Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Interferon therapy in patients with SARS, MERS, and COVID-19: A systematic review and meta-analysis of clinical studies

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ABSTRACT

Concern regarding coronavirus (CoV) outbreaks has stayed relevant to global health in the last decades. Emerging COVID-19 infection, caused by the novel SARS-CoV2, is now a pandemic, bringing a substantial burden to human health. Interferon (IFN), combined with other antivirals and various treatments, has been used to treat and prevent MERS-CoV, SARS-CoV, and SARS-CoV2 infections. We aimed to assess the clinical efficacy of IFN-based treatments and combinational therapy with antivirals, corticosteroids, traditional medicine, and other treatments. Major healthcare databases and grey literature were investigated. A three-stage screening was utilized, and included studies were checked against the protocol eligibility criteria. Risk of bias assessment and data extraction were performed, followed by narrative data synthesis. Fifty-five distinct studies of SARS-CoV2, MERS-CoV, and SARS-CoV were spotted. Our narrative synthesis showed a possible benefit in the use of IFN. A good quality cohort showed lower CRP levels in Arbidol (ARB) + IFN group vs. IFN only group. Another study reported a significantly shorter chest X-ray (CXR) resolution in IFN-Alfacon-1 + corticosteroid group compared with the corticosteroid only group in SARS-CoV patients. In a COVID-19 trial, total adverse drug events (ADEs) were much lower in the Favipiravir (FPV) + IFN-α group compared with the LPV/RTV arm ($P = 0.001$). Also, nausea in patients receiving FPV + IFN-α regimen was significantly lower ($P = 0.03$). Quantitative analysis of mortality did not show a conclusive effect for IFN/RBV treatment in six moderately heterogeneous MERS-CoV studies (log OR = −0.05, 95% CI: (−0.71,0.62), $I^2 = 44.71\%$). A meta-analysis of three COVID-19 studies did not show a conclusive nor meaningful relation between receiving IFN and COVID-19 severity (log OR = −0.44, 95% CI: (−1.13,0.25), $I^2 = 31.42\%$). A lack of high-quality cohorts and controlled trials was observed. Evidence suggests the potential efficacy of several combination IFN therapies such as lower ADEs, quicker resolution of CXR, or a decrease in inflammatory cytokines; Still, these options must possibly be further explored before being recommended in public guidelines. For all major CoVs, our results may indicate a lack of a definitive effect of IFN treatment on mortality. We recommend such therapeutics be administered with extreme caution until further investigation uncovers high-quality evidence in favor of IFN or combination therapy with IFN.

