EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2022.2004118

Clinical efficacy and safety of interferon-β–containing regimens in the treatment of patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: The aim of this systematic review and meta-analysis of randomized controlled trials(RCTs) was to investigate the efficacy of interferon (IFN)-β–containing regimens in treating patients with COVID-19.

Methods: PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched from inception to 17 July 2021. RCTs comparing the clinical efficacy and safety of IFN-β–containing regimens (study group) to other antiviral treatment options or placebo (control group) in treating patients with COVID-19 were included.

Results: Eight RCTs were included. No significant difference in the 28-day all-cause mortality rate was observed between the study and control groups (OR, 0.74; 95% CI, 0.44–1.24; I^2 = 51%). The study groups had a lower rate of intensive care unit (ICU) admissions than the control groups (OR 0.58, 95% CI 0.36–0.95; I^2 = 0%). Furthermore, INF-β was not associated with an increased risk of any adverse event (AE) or serious AE when compared with the control group.

Conclusions: IFN-β does not appear to provide an increased survival benefit in hospitalized patients with COVID-19 but may help reduce the risk of ICU admission. Moreover, IFN-β is a safe agent for use in the treatment of COVID-19.

ARTICLE HISTORY
Received 6 August 2021
Accepted 28 October 2021

KEYWORDS
COVID-19; ICU; interferon-β; mortality; SARS-CoV-2

1. Introduction

To date, more than 190 million confirmed cases of coronavirus disease 2019 (COVID-19) have been reported [1]. Unfortunately, the COVID-19 pandemic is still not under control following the implementation of vaccination and infection control prevention programs; therefore, a surge in newly diagnosed cases continues to be reported worldwide [1]. Although infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can present as asymptomatic, a significant portion of patients with COVID-19 have severe symptoms, presenting with pneumonia that requires hospitalization, acute respiratory distress syndrome, or even death [2,3]. Therefore, the effective treatment of patients with COVID-19 to improve their clinical outcomes remains a crucial issue.

In addition to antiviral agents with limited beneficial outcomes [4], the clinical efficacy of several anti-inflammatory agents, such as corticosteroids and tocilizumab, has been demonstrated through reducing the mortality of patients with COVID-19 [5,6]. Moreover, type 1 interferons (IFNs), particularly IFN-β as an immune modulator, have been proposed as potential agents to mediate the dysregulated immune response during acute viral infections, including infection by SARS-CoV-2, thus alleviating prognosis of COVID-19 [7]. In particular, previous studies have demonstrated the *in vitro* activity of IFN against SARS-CoV and Middle East respiratory syndrome coronavirus [8–10]. Recently, several randomized control trials (RCTs) have been conducted to assess the clinical efficacy and safety of IFN-β alone or with other antiviral agents in the treatment of patients with COVID-19 [11–18]; however, inconsistent results were obtained from these studies. Therefore, we conducted this systematic review and meta-analysis to provide updated evidence regarding the efficacy of IFN-β–containing regimens in the treatment/management of patients with COVID-19.

2. Methods

2.1. Study search and selection

We searched the PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases for relevant articles from inception to 17 July 2021. The following search terms were used: 'COVID-19,' 'SARS-CoV-2,' 'interferon,' and 'interferon beta.' Only RCTs that compared the clinical efficacy and safety of IFN-β–containing regimens with other

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Supplemental data for this article can be accessed here.

comparators or placebo in the treatment of patients with COVID-19 were included. The reference lists of the relevant articles were manually searched for additional eligible articles. No language limitation was applied. Studies were included if they met the following criteria: (1) examined patients with COVID-19; (2) used IFN-β–containing regimens as the intervention; (3) used other treatment options, standard of care, or placebo as comparators; (4) designed as a RCT; and (5) reported clinical efficacy and risk of adverse events (AEs) as study outcomes. *In vitro* studies, studies without adequate data for outcome analysis, non-RCTs, post-hoc analysis studies, and poster or conference abstracts were excluded. Two investigators independently screened and reviewed each study. In case of any disagreement, a third investigator was consulted. For each included study, we extracted the following data: year of publication, study design, anti-COVID-19 treatment, clinical outcomes, and risk of AEs. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [19]. The protocol was registered at PROSPERO pre-specified (reference number: CRD4202169000).

