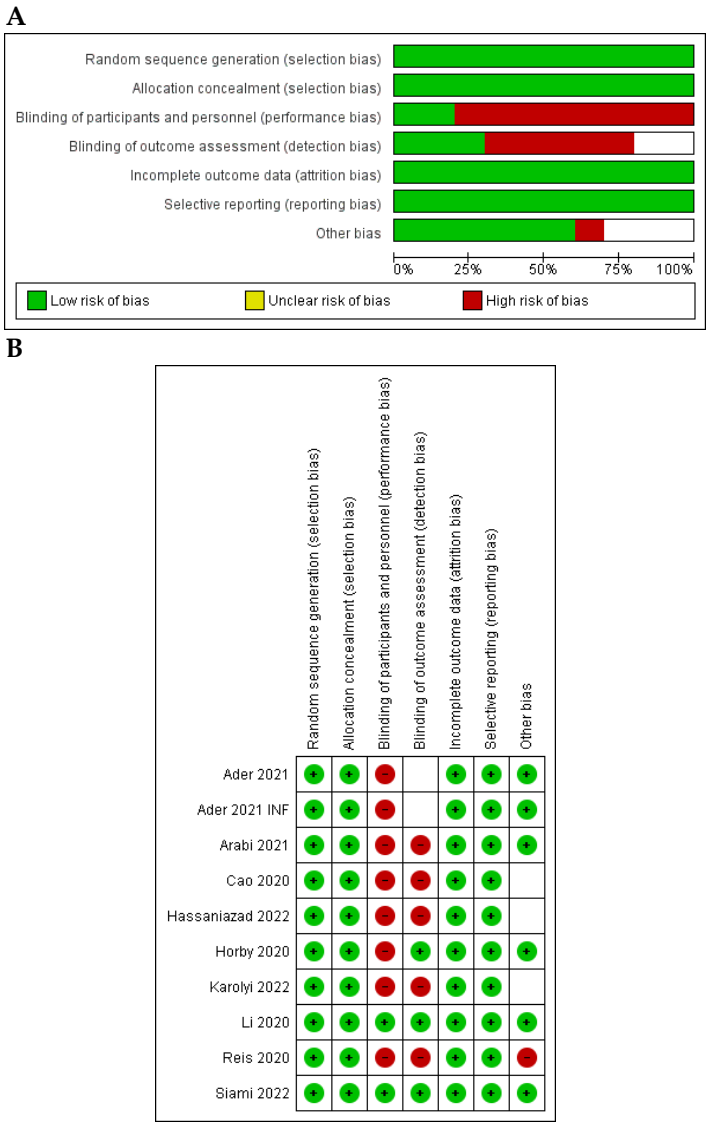


Figure 2. Quality assessment of the included studies. (**A**) Risk-of-bias graph. (**B**) Risk-of-bias summary for each study.

