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Evaluation of safety, efficacy, tolerability, and treatment-related outcomes of type I interferons for human coronaviruses (HCoVs) infection in clinical practice: An updated critical systematic review and meta-analysis

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ABSTRACT

Background: There is no vaccine or specific antiviral treatment for HCoVs infection. The use of type I interferons for coronavirus is still under great debate in clinical practice.

Materials and methods: A literature search of all relevant studies published on PubMed, Cochrane library, Web of Science database, Science Direct, Wanfang Data, and China National Knowledge Infrastructure (CNKI) until February 2020 was performed.

Results: Of the 1081 identified articles, only 15 studies were included in the final analysis. Comorbidities and delay in diagnosis were significantly associated with case mortality. Type I interferons seem to improve respiratory distress, relieve lung abnormalities, present better saturation, reduce needs for supplemental oxygen support. Type I interferons seem to be well tolerated, and don't increase life threating adverse effects. Data on IFNs in HCoVs are limited, heterogenous and mainly observational.

Conclusions: Current data do not allow making regarding robust commendations for the use of IFNs in HCoVs in general or in specific subtype. But we still recommend type I interferons serving as first-line antivirals in HCoVs infections within local protocols, and interferons may be adopted to the treatments of the SARS-CoV-2 as well. Well-designed large-scale prospective randomized control trials are greatly needed to provide more robust evidence on this topic.

1. Introduction

Coronaviruses are single – stranded and positive – sense RNA viruses. Among coronaviruses, including Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), seven coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have been known to infect human hosts and cause respiratory diseases. These seven known human coronaviruses (HCoVs) can cause respiratory diseases from mild to severe symptoms. HCoVs caused mild upper respiratory symptoms, until the unexpected outbreak of SARS in 2003 was associated with significant infectivity and high case mortality rate [1]. The clinical manifestation of coronavirus infection widely ranges from asymptomatic or mild respiratory symptoms, to rapidly progressing acute respiratory stress needing mechanical ventilation or extracorporeal membrane oxygenation (ECMO), or even acute death [2]. The initial symptoms of coronavirus infection are just common flu-like nonspecial symptoms, like cough, fever, chills, and

Abbreviations: IFNs, interferons; PEG-IFN, pegylated interferon; ECMO, extracorporeal membrane oxygenation; MERS-CoV, middle east respiratory syndrome coronavirus; NA, not available; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; RT-PCR, real-time polymerase chain reaction; RCT, randomized controlled trials; ARDS, acute respiratory distress syndrome; ICU, intension care unit; upE gene, upstream E protein; ORF 1a, open reading frame 1a

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gastrointestinal symptoms, makes it difficult to distinguish from flu [3]. Unfortunately, coronavirus infection is much more dangerous and challenging than flu cold, and usually rapidly progress into severe illness, like severe pneumonia, shortness of breath, acute respiratory distress syndrome (ARDS), respiratory failure and other related life threating comorbidities. The outbreak of SARS was a turning point that human beings think of coronavirus, and the novel coronavirus identified in a 60-year old man in Saudi Arabia in 2012 [4], known as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), strengthened the awareness and understanding of coronavirus.

Both SARS-CoV and MERS-CoV caused outbreaks affecting multiple countries, severe disease, and global threatening, for its widespread infectivity, rapid progress, high variance and mortality rate, and non-special treatment, somewhat the same as SARS-CoV-2 in Wuhan, China [5]. As for treatments, currently there is no defined primary remedy, vaccination or prophylaxis. Nowadays, treatments for such cases range from supportive treatment (including fluid balance, nutrition support, invasive ventilation, renal replacement therapy, vasopressors, corticosteroids, immunoglobulins, etc.) to antiviral treatment, or both [6–10]. The specific antiviral treatments were interferons (IFN), ribavirin, lopinavir, and other related antiviral agents. Clinically, the use of specific antivirals, especially the utility of IFNs, is still under great debate, for its efficacy, safety, and treatment-related adverse effects.

Initial in vitro investigations demonstrated type I interferons (IFN-α, IFN-β) to inhibit replication of SARS coronavirus (SARS-CoV) [11]. Based on previous studies, Morgenstern *et al.* investigated the combination effect of IFN-β and ribavirin to prevent SARS-CoV, and yield potential benefits of the ribavirin plus IFN-β for the treatment of SARS [12]. Illuminated by the possible antiviral treatment for SARS, several in vitro studies determined a possible efficacious effect of IFN-α2b and ribavirin in the treatment of MERS-COV infection [13,14]. Subsequently, the same investigators further examined the efficacy of these drugs in an animal study (macaques), 8 h after they were inoculated with MERS-CoV with favorable outcomes [15]. Strayer *et al.* concluded that the most active drugs against SARS/MERS CoV at clinically achievable serum levels were type I interferons and a TLR3 agonist, interferon inducer/activator [16].

Promising potential benefits of these antivirals successfully attracted attention of clinicians for the treatments of coronavirus infection. Though a systematic review conducted by Zumla *et al.* indicated that the application of type I IFNs may not improve clinical outcomes. There still exist several clinical trials determined that IFNs could make contributions to increase survival rate, improve oxygen saturation and associated with a more rapid resolution of pyrexia or radiographic lung opacities and respiratory improvements [17–21], or even prophylaxis efficacy [22,23].

A review of such anecdotal experiences is greatly needed for the more rational use of type I IFNs for coronavirus. Therefore, we conducted this updated systematic review and meta-analysis to recapitulate relevant studies to evaluate the safety, efficacy, tolerability and treatment-related outcomes of type I IFNs for coronavirus infection in clinical practice, with expectation to provide more robust evidence whether IFNs should be served as first-line agents for coronavirus infection, including the SARS-CoV-2.