2.2. Outcome measurements

The primary outcome was the 28-day all-cause mortality. The secondary outcomes included the use of mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO), the rate of survival of hospital discharge, intensive care unit (ICU) admission, time to clinical improvement, length of hospital stay, and risk of AEs.

2.3. Data analysis

The Cochrane risk-of-bias tool was used to assess the quality of the included RCTs and their associated risk-of-bias [20]. Statistical analyses were performed using Review Manager (version 5.3; Nordic Cochrane Center, Copenhagen, Denmark). The degree of heterogeneity was evaluated using Q statistics generated from the χ^2 test, and the I^2 measure was used to assess statistical heterogeneity. Heterogeneity was defined as significant when $p < 0.10$ or $I^2 > 50\%$. The fixed-effects model was used when the data were homogeneous, and the random-effects model was used when the data were heterogeneous. The pooled odds ratios (ORs) or mean differences (MDs) and 95% confidence intervals (CIs) were calculated for outcome analysis.

3. Results

3.1. Study selection

The search of the online databases yielded a total of 122 RCTs, of which 32 duplicate studies were excluded. In addition, 50 studies were considered irrelevant after screening the titles, abstracts, as well as failing to access the full texts of the publications. Furthermore, 32 studies were excluded after the full texts of 40 articles were screened. The causes included ongoing study (n = 21), study protocol (n = 8), no control without IFN (n = 2) and conference abstract (n = 1). Finally, eight RCTs [11,13–18,21] were included in this meta-analysis (Figure 1 and Appendix 1).

3.2. Study characteristics

The eight included RCTs comprised two phase 2 trials [16,18] and six phase 3 trials [11,12,14,15,17,21]. Four RCTs were multicenter studies [11,16,18,21], and only one was a multinational study [21] (Table 1). Five RCTs [11,14,16,18,21] investigated the efficacy of INF-β-1a, two [15,17] of INF-β-1b, and one [13] of both INF-β-1a and INF-β-1b. Subcutaneous injection was the most common route of administration for INF-β-1a and INF-β-1b; however, two studies [15,16] used the inhalation route. Overall, 4917 hospitalized patients with moderate-to-severe COVID-19 were enrolled in this study, of which 2490 received INF-β–containing treatment regimens as the study group and 2427 as the control group. Most of the included studies had a low risk-of-bias in each domain, except five RCTs had a high risk of performance bias (Figure 2).

3.3. Primary outcome

No significant difference in the 28-day all-cause mortality rate was observed between the study and control groups (OR, 0.74; 95% CI, 0.44–1.24; I^2 = 51%; Figure 3). The similarity in mortality between the study and control groups remained unchanged following the sensitivity test, in which each individual study was randomly excluded. In a subgroup analysis of six RCTs [11,12,14,16,18,21], no significant difference was observed in mortality rate between the INF-β-1a and control groups (OR 0.49, 95% CI 0.21–1.18, I^2 = 54%). In a subgroup analysis of three RCTs [12,15,17], no significant difference was observed in mortality rate between the INF-β-1b and control groups (OR 0.86, 95% CI 0.43–1.68, I^2 = 43%). A further subgroup analysis according to the route of administration did not find a significant difference in mortality rate between the study and control groups (subcutaneous: OR 0.75, 95% CI 0.42–1.35, I^2 = 62%; inhalation: OR 0.57, 95% CI 0.13–2.45, I^2 = 17%). In contrast, the subgroup analysis of three RCTs [13,14,17] focusing on patients with severe COVID-19 revealed that study group was associated with a lower mortality than control group OR (0.37, 95% CI 0.19–0.74, I^2 = 0%)