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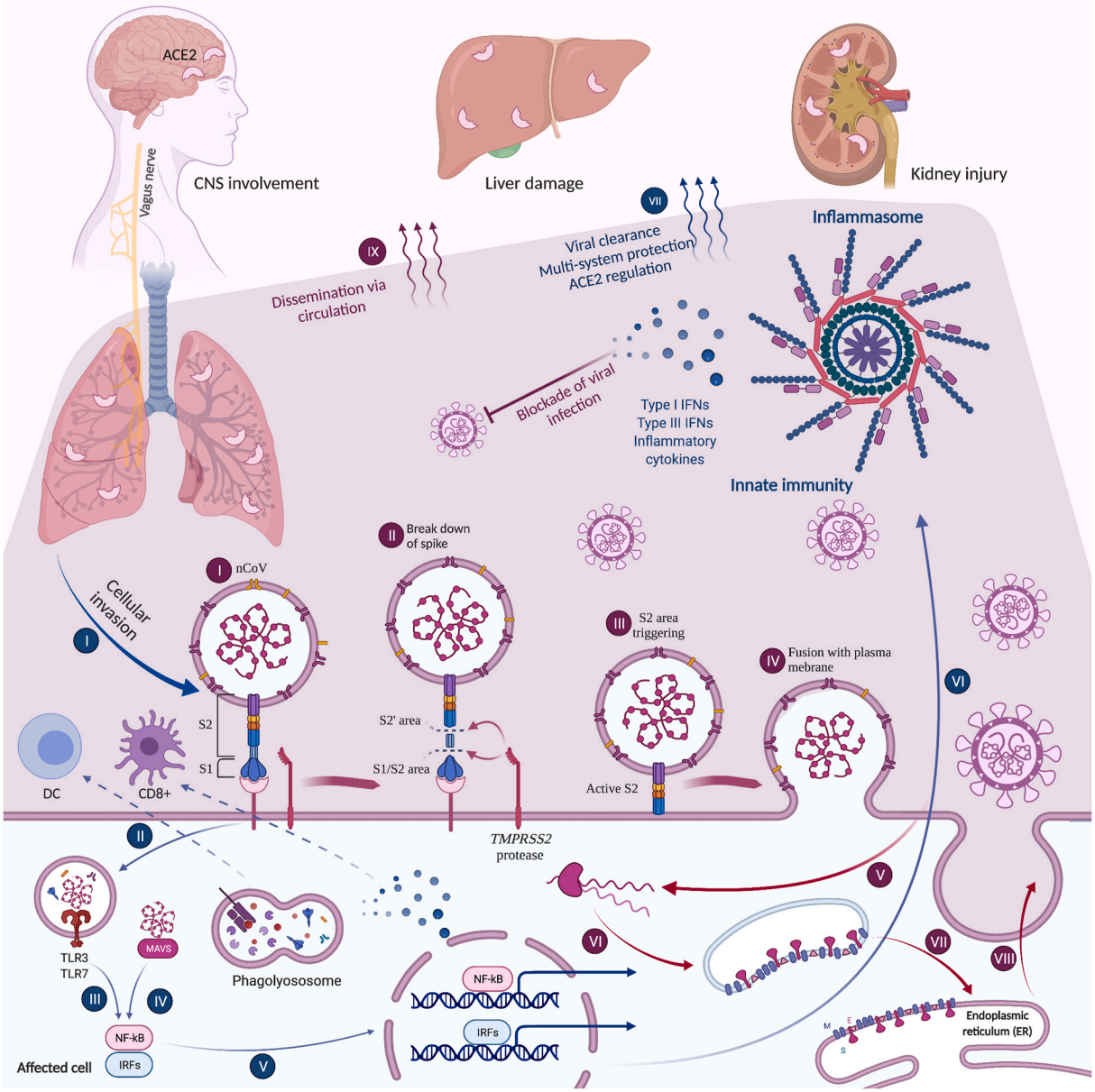

Fig. 1. Role of IFNs and other innate immunity elements in multi-system CoV disease
Among innate elements, inflammasomes, ILs, and IFNs are of high importance (Rasoulinejad et al., 2020). Innate immunity helps to prevent the spread of viruses and affects ACE2 – a major entry path for SARS-CoV2. Therefore, impairments in these elements may contribute to severe clinical disease. COVID-19 similar to its ancestors, may utilize ACE2, which can be mediated by IFN secretion. IFN may inhibit the replication chain. Retrograde synaptic pathway through which SARS-CoV2 infects the central nervous system (CNS) also involves ACE2. Here, dissemination of COVID-19 and its replication have been illustrated *(indigo, I-IX)*. Also, the activation of innate pathways that upregulate IFNs, inflammasome elements, and cytokines has been illustrated *(blue, I-VII)*. Created with BioRender.com.

1. Introduction

Coronaviruses (CoVs) are single-stranded, positive-sense, RNA containing, and enveloped viruses responsible for several major global outbreaks (Poutanen, 2012; Raoult et al., 2020). Global epidemics of atypical pneumonia were first caused by SARS-CoV1 and MERS-CoV in 2002 and 2012, respectively (Al-Osail and Al-Wazzah, 2017; Huang, 2004), and continued to affect the globe with MERS-CoV reappearing in South Korea in 2015 (Ki, 2015). Recently, coronavirus disease 2019 (COVID-19), a disease caused by a novel variant of SARS-CoV known as SARS-CoV2, emerged in Wuhan, China (Cascella et al., 2020; Hanaei and Rezaei, 2020). While showing a lower mortality rate (2.3%) compared to MERS-CoV (9.5%) and SARS-CoV1 (34.4%), the COVID-19 pandemic has raised significant concern. The concern is partly due to the high spreading potential of SARS-CoV2, which influences and causes mortality in a significantly larger population (Petrosillo et al., 2020). The novel virus has an undetermined clinical presentation (Lotfi and Rezaei, 2020), as the recent evidence has suggested non-respiratory and asymptomatic presentations (Wang et al., 2020a). Hence, the diversity in the presentations and hurdles in detecting the virus (Basiri et al., 2020a) suggest the high importance of an effective onset-to-treat period regarding the treatment of COVID-19 patients (Saleki et al., 2020).

