Review Article

Systemic Review and Meta-Analysis to Evaluate Therapeutic Effectiveness of Interferon Beta-1b in Hospitalized COVID-19 Patients

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Abstract

The COVID-19 pandemic has caused havoc in the health sector. Inflammatory cytokines play an important role in the disease condition. Existing evidence has provided certain insights into the repurposing of the drugs. This meta-analysis and systematic review aimed to explore the efficacy of the administration of interferon beta-1b (IFN β-1b) and standard care versus only standard care as the therapeutic agent for managing COVID-19 patients who are severely ill. The search was conducted in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus, and Google Scholar, which were published during the period January 1, 2020, to February 16, 2023. All the included three studies were independently assessed for eligibility. The modified data extraction form of Cochrane were used. The quality of the three included studies was assessed using the Cochrane risk of bias tool. GradePro software was used to summarize the quality grading of the primary outcome measures. The time taken for clinical improvement was (MD: -3.28 days; 95% CI: -5.65, -0.91; *P* value = 0.007) when treated with IFN β-1b. The duration of hospital stays (MD: -2.43 days; 95% CI: -4.45, -0.30; *P* value = 0.03), and need for intensive care unit (ICU) admission (RR: 0.71; 95% CI: 0.52, 0.97; *P* value = 0.03) was statistically significant. Interferon beta-1b is proven to reduce the duration of hospital stay, and the improved clinical status may become a cornerstone of COVID-19 treatment.

Keywords: Clinical improvement, COVID-19, Hospitalization, Hydroxychloroquine, ICU admission, Interferon, Interferon beta-1b, Lopinavir/ritonavir, Mortality, Ribavirin, Safety

Introduction

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has wreaked havoc on humanity. The World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on March 11, 2020.[1,2] According to current epidemiological data, the median incubation period is 6 days, and transmission can happen even before symptoms appear. Furthermore, asymptomatic cases, which account for a significant portion of infections, are likely to contribute to virus circulation.[3]

All the positive COVID-19 cases are treated with supportive treatment, symptomatic treatment, oxygen therapy, respiratory and circulation support, and therapeutics. Warm baths and antipyretic medications such as ibuprofen and acetaminophen were used to treat severe cases of high fever as supportive treatment. Patients who are having trouble breathing should be given non-invasive mechanical ventilation (NIV).[4] Most management strategies seek to enhance viral clearance and inhibit the cytokine storm by reducing the need for long hospital stays, mechanical ventilation, and COVID-19-related mortality. Several options, ranging from prophylactic vaccines to targeted antiviral drugs, are considered for this purpose. Anti-inflammatory drugs such as hydroxychloroquine (HCQ), dexamethasone, tocilizumab, and chloroquine (CQ) have been recommended to minimize the release/production of pro-inflammatory cytokines to reduce the cytokine storm

Access this article online

Quick Response Code:

Website: www.ijcm.org.in

DOI: 10.4103/ijcm.ijcm_577_22

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How to cite this article: Nayudu GS, Benny M, Thomas G, Adil Khan M, Basutkar RS. Systemic review and meta-analysis to evaluate therapeutic effectiveness of interferon beta-1b in hospitalized COVID-19 patients. Indian J Community Med 2023;48:390-400.

Received: 04-07-22, **Accepted:** 01-03-23, **Published:** 30-05-23

caused by SARS-CoV-2.[5] Remdesivir has *in vitro* activity against SARS-CoV-2. Other antivirals such as arbidol, oseltamivir, favipiravir, interferon beta-1a, darunavir, and cobicistat are under trials. Controversial studies are there for glucocorticoids because there was no improvement in the rate of radiographic recovery; hence, they are not recommended in mild cases. Early, low-dose, and short-term (1–2 mg/kg/d for 5–7 days) corticosteroids were linked to a faster improvement of clinical manifestations and absorption of focal lung lesions in severe COVID-19 cases[6]. Severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) viral loads peak 7–10 days after symptom onset; however, COVID-19 viral loads peak at the time of presentation, similarly to influenza.[7]

Inflammatory cytokines are the first line of defense against viruses. Interferons (IFNs) are divided into three families, each of which has several subfamilies. IFN-II is the only isoform with a single isoform 33: IFN-I [α, β, ω, ε, κ]; IFN-II (γ); IFNs-III and IFN λ (λ1, λ2, λ3, λ4). IFNs are naturally occurring anti-inflammatory proteins that bind to receptors on the surface of different cells and activate the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, which results in transcription of IFN-stimulated genes (ISGs) like the pro-inflammatory chemokine C-X-C Motif Chemokine Ligand 10 (CXCL10) and antiviral enzyme Ribonuclease L (RNase L).[8] Type I and III IFNs are genetically distinct, have different receptors, elicit similar pathogen detection sensors, and activate antiviral, antiproliferative, and immunomodulatory gene expression programs. IFN-l helps to reduce harmful inflammatory responses and limits viral spread from the upper respiratory tract to the lungs by contrasting viral replication in epithelial cells at the entry point. Additionally, by stimulating adaptive immunity, it protects the mucous barrier. Finally, it protects the barrier's integrity by reducing inflammation and its harmful effects caused by neutrophil activation. Type I IFNs (IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω) bind to the transcription factor type I IFN receptor (IFNAR) in a paracrine and autocrine manner in humans. Type III IFNs bind to the type III IFN receptor, which is expressed preferentially on epithelial and certain myeloid cells. Type I and III IFNs both cause ISG expression to be induced and depleted, but type I IFN signaling causes ISG expression to be induced and depleted more quickly. IFN-α and IFN-β, primarily recombinant and pegylated, have been explored to treat various disorders, including multiple sclerosis and viral hepatitis.[9,10] In contrast to antiviral activity, IFN-β is much more effective than IFN α-2 at activating the antiproliferative program, a finding that was also confirmed using the IFN α-2 variant.

As a result, a link is discovered between the administration of IFN β-1a and the improvement in the clinical course of COVID-19 disease. This finding was significant because it suggests that IFN could be a viable therapeutic option in severe COVID-19 cases. Patients admitted to hospitals with a high viral load suggest that a combination of antiviral drugs is more effective than single-drug treatments.[11] In all clinical samples, aerosol inhalation of IFN-k plus trefoil factor 2 (TFF2) in combination with standard care is proven safe and superior to standard care alone in reducing the time to viral ribonucleic acid (RNA) negative conversion.[12,13] Thus, an increasing number of researchers are focusing on the IFN treatment in COVID-19. Interferon beta-1b, ribavirin, and lopinavir/ritonavir were safer and more effective in reducing virus shedding, lessening symptoms, and allowing patients with mild to moderate COVID-19 to be discharged than lopinavir/ritonavir alone.[14,15] However, there is limited evidence to know about the impact of the administration of IFN β-1b and standard care on the prognosis of COVID-19 in severely ill patients. This meta-analysis and systematic review currently aimed to explore the efficacy of the administration of IFN β-1b and standard care role versus only standard care as the therapeutic agent for managing COVID-19 patients who are severely ill.