3.4. Secondary outcomes

The proportion of patients using MV or ECMO was similar between the study and control groups (OR 0.97, 95% CI 0.81–1.17, I^2 = 0%) in the pooled analysis of seven RCTs (Figure 4A) [11,12,14,16–18,21]. The rate of survival to hospital discharge was similar between the study and control groups (OR 1.20, 95% CI 0.80–1.57; I^2 = 38%) in the pooled analysis of five RCTs (Figure 4B) [11,14–17]. The similar portion of patients requiring MV or ECMO and rate of survival to hospital discharge between study and control group remained unchanged int the subgroup analysis of patients with severe COVID-19 [13,14,17]. The study groups had a lower rate of ICU admissions than the control groups (OR 0.58, 95% CI 0.36–0.95; I^2 = 0%) in the pooled analysis of five RCTs (Figure 4C) [12,14,15,17,18] and in the subgroup analysis of patients with

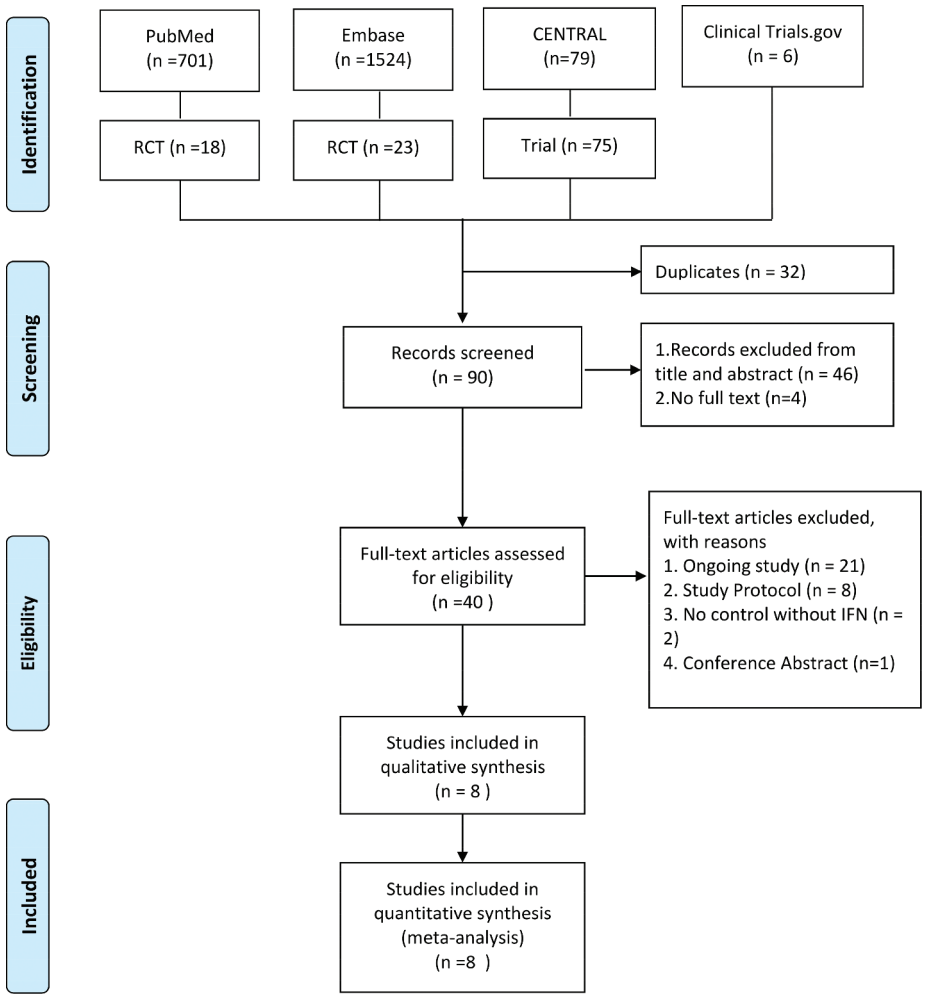

Figure 1. Algorithm of study selection. CENTRAL, Cochrane Central Register of Controlled Trials; RCT, randomized controlled trial.

severe COVID-19 (OR 0.51, 95% CI 0.28–0.91; I^2 = 0%). No significant difference between the study and control groups was observed in terms of time to clinical improvement (MD, −1.18, 95% CI, −2.83–0.46, I^2 = 85%) and length of hospital stay (MD, −1.74, 95% CI, −3.95–0.48, I^2 = 78%).

