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Efficacy of subcutaneous interferon-beta in COVID-19: a meta-analysis and systematic review

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ABSTRACT

Type 1 interferons, especially interferon-beta, has been reported to be effective in COVID-19 patients in multiple randomized controlled trials. The aim of our meta-analysis and systematic review is to assess efficacy of subcutaneous IFN-beta in regards to mortality and discharge rate. Prospective, retrospective and randomized controlled trials were included. Primary outcomes measured were 28-day mortality and discharge rate. Secondary outcomes measured were mean hospital stay and post-intervention intubation rate. A thorough literature search was conducted in Medline, PubMed, Ovid journals, Google Scholar, and Cochrane Central Register of Controlled Trials & Database of Systematic Reviews from 1 April 2020 to 28 February 2021. Relative risk was calculated using both the Mantel–Haenszel method (fixed-effects model) and DerSimonian Laird method (random effects model). The heterogeneity among studies was tested using Cochran's Q test, based upon inverse variance weights. 7 studies were included in the meta-analysis and systematic review. The IFN-beta group did not improve the 28-day mortality (RR = 1.276; 95% CI: 1.106–1.472, p = 0.001) or the discharge rate (RR = 0.906; 95% CI = 0.85–0.95, p = < 0.001). The mean hospital stay was 11.95± 2.5 days in the interferon-beta group and 11.43 ± 3.74 days in the traditional treatment group. Likewise, interferon-beta did not add any advantage to post-intervention intubation rate (RR = 0.92; 95% CI = 0.7841–1.0816, p = 0.3154). Our findings revealed that use of subcutaneous interferon-beta is futile in COVID-19.

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KEYWORDS
Interferon-beta; COVID-19; coronavirus; meta-analysis; systematic review; pandemic; efficacy; subcutaneous

1. Introduction

The global public health emergency from the coronavirus (COVID-19) pandemic has resulted in many trials to determine efficacy of various drugs. One of the only therapies to show proven efficacy with consensus so far is the use of steroids [1]. In the attempt to prove mortality benefit and efficacy in the treatment of COVID-19, Interferon-beta (IFN-β) has been used [2]. The IFN therapy in COVID-19 is hypothesized from its use with other viral diseases, such as hepatitis B and C, and further extrapolated from malignancy and autoimmune disease treatment [2,3]. The theory was further supported by an increased risk of severe disease in those who were found to have neutralizing autoantibodies against IFN. These were not found in healthy and minimally symptomatic individuals [4]. The innate immunity responds to viral entry and replication with a downstream signaling cascade that results in pro-inflammatory cytokine release. IFN are proteinaceous substances that are also released as part of this response. IFN's antiviral properties are attributed to its ability to inhibit viral replication, maturation, release and protein synthesis. Additional immunomodulatory benefits of IFN relate to other innate immune mechanism with T cell and NK cell involvement [5].

In this meta-analysis and systematic review, our objective is to compare the efficacy of IFN-beta + traditional antiviral treatment with traditional antiviral treatment in regards to 28-day mortality, discharge rate, mean hospital stay and post-intervention intubation rate in COVID-19 patients. The outcomes were assessed using the latest studies published in the last 1 year.

2. Materials and methods required

2.1. Study selection criteria

Studies that utilized either interferon beta-1a or interferon beta-1b in the treatment of COVID patients were selected. The inclusion criteria were as follows: 1) studies on patients admitted only for COVID-19 illness and its complications; 2) study designs including case series, randomized clinical trials, prospective studies and retrospective clinical

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studies; 3) studies involving only the adult population. The exclusion criteria were as follows: 1) studies in languages other than English; 2) studies published as abstracts; 3) studies that did not have a control group.

2.2. Data collection and extraction

A thorough literature search was conducted through Medline, PubMed, Ovid journals, Google Scholar, and Cochrane Central Register of Controlled Trials & Database of Systematic Reviews. The literature search included articles dated from 1 April 2020 to 28 February 2021. The search terms used were 'interferon beta-1a', 'interferon beta-1b', 'COVID-19′, 'SARS-CoV-2′ and 'Novel Coronavirus'. Two authors independently searched and extracted the data into an abstraction form. Any differences were resolved by mutual agreement. Figure 1 shows the search results

2.3. Comparison

The standard care (hydroxychloroquine and lopinavir/ritonavir, alone or in combination) for COVID-19 patients was compared with the intervention care protocol (subcutaneous IFN-β + standard care).