Methods

Types of studies

Randomized controlled trials (RCTs), open label.

Eligibility criteria

Inclusion criteria:

- RCTs of patients aged ≥18 years of both genders.
- SARS-CoV-2 patients confirmed the positive result of nasopharyngeal swabs using Real-Time Polymerase Chain Reaction (RT-PCR) with or without co-morbidities.

Exclusion criteria:

- We excluded articles with a single arm and self-comparison studies and papers with mild and moderate infection of COVID-19 subjects.
- Papers comparing the other types of interferon along with standard care versus standard care alone.

Types of interventions

- Intervention arm: IFN β-1b along with standard care that includes antiviral (lopinavir/ritonavir, ribavirin) therapy, corticosteroids, HCQ, and antibiotics.
- Control arm: The standard care of antiviral therapy (lopinavir/ritonavir, ribavirin), corticosteroids, HCQ, and antibiotics.

Types of outcome measures

Primary outcomes

Time for clinical improvement from admission to discharge with IFN β-1b:

1. Mortality at the end of the study
2. Need for ICU admission
3. Duration of hospitalization
4. Hospital admission requiring the invasive and non-invasive mechanical ventilation.

Secondary outcomes

1. Safety outcome of the study:

Electronic search

The search was performed for relevant studies which were

published from January 1, 2020, to February 16, 2023, on the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus, and Google Scholar. We searched the Clinical Trials Registry of India for ongoing studies. Manual searching was also conducted. The mesh terms "COVID-19, SARS-CoV-2, coronavirus, beta interferon, and interferon beta" were used. The search strategy is mentioned in Appendix 1. The retrieved article was imported into Zotero and converted into "ris" format for importing pooled studies into Rayyan.

Data collection and analysis

Selection of population in the included studies of this systematic review

Inclusion criteria:

- Patients ≥18 years of age from both genders.
- Patients with or without co-morbidities like diabetes mellitus, hypertension, coronary artery disease, and malignancy were included.
- Patient with the confirmed positive result of nasopharyngeal swabs using RT-PCR for COVID-19.
- Patients on the treatment of IFN β-1b and standard therapy, which includes antiviral, HCQ, and supportive therapy.

Exclusion criteria:

- Patients with known neuropsychiatric disorders, thyroid disorders, and cardiovascular diseases.
- Patient on other types of different IFN therapy like IFN β-1a, IFN α-2b, etc.
- Consumption of potentially interfering medications with lopinavir/ritonavir + HCQ, IFN β-1b, or having a history of alcoholism, or any illicit drug addiction within the past five years.
- Pregnant patients and lactating women.

Data extraction and management

All records were assessed by the reviewers (GSS, BMB, GT, and MAK) to confirm eligibility in Rayyan. The modified data extraction from Cochrane CENTRAL was used. The following details were extracted: trial ID, general information, methods, participants, interventions, and outcomes. For each intervention and comparison group, a number of participants randomized into each group, description and duration of the treatment, and timing and medium of delivery were abstracted. Similarly, for each outcome, data like relevancy of outcome, the time points, and unit of measurement were reported. Mean and standard deviations were extracted for continuous outcome variables, whereas in some studies, the outcome measures were mentioned in the median and interquartile range from which the mean and standard deviation were derived using Hozo's method.[16] The retrieved data were reviewed by the RSB.

Assessment of risk bias and summary findings of the included studies

The reviewers (GSS, RBS, BMB, GT, and MAK) separately examined the following domains using the risk of bias tool: Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases are all involved in determining whether studies have a registration number. With correct judgment and explanation, the above-mentioned biases were labeled as "low," "high," or "unclear" in a table. The data were used to create a graph and figure depicting the risk of bias. Any differences were sorted out by discussing with reviewer RSB. The overall quality grading of the outcomes, such as the size of the effect of the treatments employed in the studies and the accessible important information on the outcomes, was also examined by extracting the appropriate data into the summary of results table using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) technique.

Registration

The protocol of this systematic review and meta-analysis was registered prospectively with PROSPERO [Registration number: CRD42021284428].

Statistical analysis

All the analysis was performed with the Review Manager version 5.4 (Cochrane Collaboration, Copenhagen, Denmark), which was used to produce forest plots with pooled estimates by importing the appropriate data. As the outcome measures were continuous, the overall effect size was calculated using mean and standard deviation values. The pooled estimates were calculated using the inverse variance approach, and both random and fixed effect models were utilized. Each outcome›s estimated mean difference (MD) and 95% confidence interval (CI) were graphically and statistically represented, along with the weight assigned by each study and the risk ratio was calculated for a dichotomous variable to know the ratio of the probability of the event to occur in the intervention group to that of the control group. Cochrane›s Q (*P* values) and Higgins I^2 statistics, as well as ocular examination, were used to evaluate heterogeneity. The intertrial variability was represented in percentage with a *P* value. We used a funnel plot to assess the publication bias.

Results

Search results

Our search from various databases yielded a total of 66 studies, out of which 36 were duplicates. This resulted in getting 30 records, of these 26 studies were excluded due to reasons: The drug used as an intervention was different, and the population included was different such as patients with MERS and articles published in foreign languages. A full-text review was performed for four articles, out of which one report was removed as the route of administration of the drug was different. A set of three studies were included in the qualitative analyses. The complete search is illustrated in Figure 1.