Numerous novel efforts have been carried out in the fields of drug discovery, vaccine development (Rahmani et al., 2021), and repurposing of previously suggested candidates for SARS- and MERS-CoV infections. Indeed, researchers have evaluated pharmacologic options, comprising combination interferon (IFN) therapy, traditional medicine, corticosteroid therapy, and antivirals such as ribavirin (RBV), lopinavir (LPV), ritonavir (RTV), oseltamivir, and Remdesivir (REM). However, to date, such efforts have not brought forth adequate success. Nevertheless,

several protocols of past curatives are being used for COVID-19 patients due to a lack of effective treatments or alternatives when extreme adverse drug events (ADE) are indicated. The innate immune system comprises inflammasomes (Rasoulinejad et al., 2020), cytokines, and IFNs which help to clear viral disease and provide multi-system immunological protection (Kopitar-Jerala, 2017; Rostamtabar et al., 2021). It has been shown that SARS-CoV2 is sensitive to type I IFN therapy in human cell lines (Mantlo et al., 2020). A strong association between low type I IFN production and COVID-19 severity has been reported (Bastard et al., 2020; Bost et al., 2020; Zhang et al., 2020b). Nuclear factor-kappa light chain enhancer B (NF-kB) activation in the dendritic cells is crucial for large scale type I IFN production. In a study of COVID-19 by Meyts et al. patients with NF-kB1 or 2 mutations required hospitalization (Meyts et al., 2021), highlighting the functional role of IFNs. Administration with subcutaneous IFN β-1a has been shown to reduce morbidity in COVID-19 infected patients (Davoudi-Monfared et al., 2020). Lung infection in COVID-19 may evolve into systemic involvement. Also, IFNs specially IFN-α2b are capable of preventing lung abnormalities in such patients (Zhou et al., 2021). All of these statements emphasize the role of IFN therapy in severe acute CoVs disease. In addition to lungs, other organs like kidneys (Han and Ye, 2021), liver (Li and Xiao, 2020), and the brain (Baig et al., 2020; Saleki et al., 2020) are also involved. A major entry pathway for SARS-CoV2 is angiotensin-converting enzyme 2 (ACE2), which is present in multiple systems throughout the body. Research has shown IFNs can significantly alter ACE2 profile. ACE2 is regarded as an interferon-stimulated gene (ISG) (Ziegler et al., 2020). Thus, interferon-induced alteration in ACE2 production may be crucial for liability to COVID-19 or its corresponding adverse outcomes (Onabajo et al., 2020). Taken together, noteworthy for future research is that IFNs could play a crucial role in multi-organ involvement prevention of patients with COVID-19. The probable role of IFNs in the multi-organ involvement situation has been enlaced in Fig. 1. Intriguingly, despite contradicting *in vitro* and *in vivo* studies and the absence of sufficient high-quality randomized controlled trials (RCTs) for the use of IFNs to treat SARS-CoV2, and that several studies indicate that it is not suggested for COVID-19 therapy, antivirals such as RBV have been commonly used in combination with IFN during epidemics (Arabi et al., 2020; Morra et al., 2018; Totura and Bavari, 2019). Also, combination therapies in RCTs have been undertaken for the novel CoV (e.g., NCT04276688). Surprisingly, current Chinese guidelines include IFNs as an alternative for combination therapy (WHO, 2020). Such efforts have led to rapidly increasing clinical data on IFN administration for COVID-19 cases. Notably, CoV outbreaks share remarkable similarities, and hence, investigating the experience with the previous spreading of SARS- and MERS-CoVs may assist in discovering an effective treatment or help determine if a candidate should be removed from treatment protocols (Omrani and Shalhoub, 2015). To our knowledge, there have not been any updated systematic reviews of the literature shedding light on the effectiveness of IFN therapy with the past outbreaks in mind. In the present systematic review and quantitative analysis of the evidence, we describe the characteristics of hospitalized cases with MERS-CoV, SARS-CoV1, and SARS-CoV2 patients and assess important treatment outcomes and ADEs of various combinational and non-combinational IFN treatments.