2.4. Statistical analysis

This meta-analysis was performed by calculating relative risk of measured outcomes when COVID-19 patients were exposed to interferon beta and traditional antiviral treatment. Primary outcomes measured were 28-day mortality and discharge rate. Secondary outcomes measured were mean hospital stay and post-intervention intubation rate. The total relative risk was calculated using both the Mantel–Haenszel method (fixed-effects model) and the DerSimonian Laird method (random effects model) [6,7].

Forest plots were drawn in which the width of the point estimates represents the weight assigned to that particular study. Heterogeneity between studies was evaluated using Cochran's Q test based upon inverse variance weights, and heterogeneity was quantified using I^2 statistics [8].

Both Harbord–Egger bias indicator and Begg–Mazumadar bias indicators were utilized to test the publication and selection bias on the summary estimates [9,10]. Publication bias was further evaluated by constructing funnel plots [11,12].

3. Results

An initial search identified 124 articles, out of which 104 studies were initially excluded (studies involving

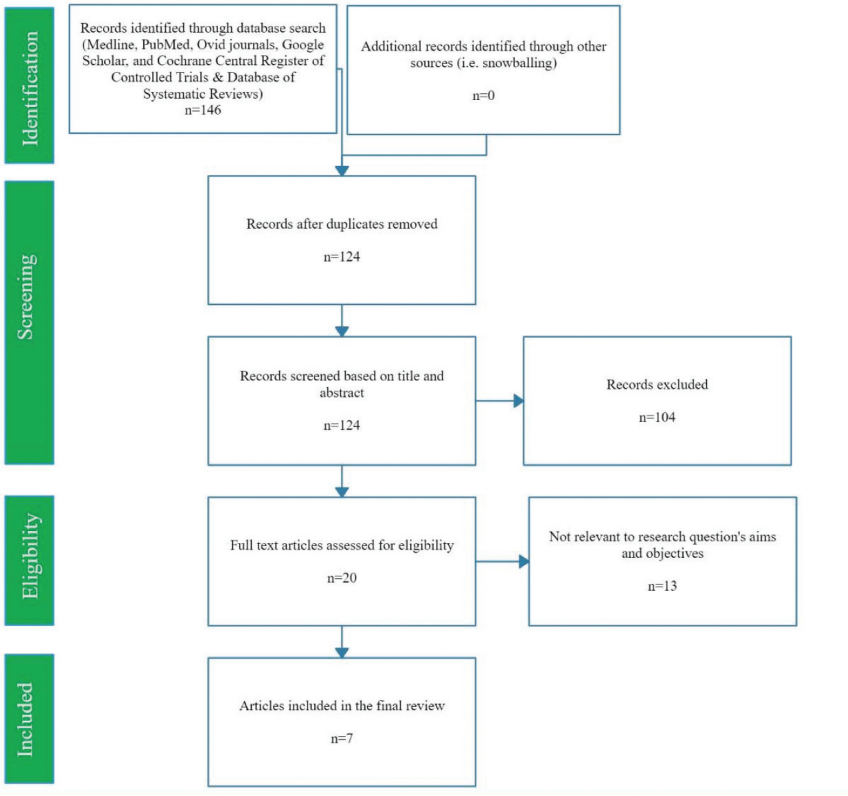

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of studies included in the review (PRISMA).

pediatric population, studies presented as abstracts and review articles). 20 relevant studies were selected and reviewed in detail. Of these 13 studies were again excluded because they either did not have a control group, or did not have data on our desired outcomes. 7 studies (N = 6078) met the final inclusion criteria [13–19]. Table 1 demonstrates the characteristics of all the studies involved. The mean age of patients undergoing interferon therapy was 57.7 ± 5.19 years, whereas the mean age of patients undergoing traditional treatment was 59 ± 5.04 years. The Interferon beta group consisted of 1,783 (62.2%) males and 1,080 (37.7%) females, whereas the traditional therapy group consisted of 1,982 (61.6%) males and 1,233 (38.3%) females. All the pooled estimates given are estimates calculated by the fixed effect model.

The relative risk of 28-day mortality was 1.276 (95% CI = 1.106–1.472, P = 0.001). A Forest plot showing the summary estimates is shown in Figure 2. Publication bias calculated using the Harbord–Egger bias indicator gave a value of −2.7042 (95% CI = −5.7839 to 0.3754, P = 0.0714). The Begg–Mazumdar indicator gave Kendall's tau b value −0.4667 (P = 0.1885), suggesting no publication bias. The funnel plot in Figure 3 shows no publication bias for studies comparing interferon treatment with traditional treatment in COVID-19 patients.