Characteristics of studies

Characteristics of the included studies are provided in Table 1. The included studies were all open-label

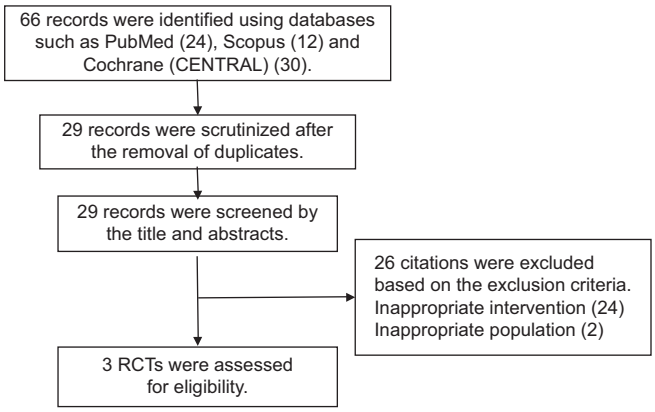

Figure 1: Flow diagram of the included studies in the review

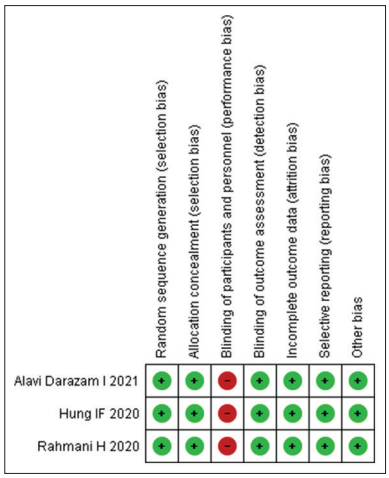

Figure 2: Risk of bias assessment of the included study

randomized controlled trials with an intervention group receiving the IFN β-1b plus standard care and the control group receiving only standard care. The IFN β-1b was given subcutaneously in all three studies. The drugs included in the standard care were mainly antiviral, that is, lopinavir and ritonavir. One of the three studies has not administered HCQ to the subjects. The included participants are adults, who had a positive RT-PCR result at the time of admission, and all the patients were having severe COVID-19 and were hospitalized. The primary outcome measure for the RCTs was to monitor the time for clinical improvement. This was measured using scales such as NEW2 and WHO 7 points scale with different parameters to measure improvement status with the therapy.

The participants included in the included RCTs had co-morbidities, mainly hypertension, type-2 diabetes mellitus, and ischemic heart disease. The majority of the selected studies have finished their trial for a shorter duration, and the long-term effects of the drug are not known.

Risk of bias assessment

The risk for random sequence generation was low in all three studies. The risk for blinding was found to be high, as the included studies were an open label. Selective reporting of primary outcomes measures was found to be low in three studies. The trial registration number was confirmed for two of the included trials, and it remains unclear for one study. The complete risk assessment of all articles is depicted as a graph [Figure 2 and Table 2].

Clinical outcome measures

Time of clinical improvement

Analysis was performed for all three studies (n = 167) with similar interventional drugs, that is, IFN β-1b along with standard care which includes the antivirals like lopinavir, ritonavir, ribavirin, and the symptomatic treatment to that of only standard care provided to the control group. The COVID-19 patient who was severely ill and treated with IFN β-1b showed rapid clinical response, that is, negative RT-PCR or improvement of any two parameters in the seven-point scale or six-point scale when compared to the only standard care group (MD: -3.28 days; 95% CI: -5.65, -0.91; *P* value = 0.007). The intertrial variability among the included studies was found to be significantly high ($\chi 2 = 62.56$; $I^2 = 97\%$; p=<0.001) [Figure 3].

Duration of hospital stay

The analysis was conducted to know the duration of hospital stays, that is, the number of days the COVID-19-infected patients were admitted to the hospital. IFN β-1b significantly reduced the duration of the hospital stay when compared to standard care (MD: -2.43 days; 95% CI: -4.45, -0.30; *P* value = 0.03). On accounting for the degree of intertrial variance, it was found to be high with a statistically significant *P* value < 0.001 ($\chi 2 = 83.62$; $I^2 = 98\%$) [Figure 4].

ICU admissions

Two included studies have measured the number of patients admitted to ICU, who had experienced severe COVID-19 infection. The results of the analysis stated that the number of admissions to ICU was statistically less when treated with IFN β-1b (RR: 0.71; 95% CI: 0.52, 0.97; *P* value = 0.03). Low heterogeneity was observed among the trials, but the results are statistically insignificant *P* value of 0.41 ($\chi 2 = 0.67$; $I^2 = 0\%$) [Figure 5].

Hospital admission with invasive mechanical ventilation

The studies have monitored the number of patients needing mechanical ventilation during the hospital stay as most patients included in studies have oxygen saturation (SpO2) <95%. The analysis of the two studies which were included depicts that there is no statistically significant difference between both the groups. The risk for invasive mechanical ventilation was not reduced when treated with IFN β-1b along with standard care (RR: 0.82; 95% CI: 0.39, 1.74; *P* value = 0.60). The intertrial variability was found to be significantly low ($\chi 2 = 0.57$; $I^2 = 0\%$; $P = 0.45$) for the included studies [Figure 6].

Hospital admission with Non-invasive mechanical ventilation

As mentioned above, the studies have also measured the need for NIV between the groups. The analysis from the included

Table 1: Characteristics table of included studies

Author, Year	Study country	Study sample	Study design	Enrolled period	Population	Age	Gender	Interventions	Co-morbidities	Outcomes
Alavi Darazam I *et al*. 2021[7]	Iran	60	Investigator initiated, three-armed, parallel group, individually randomized, open labeled, randomized controlled trial.	-	Adult hospitalized severe COVID-19	Median and IQR 69 (55–82)	Male: 51.7% and female: 48.3%	Intervention group: IFNβ1b (Ziferon) (subcutaneous injections of 0.25 mg (8,000,000 IU) on days 1, 3, 6) + Hydroxychloroquine + Lopinavir/ Ritonavir (Kaletra) Control group: Hydroxychloroquine (single dose of 400 mg on day 1, orally + Lopinavir/ Ritonavir (Kaletra) (400 mg/100 mg twice a day for 10 days)	Diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, and malignancy	Time for clinical improvement, duration of hospital stays, ICU admission, mechanical ventilation, and mortality.
Rahmani H *et al*. 2020[15]	Iran	80	Open-label RCT	April 20, 2020 to May 20, 2020	Adult hospitalized severe COVID -19	Median and IQR 60 (50–71)	Male: 59.09% female: 40.91%	Intervention group: IFN β-1b 250 mcg subcutaneously every other day for two consecutive weeks, lopinavir/ ritonavir (400/100 mg BD) or atazanavir/ ritonavir (300/100 mg daily) plus hydroxychloroquine (400 mg BD in first day and then 200 mg BD) for 7–10 days. Control group: Lopinavir/ ritonavir (400/100 mg BD) or atazanavir/ ritonavir (300/100 mg daily) plus hydroxychloroquine (400 mg BD in first day and then 200 mg BD) for 7–10 days.	Hypertension, diabetes mellitus, ischemic heart disease, asthma, COPD, malignancy, and transplantation	Time for clinical improvement, duration of hospital stays, ICU admission, mechanical ventilation. and mortality.
Hung IFN *et al*. 2020[14]	China	127	Phase-2 multi-center open-label RCT	February 10, 2020 to March 20, 2020	Hospitalized COVID-19 patients	Median and IQR 52 (32–62)	Male: 46% and female: 40%	Intervention group: lopinavir 400 mg and ritonavir 100 mg, ribavirin 400 mg every 12 h, and subcutaneous injection of one to three doses of interferon beta-1b 1 mL (8 million international units [IU]) Control group: lopinavir/ ritonavir (lopinavir 400 mg and ritonavir 100 mg) every 12 h for 14 days.	Diabetes, hypertension, coronary artery disease, cardiovascular diseases hyperlipidemia, thyroid diseases, obstructive sleep apnea, and malignancy	Time for clinical improvement, duration of hospital stay, and mortality.