Regarding the risk of AEs, INF-β was not associated with an increased risk of any AE (OR, 1.18, 95% CI, 0.71–1.97, I^2 = 40%) or serious AEs (OR, 0.50, 95% CI, 0.16–1.53, I^2 = 83%, Figure 5) when compared with the control groups. INF-β shared a similar risk for specific AEs with comparator treatment options, viz. acute kidney injury (OR, 0.92, 95% CI, 0.54–1.57, I^2 = 0%), septic shock (OR, 1.62, 95% CI, 0.41–6.33, I^2 = 54%), nosocomial infection (OR, 0.77, 95% CI, 0.06–10.14, I^2 = 77%), thrombosis (OR, 0.99, 95% CI, 0.32–3.07, I^2 = 0%), and acute respiratory distress syndrome (OR, 0.55; 95% CI, 0.30–1.02, I^2 = 0%).

4. Discussion

In this meta-analysis, eight RCTs [11,12,14–18,21] were reviewed to compare the efficacy and safety of INF-β (INF-β-1a and INF-β-1b) to other anti-SARS-CoV-2 regimens or placebo in the treatment of hospitalized patients with COVID-19. Overall, adding INF-β to treatment regimens did not significantly improve the clinical outcomes of hospitalized patients with COVID-19, which was supported by the following evidence: first, the 28-day all-cause mortality rate of patients receiving INF-β–containing treatment regimens was similar to that of the control groups in overall populations, second, this finding remained unchanged following leave-one-out analyses. In a further subgroup analysis according to the different types of INF-β or different routes of administration, the findings regarding no mortality benefit from INF-β in patients with COVID-19 remained unchanged. The only one exception was the subgroup with severe COVID-19, in which INF-β–containing treatment regimen was associated with a lower mortality rate than control group. Finally, adding INF-β could not reduce the requirements of MV or ECMO for respiratory support, could not significantly increase the rate of survival to hospital discharge, and could not shorten the time to clinical improvement and length of hospital stay in patients with COVID-19. In summary, our findings did not support the use of INF-β in the treatment of patients with COVID-19.

In contrast, we found that administering INF-β could help decrease ICU admissions in hospitalized patients with COVID-19. This finding remained significant using both the fixed-effects and random-effects models and was based on the

Table 1. Characteristics of included studies.