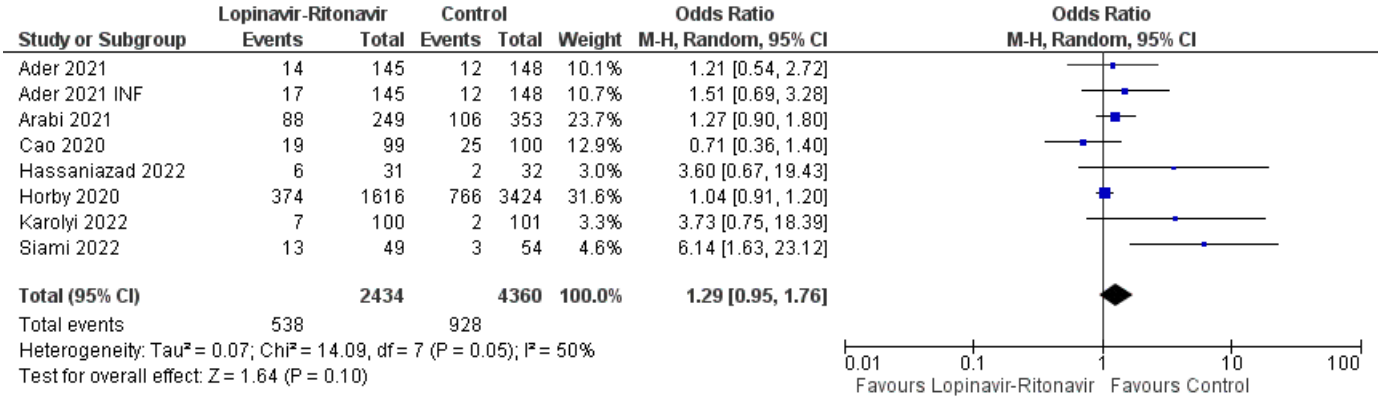


Figure 3. Forest plot analysis for mortality incidence. The sizes of the blue squares reflect the relative weight of the individual trials. The combined point estimate is shown as a black diamond. The diamond and the squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

3.3.2. Clinical Improvement

Four randomized trials were merged for analysis in this meta-analysis [31,32,35,37]. There were 344 patients in the control group and 365 in the intervention group overall. The I^2 statistic results, at 22%, showed that the four studies aggregated in this analysis had low heterogeneity. In comparison with the control group, more COVID-19 patients receiving lopinavir/ritonavir with or without interferon experienced clinical remission. The difference between the COVID-19 groups receiving lopinavir/ritonavir with or without interferon and the control group in terms of clinical improvement was an OR of 1.21, with a 95% CI of 0.80 to 1.84, favoring the groups receiving lopinavir/ritonavir with or without interferon. However, because the *p*-value was greater than the established cutoff point ($p = 0.36$), these findings were not statistically significant. Figure 4 shows a forest plot of the analysis.

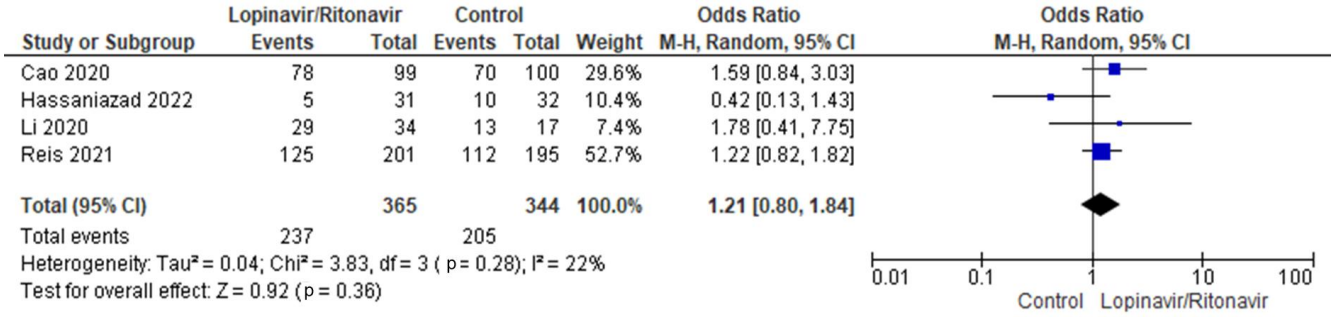


Figure 4. Forest plot analysis of clinical improvement. The sizes of the blue squares reflect the relative weight of the individual trials. The combined point estimate is shown as a black diamond. The diamond and squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

3.3.3. Length of Hospital Stay (Days)

Three papers were included for the analysis of this characteristic [31,32,36]. There were 179 patients in total in the lopinavir/ritonavir group and 186 patients overall in the control group. High levels of heterogeneity were seen in the three studies. The I^2 statistic results, at 81%, demonstrated this. The difference in length of hospital stay was an SMD of 0.07 (95% CI −0.44 to 0.57), in favor of the control group. A *p*-value of 0.79, which was above the threshold of 0.05, indicated that the difference was statistically insignificant. Figure 5 includes a graphic display of the forest plot used in this analysis.