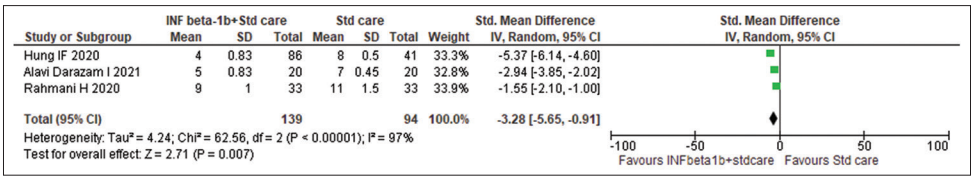

Figure 3: Forest plot showing the effect of interferon beta-1b on the time of clinical improvement versus standard care in COVID-19-infected patient

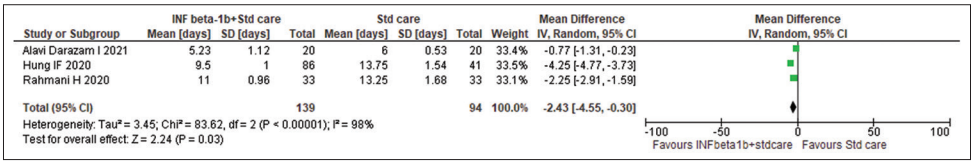

Figure 4: Forest plot showing the effect of interferon beta-1b on the duration of hospital stay versus standard care in COVID-19-infected patient

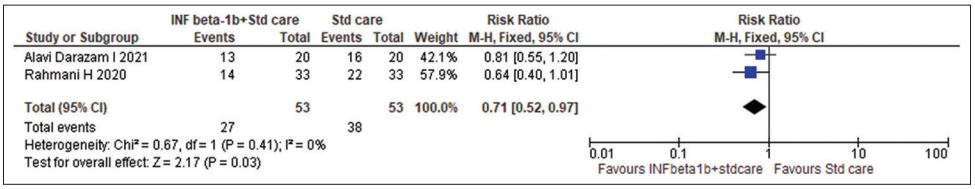

Figure 5: Forest plot showing the effect of interferon beta-1b on the need of ICU admission versus standard care in COVID-19-infected patients

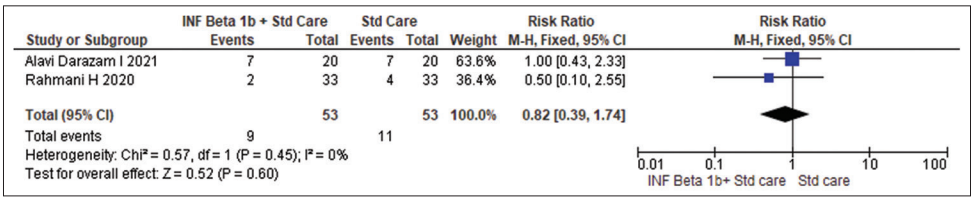

Figure 6: Forest plot showing the effect of interferon beta-1b on hospital admission with invasive mechanical ventilation versus standard in COVID-19-infected patients

studies revealed that there was no statistically significant difference between the groups (RR: 1.27; 95% CI: 0.51, 3.20; *P* value = 0.61). Low heterogeneity was observed among the trials but with a statistically insignificant *P* value of 0.57 ($\chi 2 = 0.33$; $I^2 = 0\%$) [Figure 7].

Mortality

All the included studies have noted several mortalities that occurred in both groups during the study period. The analysis results stated that there is a significant difference between the groups (RR: 0.41; 95% CI: 0.15, 1.14; *P* value = 0.09). Low heterogeneity was observed between the trials, and the results were statistically insignificant ($\chi 2 = 0.30$; $I^2 = 0\%$ *P* value = 0.59) [Figure 8].

Safety outcome

The safety outcomes were analyzed in this meta-analysis to assess if the common adverse drug reactions (ADRs) reported in the included studies are significantly different between both the groups. The ADRs reported in the studies are nausea and vomiting (RR: 1.03; 95% CI: 0.65, 1.62; *P* value = 0.90), diarrhea (RR: 0.95; 95% CI: 0.63, 1.44; *P* value = 0.81), injection site reaction (RR: 1.50; 95% CI: 0.26, 8.75; *P* value = 0.65), flu-like syndrome (RR: 1.13; 95% CI: 0.72, 1.80; *P* value = 0.59), increased aminotransferase (RR: 0.73; 95% CI: 0.49, 1.08; *P* value = 0.64), hyperalbuminemia (RR: 0.71; 95% CI: 0.20, 2.53; *P* value = 0.11), acute respiratory distress syndrome (RR: 0.63; 95% CI: 0.33, 1.19; *P* value = 0.15), acute kidney injury (RR: 0.70; 95% CI: 0.29, 1.68; *P* value = 0.42), shock (RR: 0.40; 95% CI: 0.08, 1.98; *P* value = 0.26), and increased creatinine (RR: 0.70; 95% CI: 0.29, 1.69; *P* value = 0.43). Our results showed that there was no statistically significant difference found with the severity of ADRs experienced between both the groups. The intertrial variability was found to be insignificantly low for most of the parameters except for flu-like syndrome [Figure S1].

Assessment of Reporting bias

We investigated the publication bias by using the funnel plot for all the primary outcome measures for included studies in the analysis. We found that the funnel plot was symmetrical for all the primary outcome measures [Figures S2-S7].

The outcome of GRADE approach assessment

Quality grading for the clinical outcomes was performed using the GRADE approach which is depicted in Table 3.