				Treatment			No of patients	
Author, year	Study design	Study site	Study subjects	IFN group	Control group	Regimen of INF	IFN group	Control group
Davoudi-Monfared et al. [14]	Open-label, randomized clinical trial	Single center in Iran	Severe COVID-19	INF β-1a and HCQ plus lopinavir-ritonavir or atazanavir-ritonavir	HCQ plus lopinavir-ritonavir or atazanavir-ritonavir	Subcutaneous 44 μg thrice weekly for 14 days	42	39
Rahmani et al. [17]	Open-label, randomized clinical trial	Single center in Iran	Severe COVID-19	IFN β-1b and HCQ plus lopinavir-ritonavir or atazanavir-ritonavir	HCQ plus lopinavir-ritonavir or atazanavir-ritonavir	Subcutaneous 250 μg every other day for 14 days	33	33
Khamis et al. [15]	Open-label randomized controlled trial	Single center in Oman	Moderate-to-severe COVID-19	INF-β-1b and favipiravir	HCQ	Inhaled 8 MIU twice a day for 5 days	44	45
WHO Solidarity Trial Consortium et al. [21]	open-label, randomized trial	405 hospitals in 30 countries	Hospitalized COVID-19	INF-β-1a with SoC	SoC	Subcutaneous 44 μg on days 1, 3, and 6	2050	2050
Darazam et al. [13]	Three-armed, randomized, open-label, controlled trial	Single center in Iran	Severe COVID-19	INF-β-1a or INF-β-1b plus lopinavir-ritonavir and HCQ	lopinavir-ritonavir and HCQ	INF-β-1a, subcutaneous 44 μg on days 1, 3, 6 INF-β-1b, subcutaneous 8 MIU on days 1, 3, 6	INF-β-1a: 20; INF-β-1b: 20	20
Monk et al. [16]	Phase 2 randomized, double-blind, placebo-controlled trial	Multicenter in UK	Hospitalized COVID-19 patients	INF-β-1a with SoC	Placebo with SoC	Inhaled 6 MIU once daily for up to 14 days	50	51
Hung et al. [18]	Phase 2 open-label, randomized trial	Multicenter in China	Hospitalized COVID-19 patients	INF-β-1a, lopinavir-ritonavir, and ribavirin	Lopinavir-ritonavir	Subcutaneous 8 MIU for one to three doses	86	41
Ader et al. [11]	Phase 3 open-label, adaptive, randomized, superiority-controlled trial	Multicenter in France	Hospitalized COVID-19 patients	INF-β-1a plus lopinavir/ritonavir with SoC	SoC	Subcutaneous 44 μg on days 1, 3, and 6	145	148

SoC, standard of care; IFN, interferon; HCQ, hydroxychloroquine

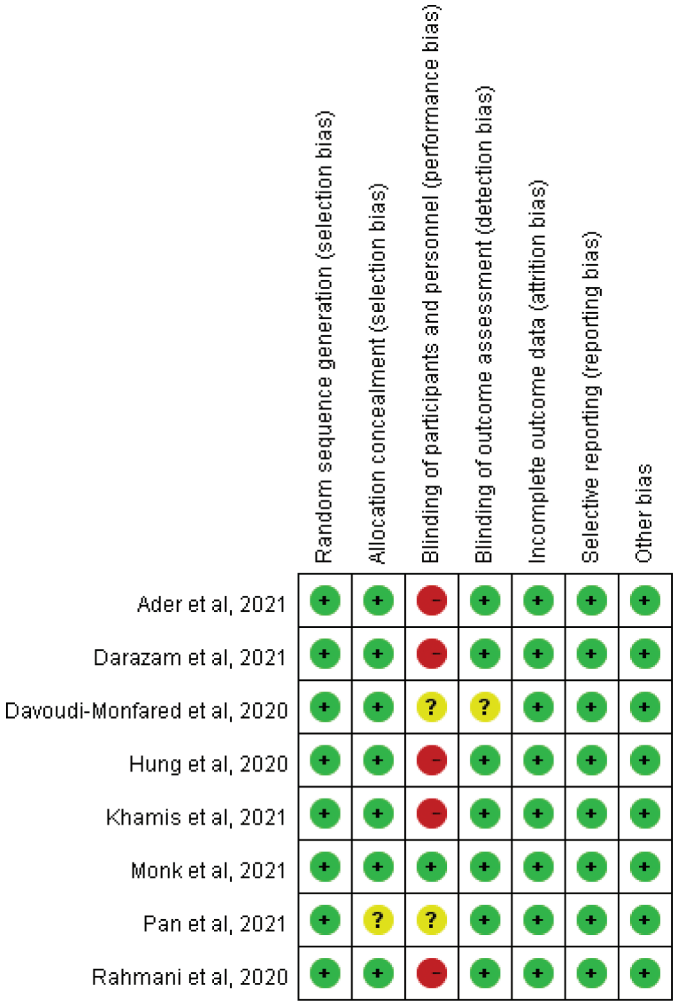

Figure 2. Summary of risks of bias in each domain.