2. Materials and methods

The present systematic review has been conducted compatible with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (Table S1). We designed the protocol to determine our scope, inclusion and exclusion criteria, and outcomes of evaluated studies. The protocol for the present study is provided in further detail in Supplementary Material.

The present study aimed to assess the outcomes of IFN treatments or IFN combination therapies in hospitalized patients infected with MERS-CoV, SARS-CoV, and SARS-CoV2. Comparator therapies comprised placebo, sham therapy, and no intervention. Moreover, researches involving no comparator group were included. Outcome measures were selected according to our protocol. We assessed the efficacy of IFN therapies with or without combination with other pharmacotherapy options. As efficacy comprises numerous parameters, we took account many clinical outcomes, including mortality, discharge, CXR, hospital durations, inflammatory state, ADEs, and disease severity. Due to limited data and the emerging situation of the COVID-19 pandemic, both published and unpublished works were included. No restrictions were considered for the date of publication and language. Our classification for treatment regimens was in line with World Health Organization (WHO) Guidelines. For SARS-CoV, these groups included RBV, LPV/RTV (Kaletra), corticosteroids, IFN, convalescent plasma, and intravenous immunoglobulin (IVIG), which have been previously utilized in similar studies (Stockman et al., 2006). MERS-CoV treatments included IFNs, RBV, LPV/RTV, polyclonal anti-MERS-CoV human immunoglobulins, humanized murine anti-S monoclonal antibodies, nucleoside viral RNA polymerase inhibitors (e.g., REM), peptide inhibitors (e.g., HR2P-M2), and mycophenolate mofetil (MMF) (Organization, 2019). Moreover, possible SARS-CoV2 interventions according to WHO and Centers for Disease Control and Prevention (CDC) Guidelines comprised hydroxychloroquine, chloroquine, REM, oseltamivir, tocilizumab, LPV/RTV, IFN-β, convalescent plasma, IVIG, and corticosteroids (Organization, 2011). Treatments were selected if used in combination with IFN. We included human studies designed as randomized and non-randomized clinical trials, observational clinical studies (e.g., retrospective and prospective cohorts), case reports, and case series.

2.1. Search strategy and study selection

In May 2020, five reviewers (K.S., S.Y., E.H., M.B., M.G.) performed a systematic search. PubMed, Scopus, Cochrane's library, Web of Science (WoS), Global Index Medicus (WHO library), Google Scholar, and Scopus were searched for articles. An additional search was done for unpublished work (e.g., from BioRxiv, MedRxiv), and Reference lists were also screened (grey literature). Unpublished articles were checked, and updated with the published version of each, if available. For all articles, corrections and retractions were also checked. For Google Scholar, the following search strings were developed with the help of a skilled librarian: ("interferon" OR "IFN") AND ("Middle East respiratory syndrome" OR "Middle Eastern Respiratory Syndrome" OR "MERS-CoV" OR "Severe Acute Respiratory Syndrome" OR "SARS-CoV" OR "COVID-19") AND ("Patient" OR "Case" OR "Human") AND (clinical OR case) -"*in vitro*" -review -"narrative review" -monkey -"rat model" -mouse -polymorphism, String #2 "Ribavirin and interferon" AND ("Middle East respiratory syndrome" OR "Middle Eastern respiratory syndrome" OR "MERS-CoV" OR "Severe Acute Respiratory Syndrome" OR "SARS-CoV")), and String 3# ("Interferon Alfacon-1" AND "SARS-COV" OR "MERS-COV") -monkey -"review article". We used hyphen, "-", to exclude phrases associated with preclinical research, as hyphen equals NOT operator in Google Scholar. All final records were imported into EndNote X9 software (Thomson Reuters, San Francisco, CA). Results were collected after duplicate removal by authors (K.S., S.Y., E.H., M.B, M.G.). A three-step screening was followed to determine eligible results by examining each title, abstract, and full-text. Five reviewers (K.S., S.Y., E.H., M.B, M.G.) screened records separately, and disagreements were solved by referring to a third author (A.S.). All included studies were updated until March 2021 (Fan et al., 2020; Fan et al., 2021; Zhang et al., 2020a; Zhou et al., 2020a). Further detail for the search strategy is provided in Supplementary Material.