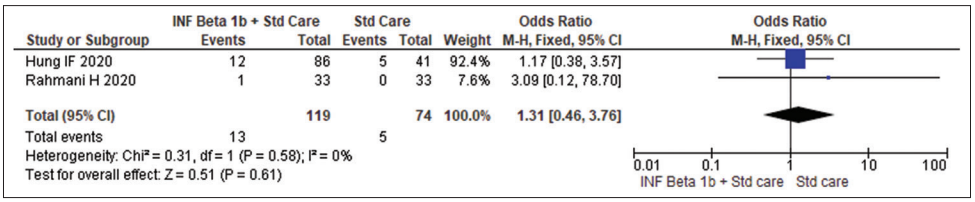

Figure 7: Forest plot showing the effect of interferon beta-1b on hospital admission with non-invasive mechanical ventilation versus standard care in COVID-19-infected patients

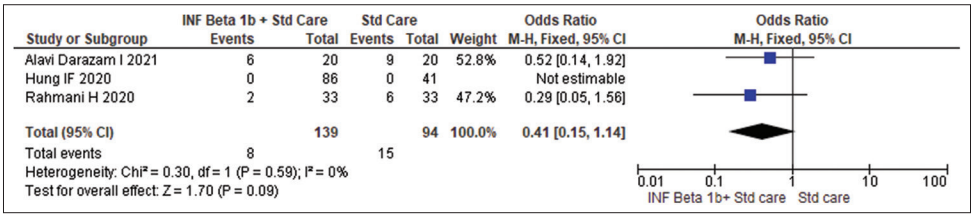

Figure 8: Forest plot showing the effect of interferon beta-1b on mortality rate versus standard care in COVID-19-infected patients

The certainty of the extracted evidence was categorized into very low to high grades for six outcomes: time of clinical improvement, duration of hospital stay, mortality, hospital admission with invasive mechanical ventilation, hospital admission with NIV, and number of ICU admission. It was found that for all the six outcomes, the certainty of the evidence was found to be moderate. Thus, further, there is a need to have a substantial number of RCTs to be conducted to achieve the certainty of evidence to be strong.

Discussion

Since December 2019, the world has been shrouded by the COVID-19 newborn idiopathic coronavirus and an increasing number of infected patients. Since then, antiviral and immunomodulatory drugs have been tested in clinical trials to see if they can prevent the coronavirus from spreading. To date, no certified antiviral drugs with proven efficacy for COVID-19 treatment have been identified. Following that, it appears critical to collect and summarize a variety of evidence to achieve an effective COVID-19 treatment.[7]

Type I IFNs are antiviral proteins that aim and prevent the replication and progression of a variety of viral pathogens while also promoting an immune response to clear virus infection. Hepatitis B and C, autoimmune disorders, SARS and MERS, and certain cancers are all treated with type I IFNs. This prompted the start of COVID-19 treatment with IFN. According to the National Health Commission of the People's Republic of China, the drug of choice for COVID-19 treatment is a combination of IFN and an antiviral.[14] A recent study carried out in Iran proposed the need for IFN therapy in severe COVID-19. IFNs cause the expression of multiple genes in the host cells to shift into an antiviral state, preventing virus propagation and secondary replication. Although there are three major forms of IFNs, type I, II, and III, type I IFN plays a major role in the antiviral response and affects the adaptive immune responses. Given the striking similarities between COVID-19 and the SARS and MERS in terms of changes in total neutrophil and lymphocyte counts in patients, it is widely assumed that SARS-CoV-2 may also inhibit type I IFNs in the early stages of COVID-19 disease.[7] Similarly, we discovered a significant relationship between the administration of IFN β-1a and the amelioration of the clinical course of COVID-19 disease. This finding was particularly significant as it suggests that IFN could be a powerful therapeutic option in severe COVID-19 cases. Because the development of a newer antiviral takes years before it is approved for clinical use, specific high active antivirals are required for any novel emerging infectious disease. As a result, in the event of a pandemic, the most feasible approach is to test existing broad-spectrum antiviral drugs that have previously been used to treat other viral infections.[14] Antiviral agents should be started as soon as possible after the onset of symptoms to control viral replication and prevent tissue viral invasion. Antiviral efficacy decreased significantly after the cytokine release phase was established in COVID-19.[15]

As of our knowledge, no meta-analysis states that the standard treatment when combined with IFNs increases the treatment efficacy and reduces hospital stay. Thus, we think it is a necessity to carry out this meta-analysis. In the current study, we found that IFN with antivirals (lopinavir/ritonavir, ribavirin) and HCQ effectively suppresses SARS-CoV-2 by reducing hospitalization time, viral-load clearance, and time for clinical improvement when compared to the standard care (lopinavir/ritonavir, ribavirin, and HCQ).

The result of our meta-analysis depicts that the patients administered with IFN along with standard care had a reduced need for ICU admission compared to the standard care group. The IFN β-1b could not prevent invasive mechanical ventilation as there is no significant difference between the groups. The number of patients that needed NIV during the hospital stay was similar in both groups. Although two of the three included studies have reported mortality in both groups,

Table 2: Risk of Bias Table

Alavi darazam I *et al.* (2020)[7]		
Methods	Investigator initiated, three-armed, parallel group, individually randomized, open labeled, randomized controlled trial	
Participants	Male, non-lactating, and non-pregnant female patients with at least 18 years of age who had confirmed COVID-19, defined as a positive test of Reverse Transcriptase Polymerase-Chain Reaction (RT-PCR).	
Intervention	Intervention group: IFNβ1b (Ziferon) (subcutaneous injections of 0.25 mg (8,000,000 IU) on days 1, 3, 6) + Hydroxychloroquine+Lopinavir/Ritonavir (Kaletra). Control group: Hydroxychloroquine (single dose of 400 mg on day 1, orally + Lopinavir/Ritonavir (Kaletra) (400 mg/100 mg twice a day for 10 days).	
Outcome	TTCI, defined as the time from enrollment to discharge from the hospital or a decline of two steps on the seven-step ordinal scale. Secondary outcomes included mortality from the date of randomization until day 21. Safety outcome measures.	
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Randomization sequence generation was generated using package "randomized R" in R software version 3.6.1
Allocation concealment (selection bias)	Low risk	Unstratified randomization was performed in a 1:1:1 ratio utilizing a block balance randomization method. The permuted block [three or six patients per block] and placed in individual sealed and opaque envelopes for allocation concealment by an outside statistician.
Blinding of participants and personnel (performance bias)	High risk	Open label: The patient and the investigator are aware of the intervention given.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor was blinded to study arms
Incomplete outcome data (attrition bias)	Low risk	All the participants who have undergone randomization their data were included for analysis
Selective reporting (reporting bias)	Low risk	All outcomes' measures were analyzed and reported
Other biases	Low risk	No
Hung IFN *et al*.(2021)[14]		
Methods	Phase 2, multi-center, Open-label and randomized controlled trial.	
Participants	Inclusion criteria: Age at least 18 years, a national early warning score 2 (NEWS2) of at least 1, and symptom duration of 14 days or less upon recruitment.	
Intervention	Intervention group: lopinavir 400 mg and ritonavir 100 mg, ribavirin 400 mg every 12 h, and subcutaneous injection of one to three doses of interferon beta-1b 1 mL (8 million international units [IU]). Control group: lopinavir/ritonavir (lopinavir 400 mg and ritonavir 100 mg) every 12 h for 14 days.	
Outcome	The primary endpoint was time to achieve a negative RT-PCR result for SARS-CoV-2 in a nasopharyngeal swab sample. Secondary clinical endpoints were time to resolution of symptoms defined as a NEWS2 of 0 maintained for 24 h; daily NEWS2 and sequential organ failure assessment (SOFA) score; length of hospital stay; and 30-day mortality	
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to the groups. Each serial number was computer generated.
Allocation concealment (selection bias)	Low risk	Simple randomization with no stratification was used, and patients were assigned to a serial number by the study coordinator.
Blinding of participants and personnel (performance bias)	High risk	Open label: The patient and the investigator are aware of the intervention given.
Blinding of outcome assessment (detection bias)	Low risk	The blinding of outcome assessor was not mentioned.
Incomplete outcome data (attrition bias)	Low risk	All the participants who have undergone randomization their data were included for analysis.
Selective reporting (reporting bias)	Low risk	All outcomes' measures were analyzed and reported one patient stopped on day 7 because of adverse events
Other biases	Low risk	No
Rahmani H *et al*. (2020)[15]		
Methods	Open labeled randomized controlled trial	
Participants	Adult patients (≥18 years old) with positive PCR and clinical symptoms/signs of pneumonia (including dyspnea, cough, and fever), peripheral oxygen saturation (SPO2) ≤ 93% in ambient air or arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) < 300 or SPO2/FiO2<315 and lung involvement in chest imaging.	