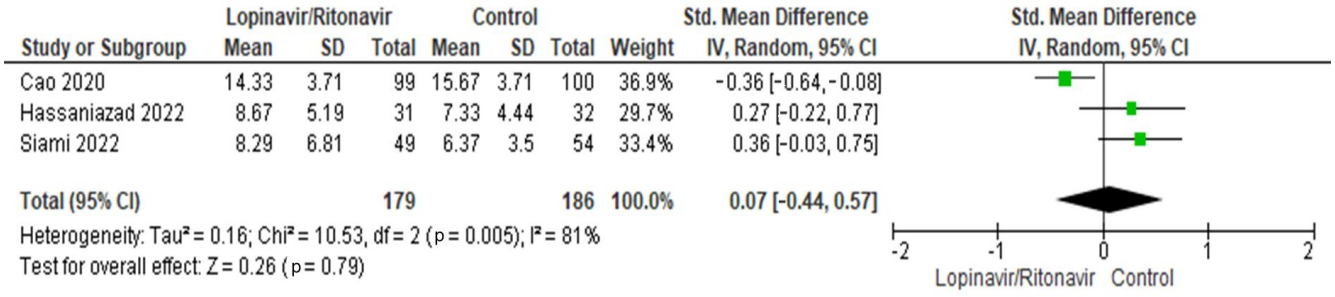


Figure 5. Forest plot analysis for length of hospital stay. The sizes of the green squares reflect the relative weight of the individual trials. The combined point estimate is shown as a black diamond. The diamond and squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

3.3.4. Adverse Events

Seven studies were considered for the analysis of adverse events [29,31,32,34–37]. There were 831 patients with COVID-19 who received lopinavir/ritonavir with or without

interferon and 819 people in the control group. Moderate levels of heterogeneity were present across the seven studies. The I^2 statistic was 60%. According to the pooled data, the groups that received lopinavir/ritonavir with or without interferon had a disproportionately high number of side effects compared with the control group. With a 95% CI of 1.09 to 2.34, the control group was better off than the experimental group in terms of the outcomes of adverse events in COVID-19 patients. The *p*-value was less than the chosen threshold ($p = 0.02$), making these findings statistically significant. Figure 6 shows the forest plot used for this analysis.

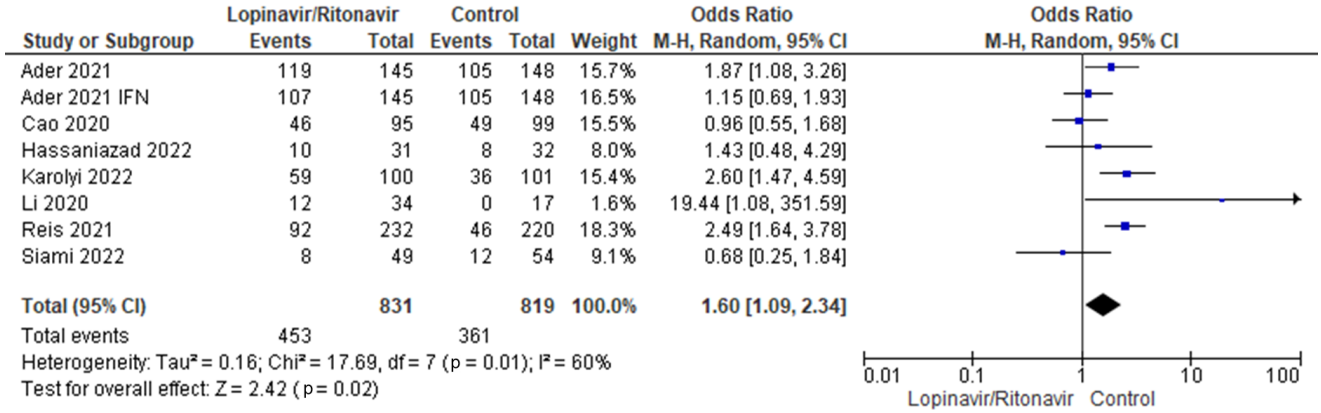


Figure 6. Forest plot analysis of adverse events. The sizes of the blue squares reflect the relative weight of the individual trials. The combined point estimate is shown as a black diamond. The diamond and squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

3.3.5. Serious Adverse Events

There were six studies of serious adverse events included in this meta-analysis [29,31,34–37]. There were 1095 patients in the control group and 1006 in the COVID-19 cohort who received lopinavir/ritonavir with or without interferon. The six studies had a moderate amount of heterogeneity. The I^2 statistic of 48% supported this. The combined data demonstrated that, in comparison with the control group, the groups that received lopinavir/ritonavir with or without interferon had a greater frequency of serious adverse events. The control group fared better than the experimental group in terms of the outcomes of serious adverse events in COVID-19 patients, with an OR of 1.42 and a 95% CI of 0.96 to 2.12. Since the *p*-value was higher (0.08) than the chosen threshold, these results were statistically insignificant. A forest plot for the analysis is presented in Figure 7.