analysis of homogeneous data (I^2 = 0%, p = 0.74). Furthermore, these findings are consistent with those of a previous multicenter, controlled, retrospective cohort study conducted in Spain, which showed that IFN β-1b recipients had lower ICU admission rates than the control group (7% [7/28] versus 19% [15/77]) [22]. However, the reduction of ICU admission did not reflect on survival benefit. This could be due to many factors that would affect the mortality, and ICU admission is just one of the risk factors. Thus, although we found that additional use of IFN-β can help reduce ICU admission, it cannot reduce mortality. Overall, these findings suggest that IFN-β may help reduce the rate of ICU admissions for patients with COVID-19 and further decrease the burden of critical care. This issue is important, especially currently when the rapidly increasing number of patients testing positive for COVID-19 may cause exhaustion of ICU capacity.

Finally, this meta-analysis assessed the safety issues associated with IFN-β. IFN-β had a similar risk to other AEs, including any AE, serious AEs, and other specific AEs, including acute kidney injury, septic shock, nosocomial infection, thrombosis, and acute respiratory distress syndrome. Therefore, our findings indicate that IFN-β is as safe as the other investigated comparators in the treatment of hospitalized patients with COVID-19.

This study had several limitations. First, most of the findings were based on the analysis of data associated with high heterogeneity (I^2 > 50%). The heterogeneity could be a result of the different regimens of INF-β and the comparators, as well as different disease severity in the included patients. Second, all included studies using INF-β-containing regiment as an experimental drug, and the combinations varied in each study, so the outcome of the study group could be due to both INF-β and other combined anti-viral agents. As a result, we cannot accurately assess the effect of only INF-β and also each combination regimen. Third, the number of included studies and the total number of patients in many RCTs were limited. Forth, among all included studies, WHO Solidarity Trial [21] was larger than all the other trials combined, and therefore the results of this trial should weigh heavily on any outcome of the present meta-analysis. However, we used a leave-one-out sensitivity test to assess the effect of individual studies and the results remained unchanged. Finally, we did not evaluate the effect of the timing of adding INF-β. In the meta-analysis of three studies, Nakhlband et al. [23] demonstrated that early administration of IFN-β in combination with antiviral drugs could help increase the overall discharge rate (RR = 3.05; 95% CI: 1.09–5.01). Consequently, further large-scale RCTs are warranted to clarify our findings.

In conclusion, while IFN-β did not provide an increased survival benefit in hospitalized patients with COVID-19, it may reduce the risk of ICU admissions. Furthermore, it was found to be a safe agent for use in the treatment of COVID-19. However, it is too early to recommend the role of IFN-β in the treatment of patients with COVID-19. Any updates about whether there are more trials to come, and the commentary around power and effect size detectable with the given dataset, would be helpful.

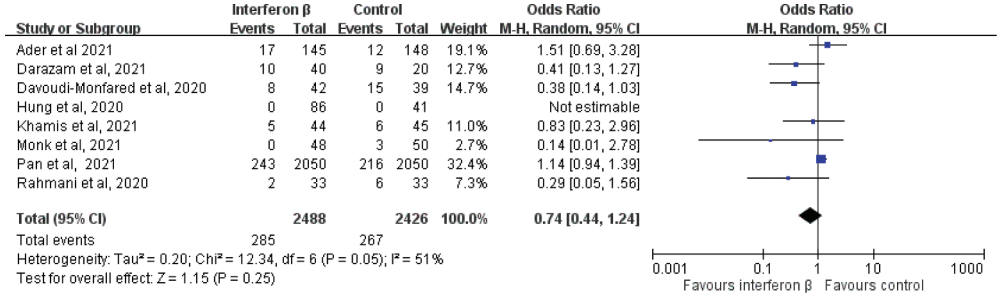

Figure 3. Forest plot of the comparison of mortality rate between study and control groups.