2. Methods

2.1. Information sources and search strategy

This study was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [24]. The systematic literature search of databases was conducted by two independent reviewers on February 2020. These articles that contained relevant information on IFN and coronavirus were initially searched on PubMed, Cochrane Library, Web of Science Database, Science Direct, Wanfang Data, and China National Knowledge Infrastructure (CNKI), without time period, language, and region restriction. A MeSH terms search and keywords search were combined. The references of the included studies and reviews were also manually searched. We used the following search terms using the Boolean operators:

#1 “interferon” OR “IFN” OR “antivir*” OR “drug effect” OR “drug ther*” OR “combination drug ther*”
And
#2 “coronavirus” OR “Middle East Respiratory Syndrome: OR “MERS-CoV” OR “MERS virus*” OR “SARS” OR “severe acute respiratory syndrome” OR “SARS-CoV”

2.2. Inclusion criteria

(1) Clinical trials regarding type I IFN (IFN-α, IFN-β) solely or combinationally for the treatment of coronavirus infections or prophylaxis;
(2) Human studies, regardless of randomized controlled trial (RCT), case-control studies, observational study, cohort studies or case series;
(3) Compared the treatment outcomes of IFN and other remedies (supportive treatment only, corticosteroids, or between IFNs).

2.3. Exclusion criteria

(1) In vitro studies or animal models;
(2) Cellular, molecular, histological, or pathological mechanism studies or hypothesis;
(3) Pharmaceutical mechanism or toxicology hypothesis addressing IFN or related agents on coronavirus;
(4) Other antiviral therapies that do not include type I IFN;
(5) Repeated studies, staged trials or studies without comparison information;
(6) Reviews, comments or letters.

2.4. Study selection and data extraction

Two investigators independently reviewed the electronically and manually retrieved articles. After screening the titles and abstracts, potentially relevant studies were selected, and a full-text review was performed. All disagreements were solved by discussion or, still unsolved, by a third supervisor.

Each included article was thoroughly reviewed, and the following baseline information were extracted (Table 1): first author, publication year, region, study type, participants, diagnostic method of coronavirus, data collection method, time from admission to treatment start, time from diagnosis to treatment start, primary endpoints, and treatment-related adverse effects. In addition, the study design, treatment plan (including IFN dosage, frequency and duration), main findings and conclusions were extracted in detail in Table 2. Data on total mortality rate, 14-day survival, 28-day survival, 3-month survival, transferring rate to intensive care unit (ICU), required intubation and mechanical ventilation, resolution of pyrexia, and respiratory improvement (days) were recorded for possible meta-analysis.

For better understanding of severity and case mortality rate of coronavirus, we divided these patients into critically ill patients and mild ill patient. Critically ill defined as coronavirus-infected patients with other severe comorbidities, respiratory distress or failure, directly or indirectly transferred to ICU, needing intubation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), when admitted to primary treatment. Mild ill patients defined as these real-time polymerase chain reaction (RT-PCR) or other laboratory confirmed coronavirus infected asymptomatic or otherwise laboratory well patients.

Table 1
Baseline characteristics of included studies.

Authors	Publication year	Region	Study type	Participants enrollment	Type of coronavirus	Diagnostic method of coronavirus	Data collection method	Baseline characteristics before treatment	Time from admission to treatment start	Time from diagnosis to treatment start	Primary endpoint	Treatment-related complications or adverse effects
Arabi et al.	2018	Saudi Arabia	RCT	Laboratory RT-PCR confirmed MERS-CoV infected adults	MERS-CoV	Laboratory confirmation of MERS-CoV infection by RT-PCR from any diagnostic sampling source	Clinical records, laboratory tests, and follow-up	Randomly allocation, to guarantee comparability	N/A	N/A	90-day mortality, mortality in the ICU, mortality in the hospital and 28-day mortality, sequential organ failure assessment scores at baseline and on study days 1, 3, 7, 14, 21 and 28	N/A
Ghamdi et al.	2016	Saudi Arabia	Retrospective cohort study	Laboratory-confirmed MERS-CoV-infected patients	MERS-CoV	PCR testing of MERS-CoV for both upE and ORF1a gene targets	Medical charts, demographic, clinical and laboratory data	NA	N/A	N/A	Total mortality rate	N/A
Imran Khalid et al.	2016	Saudi Arabia	Retrospective case series	Adult patients intubated for management of ARDS from confirmed MERS-CoV	MERS-CoV	RT-PCR testing of respiratory tract samples for upE gene and ORF1a	Medical records, laboratory values, physical and radiological findings, and follow-up	All subjects had comorbidities	N/A	N/A	ICU survival, 28- and 90-d survival, survival at 1 y from the date of intubation	Not different
Shalhoub et al.	2015	Saudi Arabia	Sequential retrospective cohort study	Confirmed MERS-CoV-infected patients	MERS-CoV	RT–PCR testing of respiratory tract samples or plasma for MERS-CoV ORF 1b, and E genes	Clinical and laboratory examinations	No statistical difference	N/A	Median 1 day [range from 1 day before diagnosis to 1 day after diagnosis]	Total mortality rate	Not different
Mohammad Khalid et al.	2015	Saudi Arabia	A preliminary report of two cases	One confined MERS-CoV patient with normal initial laboratory investigation and one suspected patient	MERS-CoV	PCR testing of MERS-CoV for both upE and ORF1b gene	Medical records	One confined MERS-CoV patient and one suspected patient	From the admission day	3 days before diagnosis	Treatment effects	N/A
Al-Quseer et al.	2015	Kuwait	Case series	Three cases	MERS-CoV	RT-PCR testing of bronchoalveolar lavage fluid for MERS-CoV upE and ORF1a	Medical records	N/A	N/A	The same day or next day	Treatment effects	Drop in hemoglobin level
Al-Hameed et al.	2015	Saudi Arabia	Prospective cohort study	8 MERS-CoV–confirmed cases that required ICU admission	MERS-CoV	RT-PCR testing using nasopharyngeal swabs or tracheal aspirates and upE gene and ORF1a	Demographic, clinical, and laboratory variables	All patients were admitted to the ICU because of respiratory distress, and all with comorbid conditions	From the admission day	N/A	Time of ICU stay, day 3, day 7, and day 14 of ICU admission	N/A
Omrani et al.	2014	Saudi Arabia	Retrospective cohort study	Adults with laboratory-confirmed MERS-CoV infection and pneumonia needing	MERS-CoV	RT-PCR testing of respiratory tract samples for MERS-CoV upE, ORF1b, and N genes	Medical record, laboratory examination tests, and follow-up	No statistical difference	N/A	median 3 days [range 0–8 days]	14-day and 28-day survival from the date of MERS-CoV infection diagnosis	Not obvious, no premature discontinuation secondary to adverse effects