The relative risk of discharge rate was 0.906 (95% CI = 0.85–0.95, p = < 0.001). A Forest plot showing the summary estimates is shown in Figure 4. Publication bias calculated using the Harbord–Egger bias indicator gave a value of 3.2462 (95% CI = −9.4084 to 15.9009, p = 0.3847). The Begg–Mazumdar indicator gave Kendall's tau b value of 0.33 (p = 0.49), suggesting no publication bias. The funnel plot in Figure 5 shows no publication bias for studies comparing interferon treatment with traditional treatment in COVID-19 patients.

The mean hospital stay was 11.95± 2.5 days in the interferon-beta group and 11.43 ± 3.74 days in the traditional treatment group. The post-intervention intubation rate was not statistically significant when the interferon-beta group was compared to the traditional group, with a relative risk of 0.92 (95% CI = 0.7841 to 1.0816, P = 0.3154).

4. Discussion

The Coronavirus pandemic has changed the world as we know it today. It has touched every aspect of modern human society including each arena of the medical field. Clinicians, researchers and scientists all over the world continue to seek the most effective treatment of this deadly disease. While social distancing remains a cornerstone in preventing the spread of SARS CoV-2, our ability to truly counter the virus will depend on finding a cure. Since the beginning of the pandemic in December of 2019, management of COVID-19 patients around the world has varied. This variation is due to a lack of uniform protocols, insufficient evidence and paucity of resources and multiple experimental drugs [13]. In this meta-analysis, we have compared the outcomes of 2,863 COVID −19 patients treated with combination of IFN-beta and antiviral medications against the outcomes of 3,215 COVID-19 patients treated only with antivirals.

The IFN-1 family, which include subtypes IFN-α, IFN-β and IFN-ω, are types of cytokine molecules, which provide innate immunity against viruses. IFN-1 is produced by host cells when receptor proteins like TLR3, TLR7 and TLR present on cell organelles detect viral RNA proteins. The IFN-1 molecules in turn bind to the cell-surface interferon-α/β receptor (IFNAR), leading to the transcription of genes that inhibit viral replication [20]. Zhang et al. and Bastard et al. conducted studies that looked into the factors causing severity of disease in certain COVID-19 patients. Deficiency of interferon was implicated as one of the factors in their studies. Zhang [21] hypothesized that genetic mutations lead to inherent deficiency of IFN. Furthermore, Bastard [4] reported development of neutralizing autoantibodies against innate IFN.

Rahmani [14] conducted the first randomized clinical trial (RCT) evaluating the safety and efficacy of IFN β subtype 1b in severe COVID-19 patients. They compared clinical improvement and 28-day-mortality in severe COVID-19 patients treated with IFN β-1b as well as national protocol medications against those who only received national protocol medications. These included lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine. Thirty-three patients were enrolled in each arm of the study. The time to clinical improvement was significantly lower in the IFN group (9 days) compared to the control group (11 days). Duration of hospitalization, ICU stay, intubation rates and 28-day mortality were reduced after IFN-beta treatment but were not statistically different between the two groups.

A retrospective case-control study compared outcomes in 152 patients treated with IFN-β-1a, Lopinavir and Ritonavir (case group) with patients receiving only lopinavir/ritonavir (control group). Duration of hospital stay was higher in the case group (13 days) as compared to the control group (6 days). This was statistically significant (p = 0.001). Thirty-four percent of patients in the case group required non-invasive ventilation, compared to 24% patients in the control group, and the difference was statistically significant. On the contrary, the mortality rate was lower in the intervention group at 11% when

Table 1. Characteristics of studies included in the meta-analysis.