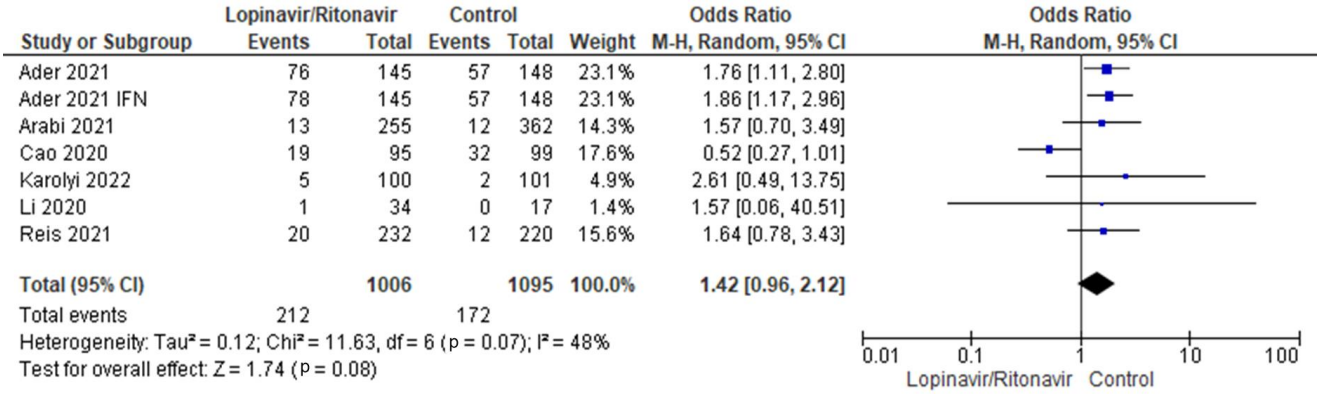


Figure 7. Forest plot analysis of serious adverse events. The combined point estimate is shown as a black diamond. The diamond and squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

3.4. Subgroup Analysis

A subgroup analysis based on treatment with lopinavir/ritonavir as a single therapy or with interferon was performed.

3.4.1. Mortality Rates

A subgroup study was conducted to determine whether the addition of interferon to the standard treatment of lopinavir/ritonavir for COVID-19 reduced mortality rates. The statistical results showed that the OR of mortality incidence for COVID-19 patients treated with lopinavir/ritonavir alone was 1.23 (95% CI 0.88 to 1.72) and the OR of mortality incidence for COVID-19 patients treated with lopinavir/ritonavir plus interferon was 1.75 (95% CI 0.87 to 3.55). Figure 8 displays the results of the test for subgroup differences, which revealed that there was no statistically significant subgroup effect ($p = 0.37$) when using interferon in conjunction with lopinavir/ritonavir for the management of COVID-19 patients.