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Table 1 (*continued*)

Authors	Publication year	Region	Study type	Participants enrollment	Type of coronavirus	Diagnostic method of coronavirus	Data collection method	Baseline characteristics before treatment	Time from admission to treatment start	Time from diagnosis to treatment start	Primary endpoint	Treatment-related complications or adverse effects
				ventilation support								
Mohammad Khalid et al.	2014	Saudi Arabia	Case series of 6 patients	Six confirmed MERS-CoV infection patients	MERS-CoV	RT-PCR detection of viral RNA targets upstream of upE gene and ORF1b on sputum samples	Medical records and healthcare screening	4 critically ill (3/4 had comorbid conditions) and 2 mild patients	Critical ill:average of 14.7 days [12–19 days]; mild ill: 1.5 days [1–2 days]	The same day	Total mortality rate and laboratory changes	Not different
Al-Tawfiq et al.	2013	Saudi Arabia	retrospective observational study of 5 cases	Five confirmed MERS patient of critically ill and under mechanical ventilation	MERS-CoV	RT-PCR testing of MERS of upE gene and ORF1a	Medical records	critically ill and under mechanical ventilation	Median 19 days (range 10–22) days	N/A	Total mortality rate, observed laboratory parameters	Inconclusive for critically ill patients
Loutfy et al.	2003	USA	Open-label preliminary study	Patients met the centers for disease control and prevention and World Health Organization criteria for probable SARS	SARS-CoV	Enzyme-linked immumosorbent assay and indirect immunofluorescent assay targeted to the SARS-CoV propagated E6 cells	Clinical and laboratory examinations	No statistical difference	N/A	N/A	Transformation rate to intension care unit, intubation and mechanical ventilation rate, 50% resolution of lung radiographic abnormalities, oxygen saturation	3/9 transferred to the ICU, 1/9 required intubation and mechanical ventilation, 0/9 died in IFN group; and 5/13 transferred to the ICU, 3/13 required intubation and mechanical ventilation, 1/13 died in corticosteroids only group
Zhao et al.	2003	China	RCT	190 patients met the defined SARS diagnostic criteria	SARS-CoV	Diagnosed by clinical criteria	Medical records, laboratory data	Approximately the same	At the time of admission	At the time of admission	Total mortality rate, resolution of pyrexia, respiratory improvement (days), mechanical ventilation rate	N/A
Turner et al.	1986	USA	RCT	51 recruited healthy young adult volunteers	General CoV-229E	Clinical symptoms and ELISA for coronavirus antigen	Laboratory data, clinical outcomes	Healthy volunteers	N/A	N/A	The proportion that met symptom criteria for a cold; Mean nasal symptom score; Mea total symptom score; Mean no. of days with total symptom score > 4	N/A
Zhou et al.	2020	China	Retrospective cohort study	77 adults hospitalized with confirmed COVID-19	SARS-CoV-2	RT-PCR testing of SARS-CoV-2 of ORF1ab and nucleocapsid protein	Medical records, laboratory data, and clinical outcomes	No statistical difference in gender, while different in age and co-morbidities, but no effect on baseline	N/A	N/A	Days from symptom onset to viral clearance, observed laboratory parameters, rate to intension care unit, Circulating cytokine levels, and	Not different, and no adverse event detected.

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Table 1 (*continued*)

Authors	Publication year	Region	Study type	Participants enrollment	Type of coronavirus	Diagnostic method of coronavirus	Data collection method	Baseline characteristics before treatment	Time from admission to treatment start	Time from diagnosis to treatment start	Primary endpoint	Treatment-related complications or adverse effects
								laboratory parameters			biomarkers of inflammation	
Fan-Ngai Hung et al.	2020	Hong Kong, China	Open-label prospective randomized study	127 recruited adult patients with virologically confirmed COVID-19	SARS-CoV-2	RT-PCR testing of SARS-CoV-2 in the nasopharyngeal swab	Clinical symptoms and signs, laboratory data, national early warning score 2,	No statistical difference	From the admission day	From the admission day	The time to providing a nasopharyngeal swab negative for SARS-CoV-2, time to resolution of symptoms, length of hospital stay, and 30-day mortality.	Not statistically different, no patients died during the study.

IFN indicates interferon; MERS-CoV, middle east respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; RT-PCR, real-time polymerase chain reaction; RCT, randomized controlled trials; ARDS, acute respiratory distress syndrome; ICU, intension care unit; upE gene, upstream E protein; ORF 1a, open reading frame 1a.

Table 2
The study designs, treatment strategies, and outcomes of included studies for evaluation of safety, efficacy, tolerability, and treatment-related outcomes of interferon for coronavirus infection in clinical practice.