Contd...

Table 2: Contd...

Rahmani *et al*. (2020)		
Intervention	Intervention group: IFN β-1b 250 mcg subcutaneously every other day for two consecutive weeks, lopinavir/ritonavir (400/100 mg BD), or atazanavir/ritonavir (300/100 mg daily) plus hydroxychloroquine (400 mg BD in first day and then 200 mg BD) for 7–10 days. Control group: lopinavir/ritonavir (400/100 mg BD) or atazanavir/ritonavir (300/100 mg daily) plus hydroxychloroquine (400 mg BD in first day and then 200 mg BD) for 7–10 days.	
Outcome	Clinical status of the patients was assessed by the six-category ordinal scale at days 0, 7, 14, and 28 of the randomizations. Need for supplemental oxygen therapy and also invasive or non-invasive respiratory supports were evaluated regularly.	
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to the groups. A biostatistician who was not involved in this study did the randomization.
Allocation concealment (selection bias)	Low risk	The method randomization was the permuted block randomization; six patients per block
Blinding of participants and personnel (performance bias)	High risk	Open label: The patient and the investigator are aware of the intervention given.
Blinding of outcome assessment (detection bias)	Low risk	The blinding of outcome assessor was not mentioned.
Incomplete outcome data (attrition bias)	Low risk	All the participants randomized were analyzed in the study group
Selective reporting (reporting bias)	Low risk	All the mentioned primary and secondary outcome were assessed
Other biases	Low risk	No

Table 3: Summary of finding

Comparison of interferon beta-1b along with standard care with standard care for severe COVID-19 patients

Patient or Population: Severe COVID-19 patients
Intervention: Interferon beta-1b with standard care
Comparison: Standard care

Outcomes	Anticipated absolute effects* (95% CI)		No. of participants (Studies)	Certainty of the evidence (Grade)
	Risk with Standard Care	Risk with Interferon Group		
Time of clinical improvement	The mean time of clinical improvement was 8.67 Days	MD 3.01 lower (4.97 lower to 1.05 lower)	167 (two RCTs)	⊕⊕⊕◯ MODERATE[a]
Duration of hospital stay	The mean duration of hospital stay was 8.57 Days	MD 2.43 lower (4.55 lower to 0.3 lower)	233 (three RCTs)	⊕⊕◯◯ LOW[a,b]
Mortality	160 per 1,000	72 per 1,000 (28 to 178)	233 (three RCTs)	⊕⊕⊕◯ MODERATE[a]
Hospital admission with invasive mechanical ventilation	208 per 1,000	170 per 1,000 (81 to 361)	106 (two RCTs)	⊕⊕⊕◯ MODERATE[a]
Hospital admission with non-invasive mechanical ventilation	68 per 1,000	86 per 1,000 (34 to 216)	193 (two RCTs)	⊕⊕⊕◯ MODERATE[a]
ICU admission	717 per 1,000	509 per 1,000 (373 to 695)	106 (two RCTs)	⊕⊕⊕◯ MODERATE[a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference. GRADE working group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. [a]Proper blinding of the investigators and participants was not followed in most of the studies along with incomplete reporting of the outcomes and selection bias. Some of the trials were not registered. [b]Findings of the study were inconsistent in case of duration of hospital stay.

our analysis results have statistically shown no difference in the number of deaths between the groups. The systematic review meta-analysis conducted by Kumar S *et al*.[17] included the studies which used interferon β-1b and β-1a in the intervention arm, whereas in this review we have included the studies conducted with interferon β-1b alone. The review conducted by Kumar S *et al*.[17] concluded that there was a significant reduction with respect to clinical improvement, and all other outcome parameters did not show any significant improvement between the intervention and the control arm. In this review, the patients who received interferon β-1b in the intervention arm have shown significant improvement in reducing the number of hospital stays, increase in clinical response, and decrease in ICU admission. Our meta-analysis also includes safety concerns. The adverse outcomes reported by each study were included in the analysis, and it was observed that there is no

statistically significant difference seen between the intervention and the control group.

As for limitations, all the included studies were open label. Hence, the subjects and investigators were aware of the treatment provided which could lead to performance bias. Though the route of administration was the same, the dose and dosing interval of IFN β-1b varied among the included studies. A substantial group of participants recruited in the studies had co-morbid conditions such as diabetes, hypertension, cardiovascular disease, and malignancy. This may increase the risk of interaction with other concomitant medications which might have an antagonistic or synergistic action with IFN β-1b or standard care treatment provided to COVID-19 patients. The concomitant medications might have an impact on the estimate of the IFN β-1b effect on COVID-19. Future RCTs must be performed to overcome the limitations mentioned in this review.