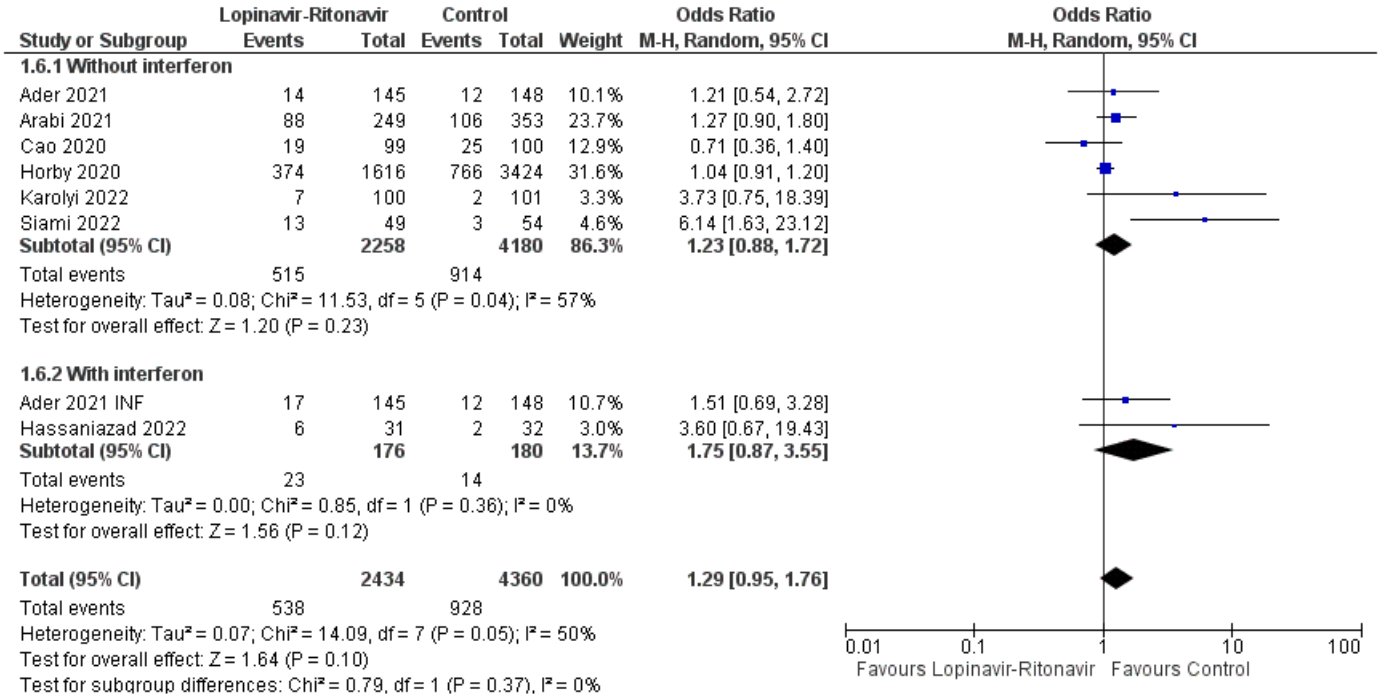


Figure 8. Subgroup analysis for mortality rates. The sizes of the blue squares reflect the relative weight of the individual trials. The combined point estimates are shown as black diamonds. The diamonds and squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

3.4.2. Adverse Events

Interferon's potential impact on adverse events in COVID-19 patients treated with lopinavir/ritonavir was tested in a subgroup analysis. In COVID-19 patients, the statistical results showed that the OR for adverse event incidence was 1.74 (95% CI 1.08 to 2.80) for lopinavir/ritonavir alone and 1.20 (95% CI 0.75 to 1.91) for lopinavir/ritonavir with interferon. Figure 9 displays the results for the subgroup differences; this test showed that there was no statistically significant subgroup effect ($p = 0.27$), indicating that interferon did not have a statistically significant effect on adverse events when used in combination with lopinavir/ritonavir to manage patients with COVID-19.