Authors	Study design	Treatment plan, dosage, frequency [a]	Main outcome (Safety, efficacy, treatment-related outcomes)
Arabi et al. 2018	RCT, standard care +lopinavir/ritonavir and recombinant IFN-β1b VS Standard care +placebo	Lopinavir/ritonavir (400 lopinavir mg/100 mg ritonavir) be administered every 12 h for 14 days. IFN-β1b will be administered as 0.25mg/ml subcutaneous injections on alternate days for 14 days (for a total of seven doses); One placebo will be given every 12 h and will comprise a sucrose tablet or capsule	This trial is ongoing and recruiting patients.
Ghamdi et al. 2016	IFN-α, IFN-β, ribavirin, mycophenolate mofetil, hydrocortisone, or combination	NA	IFN-β and mycophenolate mofetil treatment may associated with increased survival; severity of illness was the greatest predictor of reduced survival.
Imran Khalid et al. 2016	Observational case series	Ribavirin (dose adjusted based on creatinine clearance) and PEG-IFN-α2a combination + methylprednisolone	Those who survived the MERS infection and its complications remained well at 90-day and 1-year. Adverse effects of IFN were not obvious.
Shalhoub et al. 2015	Subcutaneous IFN-α2a+ribavirin (n=13) VS subcutaneous IFN-β1a+ribavirin (n=11)	IH IFN-α2a (180 μg once weekly) +PO ribavirin (loading dose of 2g followed by 600 mg every 12 h); IH IFN-β1a (44 mg 3-times weekly)+PO ribavirin (loading dose of 2g followed by 600 mg every 12 h)	The fatality rate was 85% in IFN-α2a vs 64% in IFN-β1a. Chronic renal impairment, age more than 50 years, and diabetes mellitus were significantly associated with mortality.
Mohammad Khalid et al. 2015	1st patient as treatment and 2nd patient as prophylaxis, ribavirin + IFN-α2b	IH IFN-α2b 180μg once fer week for two weeks; PO ribavirin with a loading dose of 2000mg, and adjusted by creatinine clearance	Both patients complete recovery and discharge home.
Al-Quseer et al. 2015	Case representation and comparison	**Case 1:** IH PEG-IFN-α2a 180 μg + PO ribavirin 400 mg every 12 hours with no loading dose, a second dose of PEG-IFN-α2a was given, ribavirin was discontinued as a result of gradual drop of the hemoglobin; **Case 2:** IH PEG-IFN-α2b) 1.5 μg/kg, a second and third PEG-IFN-α2b was given, associated with mechanical Ventilation and ECOM **Case 3:** Comparison, supportive treatment only	**Case 1:** Discharge home **Case 2:** Recovered from MERS-CoV, but died more than a month later, as a result of multiple hospital acquired infections with multidrug resistant organisms **Case 3:** Died. PEG-IFN-α plus low dose ribavirin seemed to be efficacious for MERS-CoV. No life threatening side effects were witnessed.
Al-Hameed et al. 2015	All patients were treated with antivirals, which included IFN-α2a and ribavirin. Broad spectrum antimicrobials were empirically added	NA	5 patients developed multi-organ system failure (MOSF) during the course of their ICU stay. All 8 patients demonstrated elevation in creatinine kinase (CK) levels during their ICU admission
Omrani et al. 2014	Subcutaneous IF-α2a+Rribavirin (n=20) VS supportive therapy only (n=24);	IH (subcutaneous injection) PEG-IFN-α2a (180 μg per week for 2 weeks) + PO ribavirin (dose based on calculated creatinine clearance), for 8–10 days	Survival rate at 14 days from the data of diagnosis was 70% versus 29% (P=0.004) and at 28 days (30% versus 17%; P=0.054); Adverse effects were similar between groups; Decreased hemoglobin level was more obvious in PEG-IFN + ribavirin group.
Mohammad Khalid et al. 2014	Four confirmed MERS-CoV infection critically ill patients + two confirmed MERS-CoV infection mild patients	IH IFN-α2b 180 μg once per week for 2 weeks; PO ribavirin with a loading dose of 2000mg, and adjusted by creatinine clearance	**Critically ill patients:** average time from admission to treatment was 14.7 days, 3/4 died at last **Mild ill patients:** average time from admission to treatment was 1.5 days, 0/2 died at last Treatment with ribavirin and IFN-α2b may be effective in patients infected with MERS-CoV. Early diagnosis and intervention was a key to increase survival rate.
Al-Tawfiq et al. 2013	Observational case series	**Case 1:** Ribavirin for 5 days, with loading dose of 2000 mg via nasogastric tube, followed by 400 mg PO every 8h +one dose of IFN-α2b 130 mg IH **Case 2:** Ribavirin for 5 days with a loading dose of 2000 mg PO, followed by 400 mg every 8h and two doses of IFN-α2b 100mg IH once per week **Case 3:** Ribavirin for 5 days, with a loading dose of 2000 mg via nasogastric tube followed by 600 mg PO every 8h, one dose of IFN-α2b 144 mg IH **Case 4:** Ribavirin for 9 days, with a loading dose of 2000 mg via nasogastric tube followed by 800 mg via nasogastric tube every 8h, two doses of IFN-α2b 100 mg IH once per week **Case 5:** Ribavirin for 11 days, with a loading dose of 2000 mg via nasogastric tube, followed by 400 mg via nasogastric tube every 8h, and two doses of IFN-α2b 100 mg IH once per week	**Case 1:** Died from multi-organ failure **Case 2:** Drop in platelet Died from multi-organ failure **Case 3:** Pancreatitis developed Died from multi-organ failure **Case 4:** Hemoglobin dropped and bilirubin increased and dialysis was required Died from multi-organ failure **Case 5:** Increased lipase Died from multi-organ failure
Loutfy et al. 2003	Subcutaneous IFN alfacon-1 +corticosteroids VS corticosteroids alone	PO prednisone 50mg bid or IV methylprednisolone 40mg Q12h if not control IV methylprednisolone 500mg qd for 3 days then taper and step down to PO prednisone to complete 20 days; IH interferon alfacone-1 for 10 days starting with 9 μg/d for at least 2 days then 15 μg/d if no response for 8-13 days	Resolution of fever and lymphopenia were similar between groups; The interferon alfacon-1 treatment group had a shorter time to 50% resolution of lung radiographic abnormalities (P =0.001), had better oxygen saturation (P =0.02), resolved their need for supplemental oxygen more rapidly (P =.02), had less of an increase in creatine kinase levels (P =0.03), compared with the group receiving corticosteroids alone.