Conclusion

Our results demonstrate that administration of interferon beta-1b along with the standard care, that is, antiviral such as lopinavir/ritonavir, ribavirin, and HCQ had reduced the need for ICU admission and had better efficacy in shortening the duration of virus shedding, reducing the cytokine response, and reducing the symptoms of COVID-19. This study also gives insight to clinicians and to have informed them about the efficacy and safety of interferon beta-1b and a reasonable therapeutic option that can be used in severely ill COVID-19 patients for a better prognosis.

Authors contributions

Greeshma Sai Sree Nayudu (GSS), Binit Mamkoottathil Benny (BMB), Grace Thomas (GT), Maria Adil Khan (MAK), and Roopa Satyanarayan Basutkar (RSB) were involved in the conception of the study from the inception of the protocol development and throughout. GSS, BMB, and GT conducted the literature search, and the relevant information was also extracted. Risk assessment was performed by MAK and GSS. Any discrepancies were sorted, discussed, and resolved by RSB. GSS had entered the data into Review Manager 5.3 and contributed to the analysis. All the tables and figures were prepared by GSS, GT, and BMB. The first and subsequent drafts of the manuscript were prepared by GSS, BMB, GT, and MAK. RSB reviewed and corrected all the drafts of the manuscript. The final version of the manuscript was approved by all authors.

Acknowledgement

The authors thank JSS College of Pharmacy, JSS Academy of Higher Education and Research, Rocklands, Ooty, The Nilgiris, Tamil Nadu, India, for the support, technical assistance, and resources provided throughout the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Search methods for identification of the studies

Population	Intervention	Comparison	Outcome
COVID-19	**Interferon beta**	**Control**	**Efficacy and Safety**
(((COVID-19[Title]) OR (SARS-CoV-2 [Title]) OR (Coronavirus)))	(((Interferon beta [Title]) OR (beta Interferon [Title])) OR (Interferon-beta [Title]))	Lopinavir/ritonavir, ribavirin therapy, corticosteroids, hydroxychloroquine	Efficacy [All Fields]
COVID-19	Beta interferon		Clinical effectiveness
COVID-19 virus disease	Interferon, beta		Effectiveness clinical
Coronavirus disease 2019	Fiblaferon		Clinical improvement
2019 novel coronavirus disease	Interferon beta		Improvement clinal
Coronavirus disease-19	Interferon, fibroblast		Hospital stays
			Hospital admission
COVID-19 virus infection	Fibroblast interferon		Duration
2019-nCoV disease	Interferon, beta-1		Intensive care unit
COVID-19 pandemic	Beta interferon		Mechanical ventilation
SARS-CoV-2 infection	Beta-1 interferon		Mortality
2019-nCoV infection	Beta-1 interferon		Death
2019 novel coronavirus infection	Interferon beta-1		Treatment effectiveness
	Interferon beta-1		Effectiveness, treatment

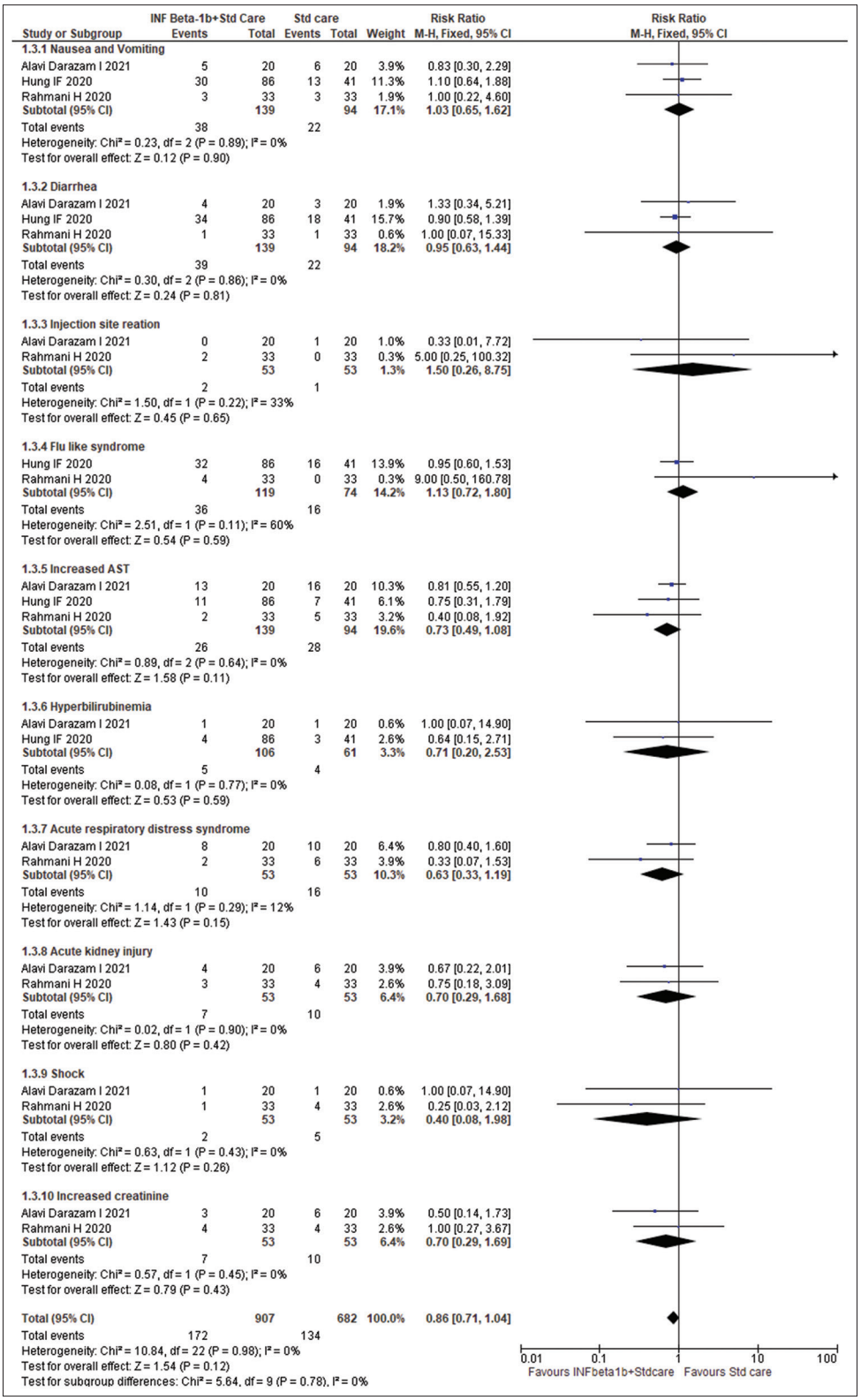

Figure S1: Forest plot showing the adverse events of interferon beta-1b versus standard care in COVID-19-infected patients