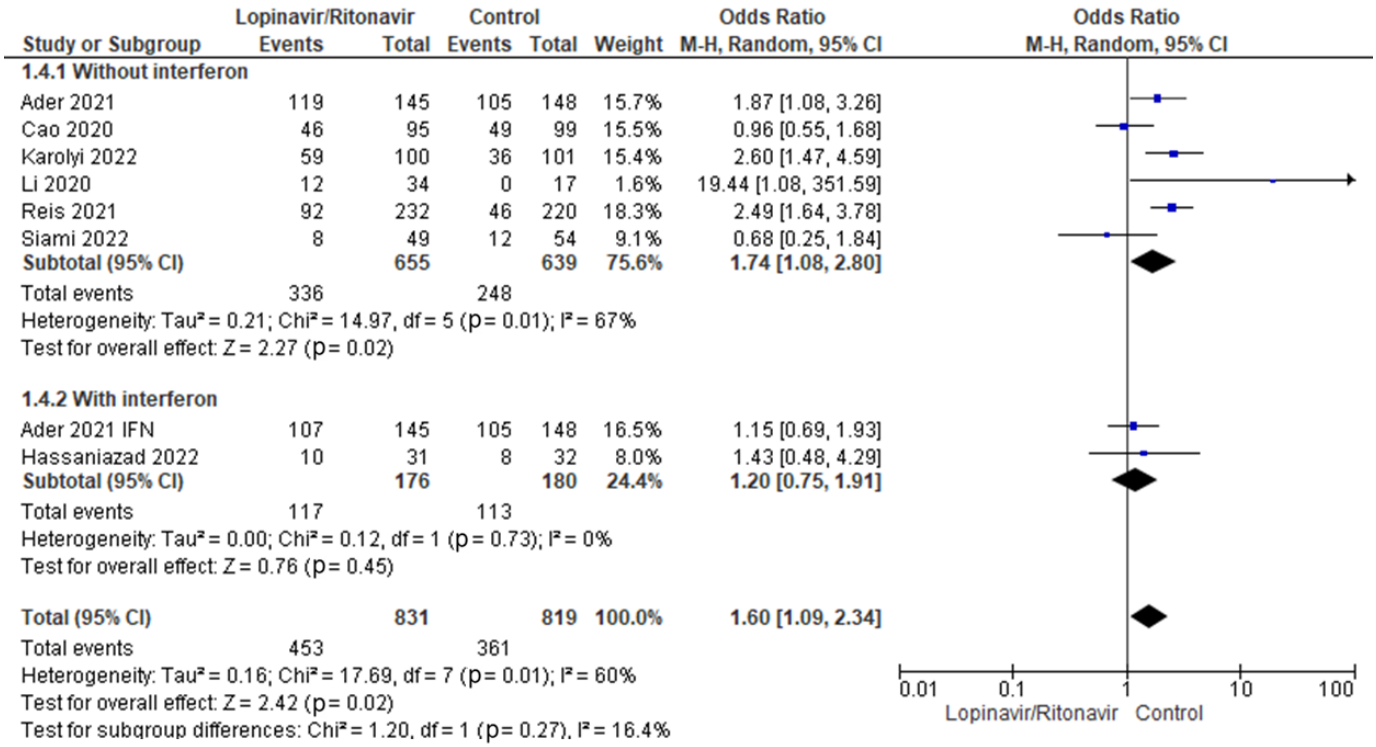


Figure 9. Subgroup analysis for adverse events. The sizes of the blue squares reflect the relative weight of the individual trials. The combined point estimates are shown as black diamonds. The diamonds and squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

3.4.3. Serious Adverse Events

A subgroup analysis was performed to test whether interferon had an effect on serious adverse events when used with lopinavir/ritonavir for treating COVID-19 patients. Statistical results showed that the OR for of adverse events incidence in COVID-19 patients was 1.32 (95% CI 0.80 to 2.18) for lopinavir/ritonavir alone and 1.86 (95% CI 1.17 to 2.96) for lopinavir/ritonavir with interferon. Figure 10 displays the results of the test for subgroup differences, which showed that there was no statistically significant subgroup effect ($p = 0.33$), indicating that adding interferon to lopinavir/ritonavir for the management of COVID-19 patients did not result in a statistically significant increase in the rate of serious adverse events.