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Table 2 (*continued*)

Zhao et al. 2003		**Group A:** IV ribavirin 0.4–0.6g qd, and CS 2.0g bid; **Group B:** IV FQ+AZ 0.4g qd, combined with recombinant IFN-α IM 3 000 000 U qd; **Group C:** IV FQ+AZ 0.4g qd, some patients were given recombinant IFN-α IM 3 000 000 U qd，MP 80–160 mg qd for 2–3 days when symptoms worsened; Group D: IV LF 0.2g bid + AZ 0.6g qd, 45 patients were given recombinant IFN-α IM 3 000 000 U qd, high-dose MP 160–1000 mg qd for 5–14 days.	
	A(n=40)	**B(n=30)**	**C(n=60)**	**D(n=60)**	
	Ribavirin	Yes			
	IFN-α	No	Yes	Some 45 patients	
	Antibiotics	CS	AZ+FQ	AZ+FQ	AZ+LF
	MP	No/low-dose	No/low-dose	Low-dose	High-dose
	CS= cefoperazone/sulbactam; AZ=azithromycin; FQ=fluoroquinolone; LF=levofloxacin; MP=methyl prednisolone.				
					A **B** **C** **D**
					Resolution of pyrexia (days) 9.4±3.6 6.7±1.9 7.2±2.8 3.0±1.4
					Respiratory improvement (days) 10.9±7.3 9.8±5.1 7.8±3.9 5.9±2.6
					Require mechanical ventilation 3/40 2/30 8/60 0/60
					Death 2/40 2/30 7/60 0/60
					Resolution of pyrexia and respiratory improvement was significantly better in IFN-α+high-dose methyl prednisolone group.
Turner et al. 1986	Recombinant interferon (rIFN) VS placebo				Recombinant IFN Placebo P-value
					Met symptom criteria for a cold 12/29 (41%) 9/26 (73%) 0.02
					Mean (± SD) nasal symptom score 5.4 ± 5.3 9.2± 7.1 0.03
					Mean (± SD) total symptom score 9.4 ± 8.6 23.2 ± 22.1 0.003
					Mean (± SD) no. of days with total symptom score >4 0.5 ± 0.9 1.6 ± 1.7 0.02
					Recombinant IFN-α2b + Arbidol (n=46) Recombinant IFN and placebo treatment was administered as a nasal spray by using a metered pump device that delivered 0.05 ml per spray (rIFN concentration of $5*10^6$ IU/ml) Inoculate CoV-229E Observe outcome and make a comparison Prophylactic intranasal rIFN effectively shortened the duration and reduced the severity of coronavirus cold symptoms.
Zhou et al. 2020	Either IFN-α2b (n=7) or Arbidol (n=24) VS combination of IFN-α2b + Arbidol (n=46)				IFN-α2b: 5mIU each time, and two times a day, i.e. 10mIU/day, 5mIU IFN-α2b (1ml) were added to 2ml of sterile water and introduced as an aerosol by use of a nebulizer and mask; Arbidol: 200 mg (2 tablets) for each, and three times a day, that's, 600 mg/day. None of the patients developed respiratory distress requiring prolonged oxygen supplementation or intubation; Hepatorenal function was almost the same between groups; Patients who received IFN-α2b (alone or in combination with Arbidol) significantly accelerated the viral clearance; Patients who received IFN-α2b (alone or in combination with Arbidol) has a lower interleukin-6 and c-reaction protein level compared with Arbidol alone; No adverse effects detected.
Fan-Ngai Hung et al. 2020	Triple combination lopinavir-ritonavir, ribavirin, and IFN-β1b group (n=86) VS control group, lopinavir − ritonavir only (n=41)				Combination group: PO lopinavir-ritonavir (lopinavir 400 mg and ritonavir 100 mg) every 12 h (via nasogastric tube to intubated patients), ribavirin 400 mg every 12 h, for 14 days, and IH one to three doses of IFN-β1b, 8 mIU each time, on alternate days (depending on the day of drug commencement); Control group: oral lopinavir-ritonavir (lopinavir 400 mg and ritonavir 100 mg) every 12 h for 14 days. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days) than the control group (12 days; hazard ratio 4.37 [95% CI 1.86-10.24], p=0.001); Antiviral therapy was safe and superior to lopinavir-ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay; Adverse events were not significantly different between the two groups; No patients died during the study.

[a] All patients adopted necessary supportive treatments, range from monitoring, immunoglobulins, corticosteroids, vasopressors, and even to invasive ventilation, renal replacement therapy or ECMO, not listed above.

IH indicates subcutaneous injection; PEG-IFN, pegylated interferon; IFN, interferon; PO, per os; MERS-CoV, middle east respiratory syndrome coronavirus; NA, not available; mIU, million international units; ECMO, extracorporeal membrane oxygenation.

2.5. Statistical analysis

Dichotomous variables were analyzed using Review Manager version 5.3 (Cochrane Collaboration, Oxford, United Kingdom) and the Mantel-Haenszel method. The crude ORs and their 95% confidence intervals (CIs) were calculated. For continuous variables, mean difference (MD) with 95% CI was applied. The single-rate meta-analysis was performed using STATA 15.0 software (Stata Corporation, College Station, Texas, USA), which assigned a weight to each study based on both within-study variance and between-study heterogeneity.