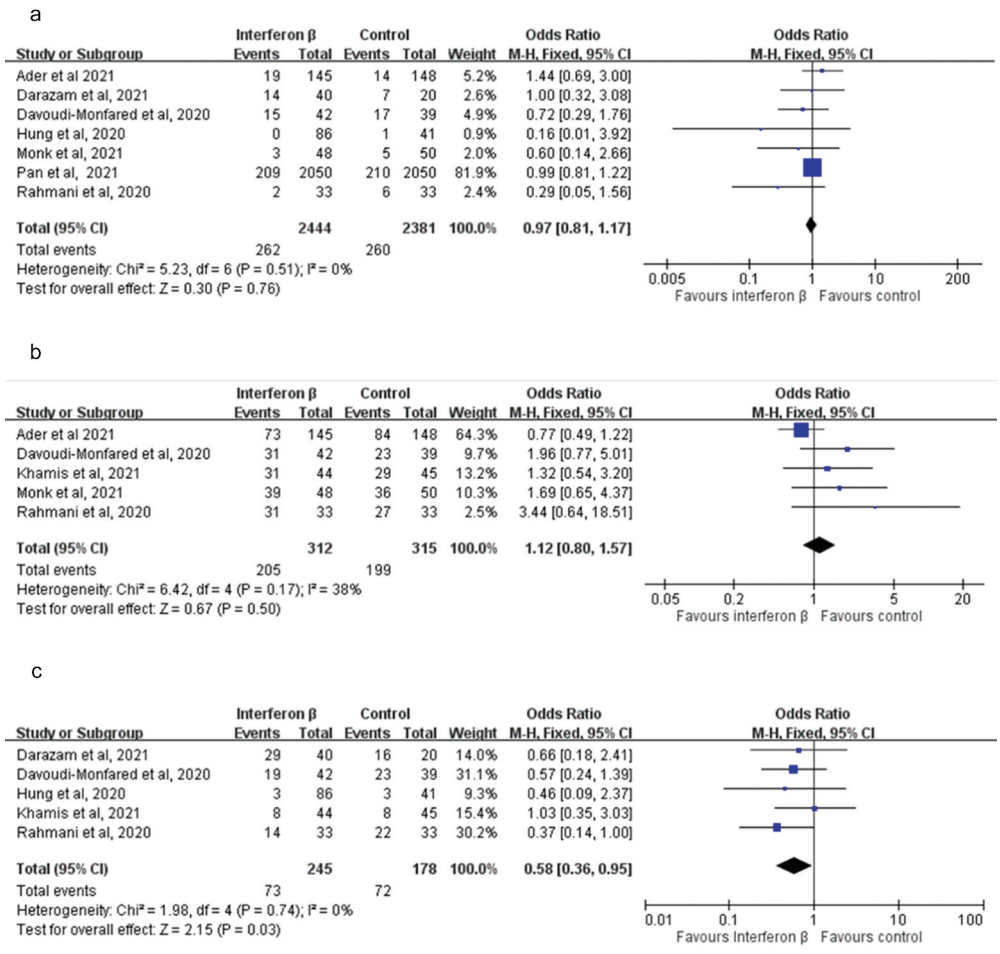

Figure 4. Forest plots of the comparison of (A) the use of mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO); (B) rate of survival to hospital discharge; (C) intensive care unit (ICU) admission rate between study and control groups.

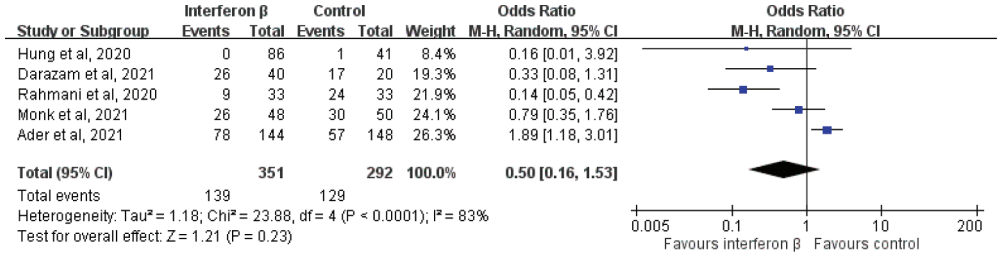

Figure 5. Forest plot of the comparison of the risk of serious adverse events between study and control groups.