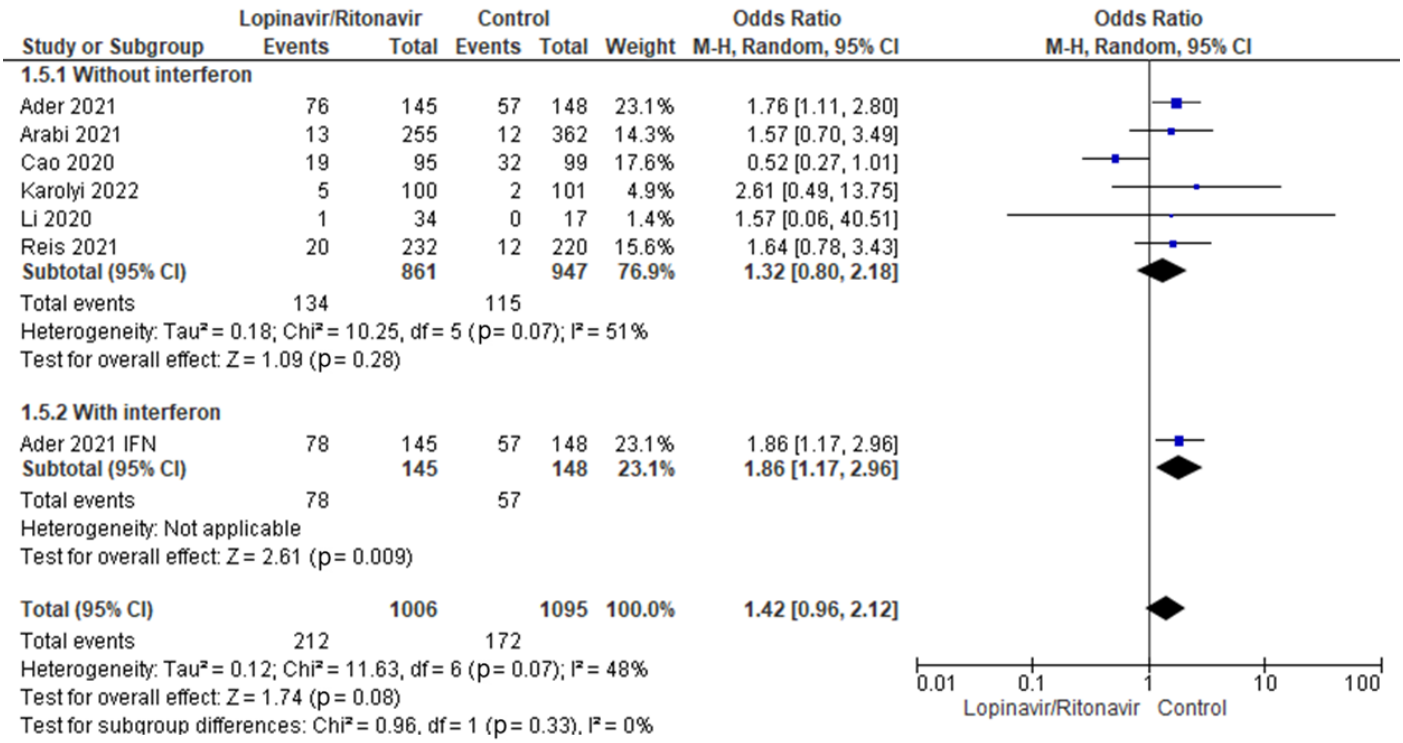


Figure 10. Subgroup analysis of serious adverse events. The sizes of the blue squares reflect the relative weight of the individual trials. The combined point estimates are shown as black diamonds. The diamonds and squares (together with the 95% CIs) located beyond the vertical line (indicating the unit value) show that a result was statistically significant.

4. Discussion

To combat COVID-19, we urgently need effective and safe medications, and thus researchers are looking into every possibility in a range of assessment frameworks. The pharmaceutical combination lopinavir/ritonavir was among the first to be used to treat SARS-CoV-2 because of its efficacy in treating SARS-CoV [38]. Both medications function by inhibiting the activity of a specific protein in the body; in this case, it is the protease in the human immunodeficiency virus (HIV protease) [39]. Ritonavir is recommended alongside lopinavir in modest doses because it enhances pharmacokinetics [40]. Ritonavir also prevents the CYP450-mediated metabolism of other protease inhibitors, and this improves bioavailability and reduces the dosage and frequency of administration of the second protease inhibitor [41,42].

The clinical efficacy and safety of the lopinavir/ritonavir combination have not been established, despite the fact that they have proved to be effective binders against the viral protease. There is conflicting evidence as to whether or not lopinavir/ritonavir inhibits the major protease activity of SARS-CoV-2 in vitro [43,44]. Lopinavir/ritonavir was effective on SARS-CoV-2 replication in vitro. However, it did not extrapolate to sufficient serum levels to kill the virus in clinical cases [45]. In another in vitro study, lopinavir/ritonavir effectively suppressed SARS-CoV-2 at the usual plasma levels [46]. Our study therefore attempted to determine the efficacy, safety, and justification for using lopinavir/ritonavir as a single therapy or in combination with interferon by pooling data on the following outcomes: mortality rates, length of hospital stay, clinical efficacy, safety, and major adverse events.