2.2. Data collection

The following information was retrieved for each study: first author's name, year of publication, location, type of study, the period of data collection, personnel, setting, essential intervals (e.g., onset to treat

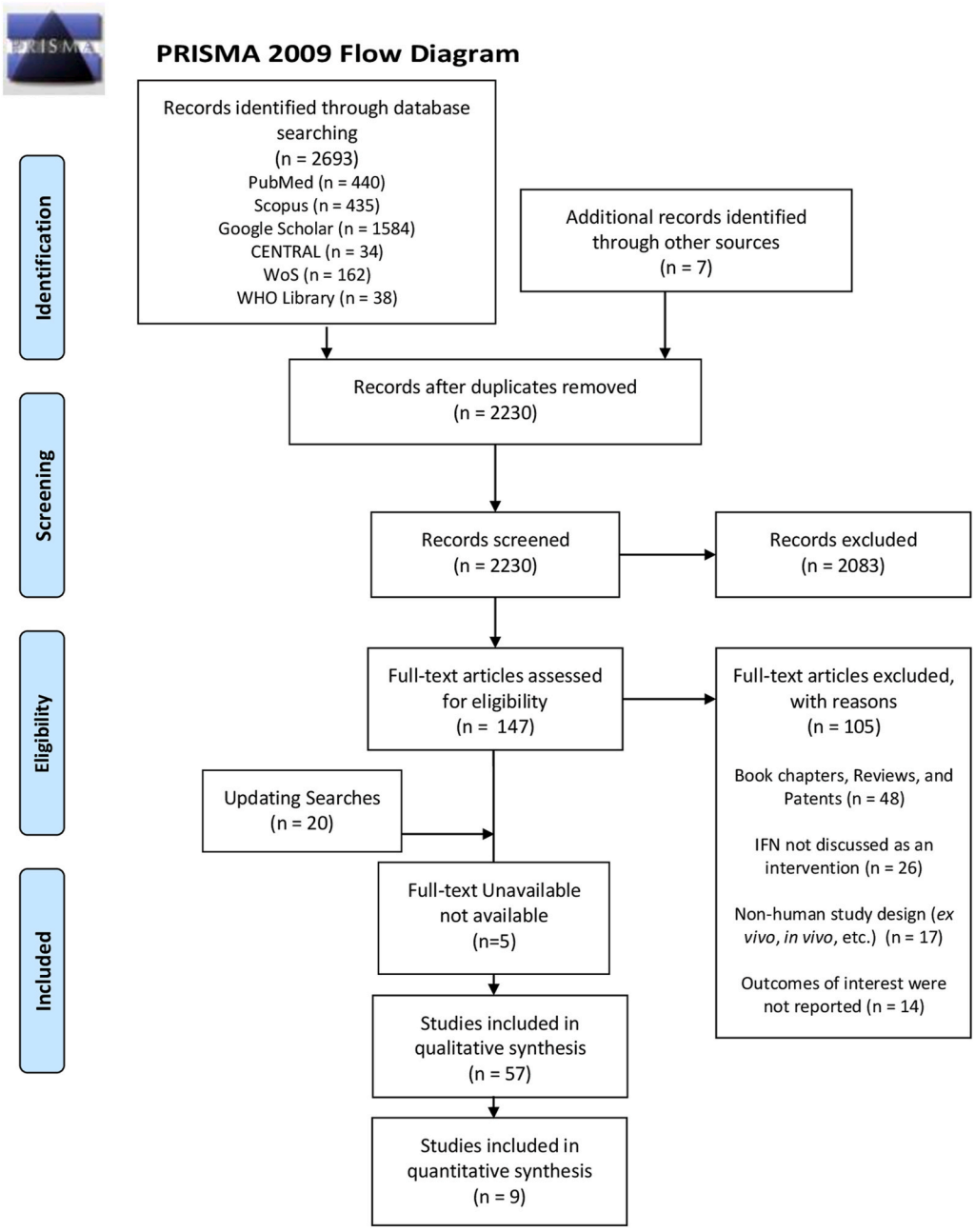

Fig. 2. PRISMA flow diagram.

period), number of patients, gender, disease severity, contact history, comorbidities, diagnostic methods, symptoms, drug information (e.g., name, dosage, duration, along with route and frequency of administration), and non-drug interventions. The extracted outcomes of interest were mortality, the number of discharged patients, inflammatory cytokines, ADEs, and chest imaging results.