Heterogeneity of these manuscripts was tested using both the chi-square test (with a low p-value indicating high heterogeneity, and p-value $\geq$ 0.1 indicating low heterogeneity) and I^2 index statistics (0% indicating no inter-study heterogeneity) [25]. When I^2 was < 50%, the fixed effects model was applied; otherwise, the random effects model was applied [26]. In all analysis, *P*-value less than 0.05 was considered significant.

3. Results

The initial database search yielded 1073articles (Fig. 1). In addition, six articles were added by manual searching from retrieved study lists and relevant reviews, and two papers added by expert suggestion. After eliminating 161 duplicate articles, 920 titles and abstracts were screened. After comprehensively screening 38 full texts, only 15 studies complied with the eligibility criteria and were included at last. Among these, three were RCTs [18,22], one of which has not published yet [27], four were retrospective cohort studies [6,20,28,29], four were case series [6,19,21,23], one prospective cohort study [30], one open-label preliminary study [17], one open-label prospective randomized study [31], and one retrospective observational study [32].

Turner *et al.* firstly explored whether the prophylactic recombinant IFNs could decrease CoV-229E catch rate or reduce the severity of coronavirus cold symptoms in 1986 in a well-design randomized placebo-control study [22]. They recruited absolutely healthy volunteers for participants. In their study, they found that the cold-catch rate, the mean nasal symptom score, the mean total symptom score, and the mean number of days with total symptom score > 4 were much lower in IFNs prophylaxis group than placebo group, all reached significant difference (Table 2). As a consequence, they concluded that prophylactic intranasal recombinant IFNs effectively shortened the duration and reduced the severity of coronavirus cold symptoms. This trial seemed to be the first research to establish the role of IFNs in antiviral agents.

During the SARS period, Zhao *et al.* conducted a RCT to compare four groups receiving different remedies in 2003 [18]. In their study, IFNs, ribavirin, antibiotics, methylprednisolone were assigned into each group to make a comparison. Regarding the complexity of comprehensive treatment and defect of original design, the results were inconclusive. We could still realize some trends in treatment outcomes,

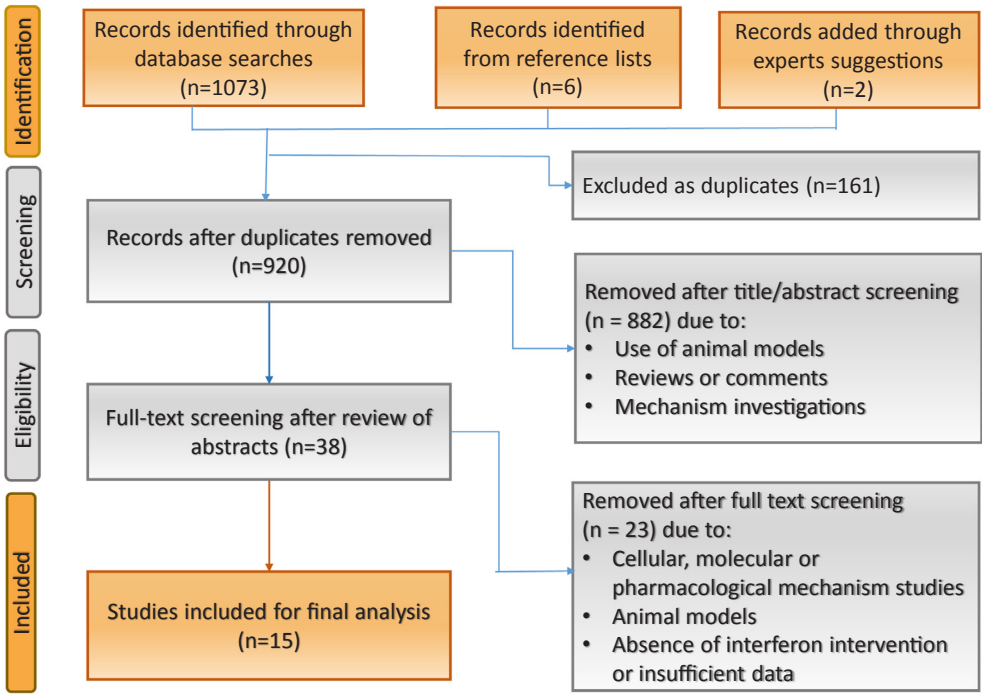

Fig. 1. Flow diagram of studies identification and inclusion.

resolution of pyrexia and respiratory improvements were better in IFN-used group. In addition, combination of IFN-α and high-dose methylprednisolone played the most vital role in resolution of pyrexia and respiratory improvement.

In 2003, an open-label preliminary study was conducted in the USA, in which the authors compared the treatment effects of combination of IFN-α1 and corticosteroids and corticosteroids only for SARS-CoV [17]. Corticosteroids was vital in SARS. According to the study, the combination of IFN-α1 and corticosteroids treatments associated with improved oxygen saturation ($P = 0.02$) and more rapid resolution of radiographic lung opacities ($P = 0.001$), less need for supplemental oxygen ($P = 0.02$), less of an increase in creatine kinase levels ($P = 0.03$) than systemic corticosteroid alone (Table 2).

A relatively large retrospective cohort study included 44 adult patients was designed by Omrani *et al.* in 2014, after the outbreak of MERS-CoV [6]. Of those patients, 20 patients received subcutaneous pegylated interferon-α2a (PEG-IFN-α2a) and oral ribavirin and 24 patients (control group) received supportive treatment only. The 14-day survival rate from the date of diagnosis was statistically higher in the treatment group compared with the control group (70% versus 29%; $P = 0.004$), and 28-day survival rate was still higher in antiviral group (30% versus 17%; $P = 0.054$), though didn't reach significant difference. Adverse effects were similar between groups, decreased hemoglobin level was more obvious in combination of PEG-IFN- α2a and ribavirin group, but there were no life-threating adverse effects were detected, and no premature discontinuation secondary to adverse effects happened.