Of the nine trials considered here, seven provided death rates. The effect of lopinavir/ritonavir on mortality rates in COVID-19 patients relative to the control group was statistically significant in only one experiment [36]. In this trial, the group that received lopinavir/ritonavir had a higher mortality rate (26.5%) than the control group (5.6%). Six studies found no significant impact of lopinavir/ritonavir as a single therapy or when

combined with interferon on mortality rates as compared with the control group. There was no discernible difference in mortality rates between the experimental and control groups in this meta-analysis (OR 1.29; 95% CI 0.95 to 1.76). This study's results were in line with those of a previous meta-analysis and systematic review by Bhattacharyya et al., who also concluded that lopinavir/ritonavir monotherapy did not significantly reduce mortality rates when compared with placebo or treatment with other drugs [41].

Regarding clinical remission, treatment with lopinavir/ritonavir resulted in greater clinical improvement in COVID-19 patients than in control individuals in three studies. However, one trial found that lopinavir/ritonavir with interferon was likely to enhance clinical outcomes in a limited proportion of patients as compared with the control individuals. The results from all four trials that reported data on clinical improvement showed that the difference between the two treatment arms was statistically insignificant. Similarly, patients with COVID-19 who received lopinavir/ritonavir as monotherapy or in combination with interferon fared no better than those who received placebo or alternative COVID-19 therapeutic options (p = 0.36), according to pooled data from the studies included in this meta-analysis. The heterogeneity test returned a low I^2 result of 22%.

The current meta-analysis found that lopinavir/ritonavir with or without interferon did not reduce the length of the hospital stay, although these findings were not statistically significant when compared with the control individuals (SMD 0.07; 95% CI −0.44 to 0.57). The length of hospital stay in the lopinavir/ritonavir arm was significantly shorter than in the control arm in one of the included studies [31]. The overall heterogeneity of the included studies was substantial. A sensitivity analysis revealed that excluding a single research study [31] significantly impacted the mean time of hospitalization. Amani et al. conducted a meta-analysis of three studies and found no statistically significant difference in hospitalization duration between the group who received lopinavir/ritonavir alone and the group that received the combination treatment [47]. Another prior study discovered that lopinavir/ritonavir as a single medication was associated with significantly shorter hospital stays than the comparison group [41].

In terms of safety, this study investigated the association between lopinavir/ritonavir as a single therapy or with interferon and adverse events or serious adverse events in COVID-19 patients compared with the control individuals. Lopinavir/ritonavir with or without interferon was associated with a significantly higher number of adverse events in COVID-19 patients, such as moderate to severe kidney injury, compared with the control individuals (p = 0.02). Common adverse events of lopinavir/ritonavir in patients with COVID-19 are gastrointestinal disturbances, in particular diarrhea, diabetes mellitus, dyslipidemia, hepatic disorders, and pancreatitis [47]. This investigation discovered no significant difference between the two groups in terms of major adverse events. The occurrence of adverse events was more likely with lopinavir/ritonavir alone in COVID-19 patients (OR = 1.74, 95% CI 1.08 to 2.80) compared with lopinavir/ritonavir with interferon (OR = 1.20, 95% CI 0.75 to 1.91), although this was not statistically significant (p = 0.27). The findings were similar for serious adverse events.

The fact that this study only included randomized clinical trials and recent studies was its main strength. It is also worth noting that out of the nine RCTs included in this study, only two investigated the efficacy and safety of lopinavir/ritonavir with interferon in managing COVID-19. Before drawing conclusions about the efficacy and safety of lopinavir/ritonavir plus interferon, more research is necessary.

5. Conclusions

This study compared lopinavir/ritonavir with or without interferon to placebo and conventional treatment in terms of mortality rates, clinical improvement, length of hospital stay, and the appearance of mild or severe side effects. In the current meta-analysis, patients with COVID-19 receiving lopinavir/ritonavir with or without interferon showed no improvement in mortality rates, clinical status, or length of hospital stay compared with groups receiving a placebo. In terms of safety, this study discovered that groups

receiving lopinavir/ritonavir with or without interferon had more adverse events and serious adverse events than groups receiving placebo. Large randomized clinical trials are needed to assess the efficacy and safety of lopinavir/ritonavir with interferon in the treatment of COVID-19. These studies work best when conducted in a double-blind fashion at multiple locations.

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