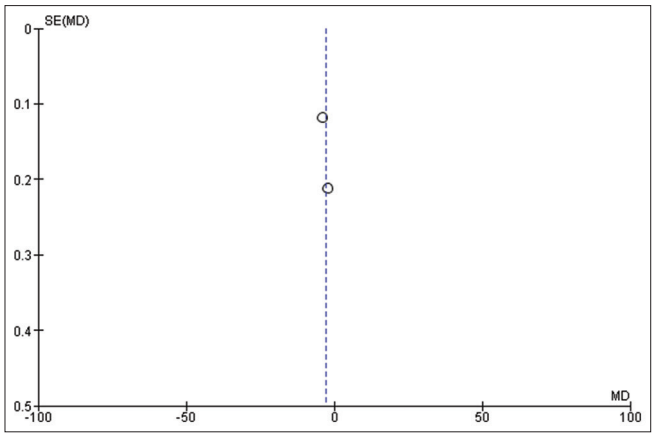

Figure S2: Funnel plot showing the effect of interferon beta-1b on the time of clinical improvement versus standard care in COVID-19-infected patients

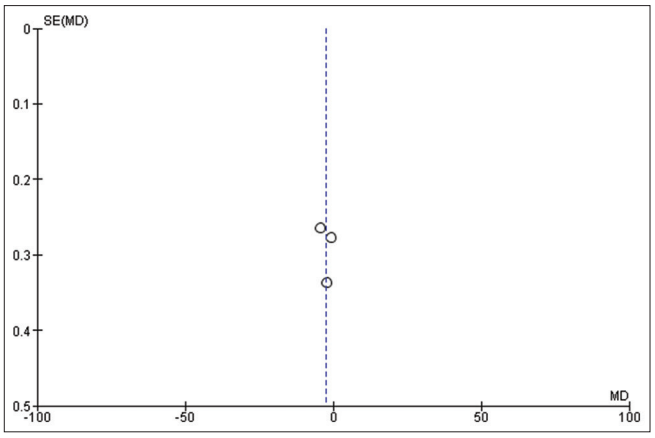

Figure S3: Funnel plot showing the effect of interferon beta-1b on the duration of hospital stay versus standard care in COVID-19-infected patients

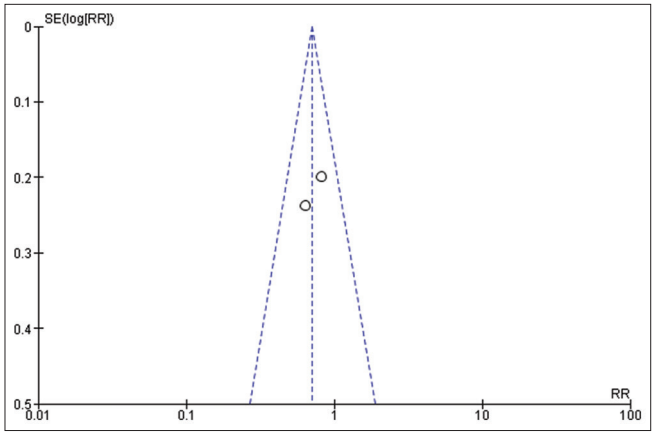

Figure S4: Funnel plot showing the effect of interferon beta-1b on the need for ICU admission versus standard care in COVID-19-infected patients

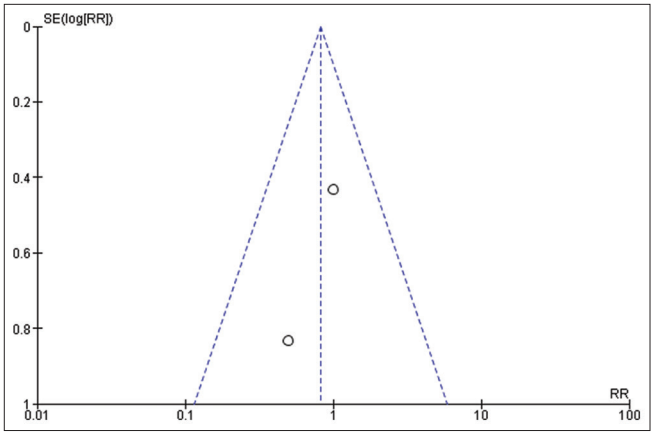

Figure S5: Funnel plot showing the effect of interferon beta-1b on hospital admission with invasive mechanical ventilation versus standard care in COVID-19-infected patients

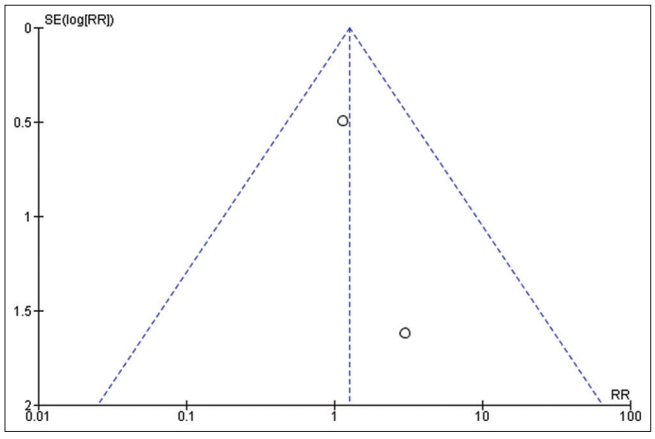

Figure S6: Funnel plot showing the effect of interferon beta-1b on hospital admission with non-invasive mechanical ventilation versus standard care in COVID-19-infected patients

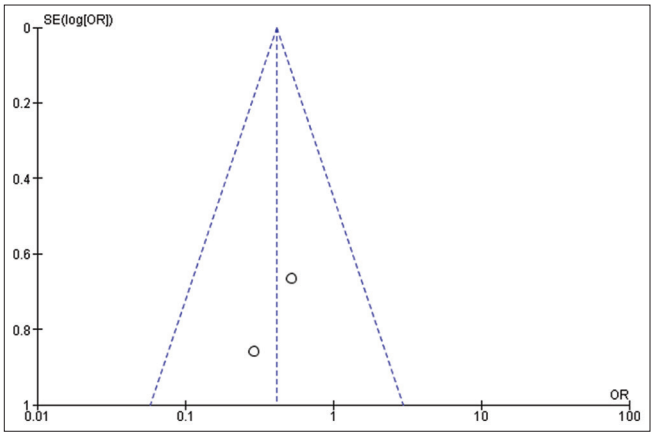

Figure S7: Funnel plot showing the effect of interferon beta-1b on mortality rate versus standard care in COVID-19-infected patients