In 2015, another retrospective cohort study was conducted on 24 MERS cases confirmed by RT-PCR in Saudi Arabia [28]. The authors compared the treatment difference between IFN-α2a and IFN-β1a, of these included patients, 13 received combination of ribavirin and IFN-α2a subcutaneous once weekly and 11 received combination of ribavirin and IFN-β1a subcutaneous three times weekly. The fatality rate was 85% in IFN-α2a vs 64% in IFN-β1a ($P = 0.24$). All patients tolerated well and no obvious severe adverse effects were detected.

Similarly, Al-Quseer *et al.* and Mohammad *et al.* also concluded that IFN plus ribavirin presenting possible efficacious for MERS-CoV, according to their case series experience, regardless of critically ill or mild ill coronavirus-infected patients [19,21]. There was still no life threating adverse effects detected. In a retrospective observational study of five critically ill patients under mechanical ventilation, though all patients died of multi-organ failure eventually, IFNs still played a vital role during supportive treatments. Moreover, several side effects were detected among these five severely ill patients, including drop in platelet, drop in hemoglobin, rise in lipase, and emergence of pancreatitis, but this should not only roughly ascribe to the effect of IFN [32].

On account of insufficient data, inconsistent initial study design, and complexity of human bodies and case variance, statistical synthesizing was impossible regarding abovementioned parameters (Table 1). As for total mortality rate, we investigated the variance between critically and mild ill patients. On the basis of our analysis, the mortality rate was 69.0% (95% confidence interval: 61.2–76.8%, $I^2 = 71.1\%$) and 11.2% (95% confidence interval: 1.9–20.5%, $I^2 = 98.5\%$) in critically and mild ill coronavirus-infected patients. Both presented high heterogeneity and the random effect model was used (Fig. 2).

4. Discussion

Our study systematically investigated the application of type I interferons for HCoVs infection in clinical practice. According to our review, IFNs mainly acted a vital role in rapid resolution of lung abnormalities, respiratory improvements, better oxygen saturation, reduced needs for supplemental oxygen support, and less of an increase in creatine kinase level, which are indispensable for advanced life support and further increase survival. In the meantime, several adverse effects were detected, including drop in platelet, drop in hemoglobin, rise in lipase or bilirubin, and emergency of pancreatitis (only one critically ill case at terminal phage of disease), but these treatment-related outcomes couldn't rule out the effects of other agents like ribavirin, and still need further investigation [33]. These side effects were not life threating, and much easier to solve compared with respiratory distress, intractable hyoxemia, or rapid progress of renal or hepatic failure. The tolerability of type I IFNs was acceptable, and no premature discontinuation of IFN secondary to adverse effects was found in all case. Apart from remedy effect of IFN in coronavirus