No.	Author	Country	Study Design	Intervention/ Standard therapy	Age	Males	Females	Total patients	Interval between symptom and treatment (days)	Number of ICU admits	Number of patients on mechanical ventilation	Number of deaths	Hospital stay (in days)	ICU stay (in days)	Post intervention intubation	Time to clinical response (in days)	Time to negative nasopharyngeal swab (in days)	Number of patients discharged
1a	Rodriguez-Gonzalez CG et al [13]	Spain	Retrospective non-randomized	LPV/r + HCQ + IFN-β1b ± AZT	65	289	211	500	6			143	11	17				334
1b	Control group			LPV/r ± HCQ ± AZT	65	432	316	748				120						604
2a	Rahmani H et al [14]	Iran	Open-label, randomized clinical trial	IFN β-1b + LPV/r or atazanavir/ ritonavir + HCQ	60	20	13	33	8			2	11		2	9		31
2b	Control group			LPV/r or atazanavir/ ritonavir + HCQ	61	19	14	33	8			6	13		6	11		27
3a	Hung IF et al [15]	Hong Kong	Phase 2, multicenter, open-label, randomized trial	IFN β-1b + LPV/r, ribavirin	51	45	41	86	5			0	9		0	4	7	
3b	Control group			LPV/r only	52	23	18	41	4			0	14.5		1	8	12	
4a	Baghaei P et al [16]	Iran	Retrospective (a nested case-control) study	IFN-													β1-a + LPV/r	56
104	48	152	7	51	17	17	13		17			135						
4b	Control group			LPV/r	56	208	96	304	7	74	43	40	6		43			264
5a	Davoudi-Monfared E et al [17]	Iran	Randomized clinical trial	IFN β-1a + HCQ + LPV/r or atazanavir-ritonavir	56.5	22	20	42	11.70 ± 5.71	19		8	14.80 ± 8.45	7.71 ± 8.75	15	9.7 ± 5.8		28
5b	Control group			HCQ + LPV/r or atazanavir-ritonavir	61	22	17	39	9.31 ± 4.45	23		17	12.25 ± 7.48	8.52 ± 7.48	17	8.3 ± 4.9		17
6a	Gaibani P et al [18]	Italy	Case control study	IFN β-1a + HCQ + LPV/r				5	7	5	5	2		12 ± 2			13 ± 3.9	

(*Continued*)

Table 1. (Continued).

No.	Author	Country	Study Design	Intervention/ Standard therapy	Age	Males	Females	Total patients	Interval between symptom and treatment (days)	Number of ICU admits	Number of patients on mechanical ventilation	Number of deaths	Hospital stay (in days)	ICU stay (in days)	Post intervention intubation	Time to clinical response (in days)	Time to negative nasopharyngeal swab (in days)	Number of patients discharged
6b	Control group			HCQ				3		3	3	2		15 ± 2			11 ± 3.9	
7a	WHO Solidarity Trial		Consortium et al [19]	30 countries					International								randomized trial	IFN β-1a + LPV
	1303	747	1656			139	150			209								
7b	Control group			LPV/ standard of care		1278	772	1650			130	129			210			

Abbreviations: IFN β, Interferon-beta; LPV/r, lopinavir/ritonavir; HCQ, hydroxychloroquine; AZT, azithromycin.

Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Baghaei P et al	17/152	40/304	0.850	0.499 to 1.448			7.35	19.36
Davoudi-Monfared E et al	8/42	17/39	0.437	0.213 to 0.896			4.05	15.60
Gaibani P et al	2/5	2/3	0.600	0.157 to 2.289			1.17	7.53
WHO Solidarity Trial Consortium	150/1656	129/1650	1.159	0.925 to 1.451			41.17	25.57
Rodriguez-Gonzalez CG et al	143/500	120/748	1.783	1.438 to 2.209			45.36	25.74
Rahmani H et al	2/33	6/33	0.333	0.0725 to 1.533			0.90	6.19
Hung IF et al	0/86	0/41	-					
Total (fixed effects)	322/2474	314/2818	1.276	1.106 to 1.472	3.344	0.001	100.00	100.00
Total (random effects)	322/2474	314/2818	0.923	0.599 to 1.420	- 0.366	0.714	100.00	100.00

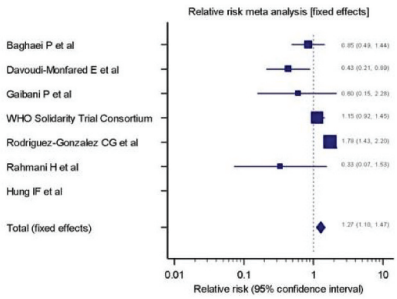

Figure 2. Forest plot of 28-day mortality assessed in COVID-19 patients comparing interferon beta group with standard treatment group.