Data from full-text of 12 eligible studies were extracted in piloted forms by two reviewers (K.S., S.Y., E.H., M.B, M.G.), independently. Consensus agreement in extracted form was accomplished through discussion with a third-author (A.S.). Table S2 is the table of data extraction.

2.3. Quality assessment

To assess the risk of bias, the following tools were used for each study design: Cochrane risk of bias tool for randomized clinical trials (Sterne et al., 2019), risk of bias in non-randomized studies of interventions (ROBINS-I) tool for non-randomized trials (Sterne et al., 2016), Newcastle-Ottawa Scale (NOS) for Cohort Studies (Penson et al., 2018), National Institute of Health (NIH) tool for case-series and descriptive cross-sectional studies (National Heart), and a recently suggested tool for case reports (Murad et al., 2018).

The studies were further assessed according to the U.S. Preventive Services Task Force scoring protocol, in which Level of Evidence (LOE) is determined as follows (Mohamed et al., 2020a):

Level I: Evidence acquired from a minimum of one properly designed RCT;

Level II-1: Evidence acquired from properly-designed controlled trials with no randomization;

Level II-2: Evidence acquired from a properly-designed cohort or

Table 1
Characteristics of included SARS-CoV-2 studies *(n = 29)*.

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Non-intervention treatments	Age[a]	Intervention
Rui et al. (2020)	China	Case-series (LOE II)	SARS-CoV-2	Pharyngeal swab RT-PCR	28	DM, HTN, SLE, Hyperthyroidism, Hepatitis B	Fever, Cough, Chest tightness, Runny nose, Sore throat, Myalgia, Headache, Fatigue, Cold	LPV, RTV, IVIG, Methylprednisolone, Antibiotic, Flora	M(-44.5), R(11–68)	IFN-α inhalation 5000000U (injected with 2 ml of sterile water, BD) (28)
Jian-ya (2020)	China	Case-series (LOE II)	SARS-CoV-2	RT-PCR	51	CHB, Schizophrenia, HTN, DM	NI	LPV, RTV, Oseltamivir, ARB, IVIG, IM Thymopentin, Glucocorticoid treatment, TCMD, Antibiotics, Bacillus licheniformis capsules, Human Albumin infusion	M(-45), R(16–68), I (34–54)	Inhalation of recombinant human IFN a-1b (51)
Liu et al. (2020b)	China	Case-series (LOE II)	SARS-CoV-2	Swab and BALF RT-PCR	12	CHD, COPD, CKD, HTN, DM	Fever, Cough, Diarrhea, Chill, Myalgia	RBV, Oseltamivir, Immunoglobulin, Corticosteroids	R(10–72), Patient 1: 65, Patient 2: 66, Patient 3: 62, Patient 4: 63, Patient 5: 63, Patient 6: 36, Patient 7: 10, Patient 8: 35, Patient 9: 51, Patient 10: 65, Patient 11: 72, Patient 12: 56	IFN (12)
Liao et al. (2020)	China	Retrospective case-series (LOE II)	SARS-CoV-2	Throat Swab or Lower Respiratory tract RT-PCR	46	Obesity, DM, COPD, Hyperthyroidism, Kidney Stones, Arthrolithiasis.	Fever, Cough, Shortness of breath, Chest tightness, Myalgia, Dizziness, Fatigue, Nausea, Diarrhea, Pharyngalgia, Anorexia, Erythra	Budesonide, Antifungal, NAC, Antiviral	R(10–35)	IFN-α inhalation (46)
Liu et al. (2020)	China	Retrospective case-series (LOE II)	SARS-CoV-2	Nasal and Throat Swab RT-PCR	10	HTN, CVA, Chronic liver disease	Fever, Cough, Chest pain, Phlegm, Sore throat, Headache, Nausea, Anxiety	LPV, ARB, IVIG, Methylprednisolone, Antibiotic, HSA	M(-42), R(30–62), I (34–50), Patient1: 45, Patient2: 30, Patient3: 62, Patient4: 53, Patient5: 51, Patient6: 47, Patient7: 40, Patient8: 33, Patient9: 34, Patient10: 35	RH–IFN– a2b 50 μg BD (9)
Xiao-Wei et al. (2020)	China	Retrospective case series (LOE II)	SARS-CoV-2	Sputum and Throat swab RT-PCR	62	HTN, DM, COPD, CVA, CKD, liver disease	Fever, Cough, Myalgia, Headache, Diarrhea, Expectoration, Haemoptysis	LPV, RT, ARB, IVIG, Corticosteroid, Quinolones, second generation of β-lactam (oral and IV), Flora therapy	M(-41), I(32–52)	IFN-α-2b inhalation 5000000U BD (33)
Huang et al. (2020b)	China		SARS-CoV-2	RT-PCR	36	HTN, Cerebrovascular, Diabetes, CHD, COPD, Chronic	Fever, Cough, Dyspnea, Sputum	RBV, Oseltamivir, IVIG, Corticosteroid, Antibiotic,	M(69.22), S(9.64), R(50–90)	IFN-α inhalation (6)