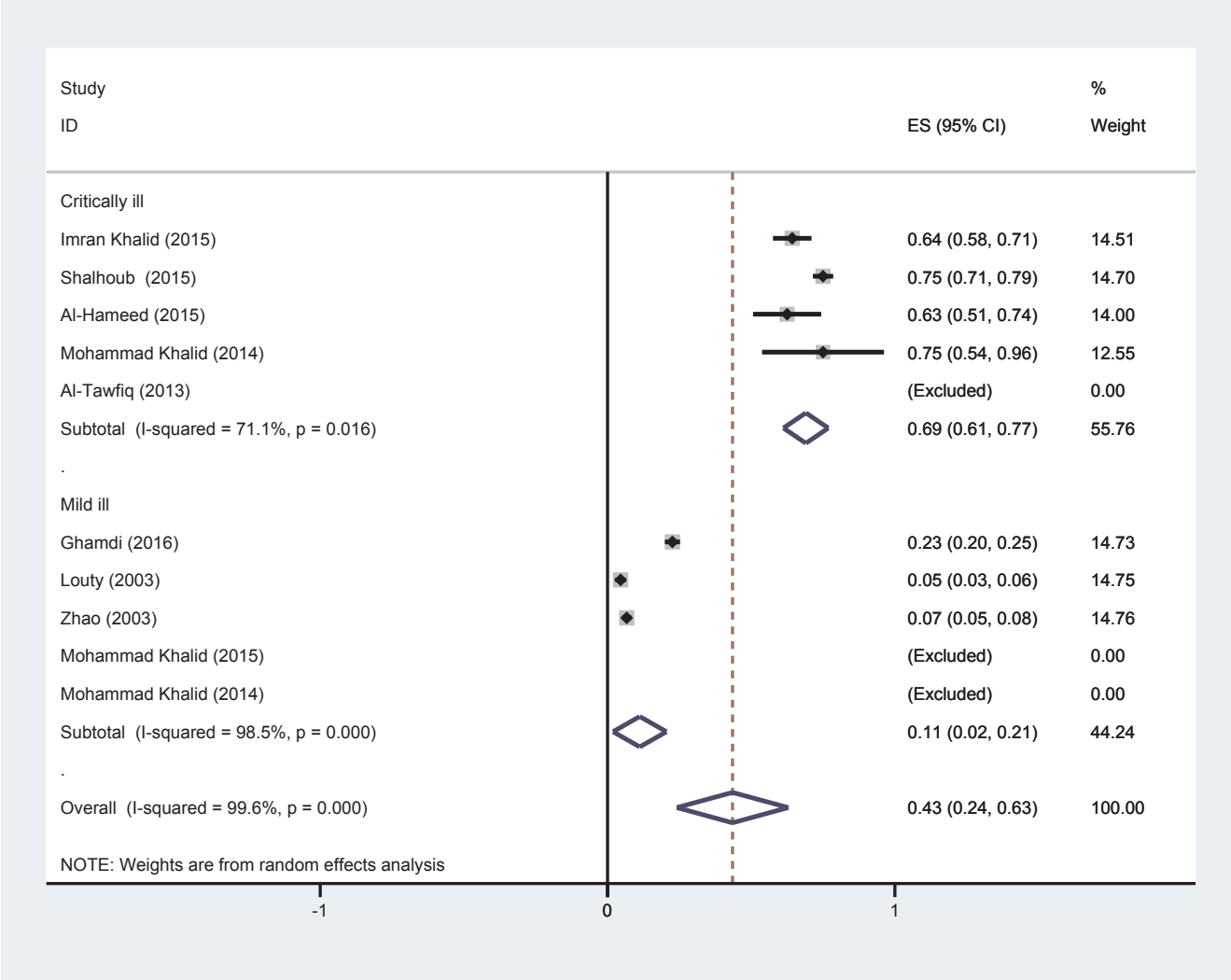

Fig. 2. Forest plot of total mortality rate of MERS or SARS coronavirus-infected patients regarding critically ill and mild ill phenotypes by single-rate meta-analysis. The random effect model was used.

infection described above, we also found the prophylaxis efficacy of IFN in coronavirus infection [22,23], which increased and enhanced the utility of IFN in clinical practice.

Al-Tawfiq *et al.* reported their experience of five critically ill patients that were all died of multi-organ failure after treatment of IFN plus ribavirin and concluded that combination antivirals may not contribute to MERS-CoV-infected patients [32], as preclinical data suggested. In addition, vast majority of adverse effects were reported by them. We think this conclusion may be not objective. They included only critically ill patients with multiple comorbidities, all under mechanical ventilation and, most importantly, diagnosed late in admission. The mortality rate was significantly related with comorbidities, like chronic renal failure, diabetes mellitus, coronary artery disease, hypotension, elevated creatinine, anemia, etc., and age more than 50-year [20,28]. What's more, severity of illness was the greatest predictor of reduced survival in the multivariate analysis [20]. As for adverse effects, this couldn't absolutely ascribe to IFN alone, critically ill patients may suffer from respiratory abnormality, internal environment disturbance, and other disease-related complications. Beyond this, some side effects, at least drop in hemoglobin level, was found related with ribavirin, for its temporal toxicity [21,33].

Cheng *et al.* concluded from their research that even with steroid therapy alone, the mortality rate appeared to be low when compared with conservative treatment for pneumonia caused by SARS-CoV, and the combination of an effective antiviral and steroid was associated with a better outcome [34]. The same results from Omrani *et al.*, a retrospective cohort study, IFN plus ribavirin have a decreased mortality rate than supportive treatment only, and didn't significantly increase adverse effects.

Apart from antiviral therapy, management should primarily focus on strict lung-protective ventilation [35]. Our analysis indicated that the overall mortality rate of coronavirus-infected critically ill patients was about 69.0%, and 11.2% in mild ill patients, in accordance with Imran Khalid's conclusion that delay in remedy would increase mortality [35]. But this caculated mortality rate may be higher that its actual level, for publication bias. As a consequence, early dignosis and intervention would greatly improve outcomes [19]. This also suggested us paying attention to early screen of close contacts and suspected patients of such disease was equally crucial.

Zumla *et al.* summerized the therapeutic options for coronavirus in 2015 [36]. In the absence of a targeted vaccine with proved effects or a pathogen-specific antiviral, broad-spectrum antivirals would still function to limit virus spread. Type I interferons could inhibite the replication of both RNA and DNA viruses at different stages of their replicative cycles, and activate immune cell population to clear virus infection [37]. Combined with clinical and molecular mechanism researches, type I interferon presented as an ideal candidate broad-spectrum antivirals.

There is no doubt exist plenty of limitations in this descriptive analysis. Vast majority of studies are retrospective designs or case series, the baseline characteristics of patients in different studies, comorbidities, intervetion strategies, between-study heterogeneities are all impossilble to ignore. And most importantly, many of these studies reported the effect of combination treatment and not IFN alone, thus this conclusion should be interpreted with great caution. Given insufficient data, inconsistent study design, and case variances, statistical synthesizing is impossible to conduct currently. Data on IFNs in HCoVs are limited, heterogenous and mainly observational. Current data do not allow making regarding robust commendations for the use of IFNs in HCoVs in general or in specific subtype. But we still recommend the clinical use of IFNs in HCoVs within local protocols.

Clinically, combination of IFN and ribavirin are reletively widely adopted to coronavirus onfection, though lack of robust evidence [3]. One well-designed randomized placebo-control trial regarding effects of recombinant IFN-β1b plus opinavir/ritonavir was registed in 2018 and still pending completion [27]. In this RCT, primary and secondary outcomes are mortality in the ICU, mortality in the hospital and 28-day mortality, 90-day mortality, sequential organ failure assessment scores at baseline and on study days 1, 3, 7, 14, 21 and 28. This seems to be the best conceived trial to determine the efficacy of antivirals in coronavirus infection. We are looking forward to the successful administration of this clinical trial, and calling for large-scale prospective randomized studies to assess the role of antivirals for the treatments of coronavirus, to better guide clinical practice.

In conclusion, type I interferons seem to improve respiratory distress, relieve lung abnormalities, present better saturation, reduce needs for supplemental oxygen support. Type I interferons seem to be well tolerated, and don't increase life threating adverse effects. We still recommend type I interferons serving as first-line antivirals in coronavirus infections within local protocols, with timely administration and monitoring of adverse events. And interferons may be used to treat SARS-CoV-2 infected patients. Well-designed large-scale prospective randomized control trials are greatly needed to provide more robust evidence on this topic.

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Ethical approval

Not required.

CRediT authorship contribution statement

Chengjun Yu: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft. **Lian Kang:** Data curation, Formal analysis, Investigation, Software. **Jiadong Chen:** Data curation, Formal analysis, Software. **Na Zang:** Conceptualization, Funding acquisition, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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