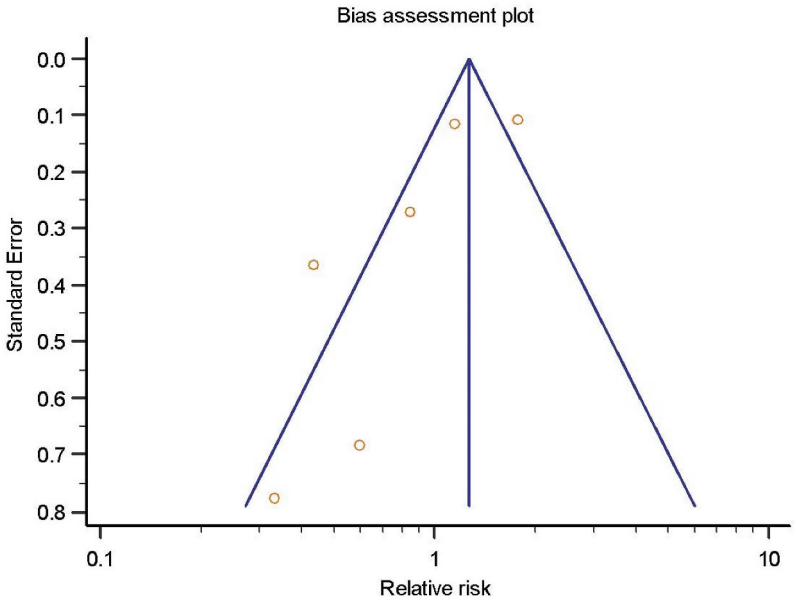

Figure 3. Forest plot demonstrating no publication bias.

Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Baghaei P et al	135/152	264/304	1.023	0.952 to 1.098			45.60	31.19
Davoudi-Monfared E et al	28/42	17/39	1.529	1.009 to 2.319			1.34	12.60
Rodriguez-Gonzalez CG et al	334/500	604/748	0.827	0.771 to 0.888			46.09	31.21
Rahmani H et al	31/33	27/33	1.148	0.956 to 1.378			6.96	24.99
Total (fixed effects)	528/727	912/1124	0.906	0.859 to 0.955	- 3.674	<0.001	100.00	100.00
Total (random effects)	528/727	912/1124	1.037	0.858 to 1.252	0.373	0.709	100.00	100.00

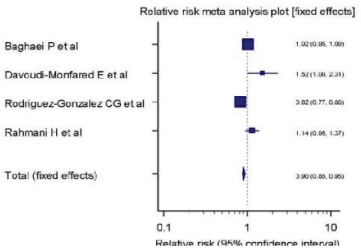

Figure 4. Forest plot of discharge rate assessed in COVID-19 patients comparing interferon beta group with standard treatment group.

compared to 13% in the control group; however, statistical significance in the difference was not determined [16].

Another study comparing the outcomes in COVID-19 patients treated with IFN β-1a + hydroxychloroquine and lopinavir-ritonavir to those treated with hydroxychloroquine alone found no significant difference in the mortality and discharge times [18]. Davoudi-Monfared [17] conducted a similar randomized clinical trial on a small sample population constituting 42 patients in the IFN-beta 1a group and 39 patients in the standard treatment group. The primary outcome, i.e., time to clinical response, was not statistically different between the IFN-beta 1a (9.7 ± 5.8 days) and the control group (8.3 ± 4.9 days). When comparing the IFN group with

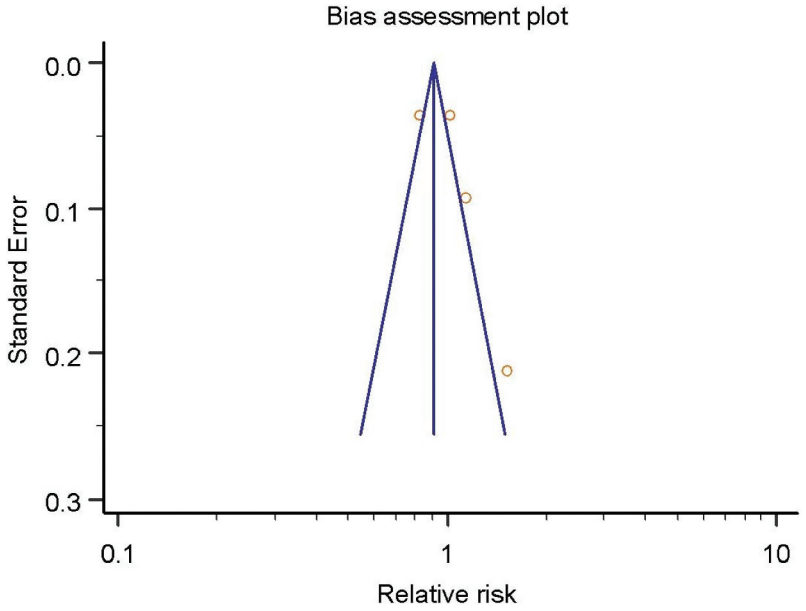

Figure 5. Forest plot demonstrating no publication bias.

the control group, the discharge rate was higher (66.7% vs 43.6%), and the 28-day mortality rate was lower (19% vs 43.6%).