(*continued on next page*)

Table 1 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Non-intervention treatments	Age[a]	Intervention
		Retrospective case-series (LOE II)				renal diseases, Cancer, Hyperlipidemia, ARDS, Electrolyte disturbance, AKI	production, Myalgia, Fatigue, Diarrhea, Disturbance of consciousness, Haemoptysis	Ganciclovir, umifenovir hydrochloride		
Chen/Zhang et al. (2020a)	China	Retrospective cohort (LOE II)	SARS-CoV-2	RT-PCR OA(57) or clinical diagnostic Criteria OA(44)	134	Cerebrovascular and cardiovascular, Endocrine, tumor, Nervous system disease, Respiratory system disease	Fever, Cough, Shortness of breath, Sore throat, Myalgia, Headache, Diarrhea, Haemoptysis, Chill, Malaise	LPV, RTV, RBV, Oseltamivir, IVIG, Corticosteroid, Antibiotic, Ganciclovir, Thymosin, Antifungal treatment	M(60.78), S (12.98), R(24–83)	Yes
Cheng et al. (2020)	China	Prospective cohort study (LOE II)	SARS-CoV-2	RT-PCR	701	CKD, COPD, HTN, DM, tumor, AKI	Fever, Respiratory symptoms, Proteinuria, Haematuria	LPV/RTV, RBV, Oseltamivir, Glucocorticoids, Antibiotic, RAAS inhibitors, ARB, Ganciclovir, Antidiabetics, Diuretics	M(-63), I(50–71)	Yes (OA(129), D (169))
Zhou et al. (2020b)	China	Cohort (LOE II)	SARS-CoV-2	Throat swab RT-PCR	77	HTN, diabetes, COPD, chronic bronchitis, heart disease, cancer	Fever, Cough, Chest tightness, Runny nose, Sore throat, Myalgia, Headache, Fatigue, Nausea, Diarrhea	ARB	M(IFN group: 41.3, IFN+ARB group: 40.4, ARB: 64.5), R (IFN group: (27–68), IFN+ARB: (25–80), ARB group (37–73))	5 mIU IFN-α-2b (1 ml) was added to 2 ml of sterile water and was nebulized. (53)
Qiu et al. (2020)	China	Retrospective cohort (LOE II)	SARS-CoV-2	Upper nasopharyngeal swabs RT-PCR	36	None	Fever, Cough, Shortness of breath, Runny nose, Sore throat, Headache, Vomiting, Diarrhea	LPV/RTV	M(8.3), S(3.5)	IFN-α by aerosolization (b.i.d.) (36)
Wan et al. (2020)	China	Case-series (LOE II)	SARS-CoV-2	Throat Swab RT-PCR	135	Diabetes, CVD, HTN, Malignancy, Pulmonary Disease, Chronic liver disease, Malignancy	NI	LPV/RTV, Corticosteroid, TCM, Antibiotic	M(47), I(36–55)	IFN or Kaletra (135)
Du et al. (2020)	China	Retrospective case-series (LOE II)	SARS-CoV-2	RT-PCR	85	HTN, DM, CHD, Cerebrovascular diseases, CLD, Malignancy, CKD, COPD	Fever, Cough, Shortness of breath, Chest tightness, Sore throat, Myalgia, Headache, Fatigue, Vomiting, Diarrhea, Anorexia, Abdominal pain	LPV/RTV, RBV, Oseltamivir, ARB, Glucocorticoids, Meropenem, Imipenem/cilastatin, Moxifloxacin, Levofloxacin, Linezolid, Vancomycin, Teicoplanin, Tigecycline, Piperacillin/Tazobactam, Ceftriaxone sodium, Cefoperazone/sulbactam, Ceftazidime tazobactam, Caspofungin, Voriconazole, Fluconazole, Kidney replacement	M(-65.8), S(14.2), R(14–86)	Recombinant human IFN-2b (32)