Author contributions

Conception: WCC, CKH, CYC, SHH, and WTL
Study design: WCC, CKH, CYC and CCL
Analysis and interpretation: WCC, CKH, CYC and CCL
Drafted or written: CCL, SHH and WTL
Substantially revised or critically review: SHH and WTL

All authors have agreed on the journal to which the article will be submitted and reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. In addition, all authors agree to take responsibility and be accountable for the contents of the article and to share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

Funding

This paper was not funded.

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. WHO. [cited 2021 Jul 20]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Lai CC, Liu YH, Wang CY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. J Microbiol Immunol Infect. 2020;53(3):404–412.
3. Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924.
4. Lai CC, Chao CM, Hsueh PR., et al. Clinical efficacy of antiviral agents against coronavirus disease 2019: a systematic review of randomized controlled trials. J Microbiol Immunol Infect. 2021;(5). DOI: 10.1016/j.jmii.2021.05.011.
5. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, Godolphin PJ, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA. 2021 Jul 6:e2111330. DOI:10.1001/jama.2021.11330.

•• **The updated meta-analysis of IL-6 antagonist for treating patients with COVID–19**

6. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA. 2020;324(13):1330–1341.

•• **The updated meta-analysis of corticosteroid for treating patients with COVID-19**

7. Sallard E, Lescure FX, Yazdanpanah Y, et al. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020;178:104791.
8. Spiegel M, Pichlmair A, Mühlberger E, et al. The antiviral effect of interferon-beta against SARS-coronavirus is not mediated by MxA protein. J Clin Virol. 2004;30(3):211–213.
9. Sainz B Jr., Mossel EC, Peters CJ, et al. Interferon-beta and interferon-gamma synergistically inhibit the replication of severe acute respiratory syndrome-associated coronavirus (SARS-CoV). Virology. 2004;329(1):11–17.
10. Hensley LE, Fritz LE, Jahrling PB, et al. Interferon-beta 1a and SARS coronavirus replication. Emerg Infect Dis. 2004;10(2):317–319.
11. Ader F, Peiffer-Smadja N, Poissy J, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. Clin Microbiol Infect. 2021. DOI:10.1016/j.cmi.2021.05.020.
12. Alavi Darazam I, Hatami F, Mahdi Rabiei M, et al. An investigation into the beneficial effects of high-dose interferon beta 1-a, compared to low-dose interferon beta 1-a in severe COVID-19: the COVIFERON II randomized controlled trial. Int Immunopharmacol. 2021;99:107916.
13. Alavi Darazam I, Shokouhi S, Pourhoseingholi MA, et al. Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial. Sci Rep. 2021;11(1):8059. Sci. Rep.:8059.
14. Davoudi-Monfared E, Rahmani H, and Khalili H, et al. A randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe COVID-19. Antimicrob Agents Chemother. 2020;64 (9) :e01061–20.
15. Khamis F, Al Naabi H, Al Lawati A, et al. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. Int J Infect Dis. 2021;102:538–543.
16. Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2021;9(2):196–206.
17. Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. Int Immunopharmacol. 2020;88:106903.
18. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1695–1704.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol. 2021;134:103–112.
20. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(oct18 2):d5928.
21. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for covid-19 – interim WHO solidarity trial results. N Engl J Med. 2021;384:497–511.
22. Tortajada C, Añón S, Ortiz MM, et al. Interferon β-1b for patients with moderate to severe COVID-19 in the inflammatory phase of the disease. J Med Virol. 2021;93(7):4102–4107.
23. Nakhlband A, Fakhari A, Azizi H., et al. Interferon-beta offers promising avenues to COVID-19 treatment: a systematic review and meta-analysis of clinical trial studies. Naunyn Schmiedebergs Arch Pharmacol. 2021;394(5):829–838.