An open label, randomized, phase 2 trial in COVID-19 patients from six hospitals estimated the efficacy of combined interferon beta-1b, lopinavir-ritonavir, and ribavirin. Patients receiving lopinavir and ritonavir acted as the control group. The study concluded that the combination group had a significantly shorter median time to achieve a negative nasopharyngeal swab than the control group (7 days vs 12 days, respectively). Median hospital stay was also significantly reduced in the combination group (9 days) when compared with the control group (14.5 days). Mortality rate could not be assessed as the study did not observe any deaths in either group [15].

A large mortality trial of four drugs conducted across 30 countries by the World Health Organization concluded that interferon regimen had no effect on overall mortality, duration of hospital stays and initiation of ventilation in COVID-19 patients [19]. These results were in contrast to the findings of much smaller trials that supported the early use of interferon therapy in the disease course.

The majority of the studies mentioned above had the limitation of comprising a small sample size, necessitating the need for a meta-analysis to interpret the outcomes accurately. A recent meta-analysis utilizing only three studies compared the discharge rate of standard care protocol with standard care plus interferonbeta in COVID -19 patients. IFN-beta was noted to increase overall discharge rate with relative risk of 3.05 (95% CI: 1.09–5.01). However, due to lack of studies, mortality rate was not calculated using the meta-analysis. Median days of hospitalization (9 days vs 12.25 days) and average mortality rate (6.195% vs 18.02%) were both lower in the intervention group when compared to the control group [2].

We conducted a meta-analysis to evaluate the 28-day mortality rate among 7 studies and the discharge rate among 4 studies. When comparing the intervention group with the control group, the relative risk of 28-day mortality was 1.276 (95% CI = 1.106–1.472, P = 0.001); and the relative risk of discharge rate was 0.906 (95% CI = 0.85–0.95, p = < 0.001). The mean hospital stay was 11.95± 2.5 days in the intervention group and 11.43 ± 3.74 days in the control group. Results from our meta-analysis showed that there is no significant difference in 28-day mortality between the interferon-beta intervention group and the control group receiving traditional treatment. Our study also showed no significant difference in the discharge rate in the IFN and non-IFN group. The mean hospital stay was similar in both arms of the study, and no statistically significant difference was noted in post-intervention intubation rates in both groups. Our analysis suggests that treatment with subcutaneous IFN β-1b does not provide additional benefits to COVID-19 patients when compared to traditional therapies.

This meta-analysis and systematic review has several strengths, which include solid inclusion and exclusion criteria as well as comprehensive search strategy. Every study included was of high-quality and low publication bias. Our meta-analysis also included retrospective studies in addition to prospective studies and randomized/ non-randomized clinical trials.

However, our meta-analysis is not without a few limitations. Firstly, combinations of medications used with interferon-beta in the intervention groups are varied in different studies. Similarly, the combinations of medications in the control groups are also different in the different studies. Secondly, the definition of treatment response was not consistent between studies. Lastly, the treatment duration is also varied in each study. Concomitant medication in both intervention and control groups may have confounding effects on the results.

5. Conclusions

Based on our meta-analysis results, use of IFN-beta in COVID-19 patients treatment did not provide any additional benefit when compared with traditional therapy. Our meta-analysis negates the findings of small sample size randomized controlled trials that claimed IFN beta to be beneficial and supports the decision to withdraw use of interferon beta in COVID-19 patients' treatment, given its futile nature.

Disclosure statement

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Authors' contribution

Conceptualization: Asif AA, Chatterjee T, Hussain H, Senthil Kumaran S

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Writing - review and editing: Asif AA, Senthil Kumaran S, Varun V, Singhal M, Rangwala US

Approval of final manuscript: Asif AA, Hussain H, Senthil Kumaran S, Syed SB, Vanka V, Tharoor M, Rangwala US, Rathore U, Singhal M, Chatterjee T

Ethics approval

Our meta-analysis is exempted from ethics/ IRB approval because we collected and synthesized data from previous clinical trials in which informed consent had already been obtained by the trial investigators, and our meta-analysis addresses very similar questions to the research question for which the data were collected (and to which patients gave consent).

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