(*continued on next page*)

Table 1 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Non-intervention treatments	Age[a]	Intervention
								therapy, COVID-19 recovered patient plasma treatment 1		
Fernández-Ruiz et al. (2020)	Spain	Retrospective case series (LOE II)	SARS-CoV-2	Nasopharyngeal swab or Sputum RT-PCR	18	PKD, HTN, prostaticadenocarcinoma, nephropathy, DM, peripheral artery disease, ESRD, coronary artery disease, obesity, Chronic interstitial nephritis, sleep apnea, Hepatitis, cirrhosis, HCC, asthma, bronchiectasis, splenectomy, Acute liver failure, cardiomyopathy, inflammatory bowel disease, primary sclerosing cholangitis, lung cancer, Congenital heart disease, cardiac allograft vasculopathy	Fever, Cough, Shortness of breath, Runny nose, Sore throat, Myalgia, Diarrhea, Hyporexia, Epigastric pain, Malaise	LPV, RTV, IVIG, Methylprednisolone, HCQ	M(-71), S(12.8), Patient 1: 78, Patient 2: 73, Patient 3: 80, Patient 4: 71, Patient 5: 72, Patient 6: 76, Patient 7: 39, Patient 8: 65, Patient 9: 63, Patient 10:72, Patient 11: 79, Patient 12: 73, Patient 13: 76, Patient 14: 46, Patient 15: 64, Patient 16: 67, Patient 17: 63, Patient 18: 38	IFN-β (3)
Cai et al. (2020a)	China	Non-randomized Clinical Trial (LOE II)	SARS-CoV-2	RT-PCR	80	NI	NI	LPV/RTV, antipyretics, analgesics, antiemetic drugs	M(Total: −47, FPV+IFN: −43, LPV/RTV+IFN: −49), I(Total: (35.75–61), FPV+IFN: (35.5–59), LPV/RTV+IFN: (36–61))	IFN-a by aerosol inhalation (5 million U b.i.d.) (80)
Wang et al. (2020a)	China	Case reports (LOE III)	SARS-CoV-2	Throat swab RT-PCR	2	NI	Asymptomatic Couple	LPV/RTV, ARB, TCM	Patient 1: 54, Patient 2: 55	Both Patients: atomization inhalation of recombinant human IFN-α-2b injection (6.0 × 106 IU with 2 ml of sterilized water for injection b.i.d.)
Hung et al. (2020)	China	Phase II, Randomized Clinical Trial (LOE I)	SARS-CoV-2	Nasopharyngeal swab, posterior oropharyngeal, Saliva, Throat RT-PCR	127	DM, HTN, Coronary artery disease, cerebrovascular disease, Hyperlipidemia, Thyroid disease, sleep apnoea, Crohn, Epilepsy, TB, hepatitis, Malignancy, smoker	Fever, Cough, Shortness of breath, Chest tightness, Runny nose, Sore throat, Myalgia, Headache, Nausea, Diarrhea, Phlegm, Malaise, Anosmia, Anorexia	LPV/RTV, RBV, Hydrocortisone, Antibiotics	M(LPV/RTV + RBV + IFN-beta (−51), LPV/RTV (−52)), I(LPV/RTV + RBV + IFN-beta (31–61), LPV/RTV (33.5–62.5))	LPV/RTV + RBV + IFN-β group: Three doses of 8 mIU of IFN-β-1b on alternate days, S.C. (1 ml) (86)
Huang et al. (2020a)	China	Retrospective case-series (LOE II)	SARS-CoV-2	RT-PCR swab	54, due to incomplete data, 40 were included in	HTN, Cardiovascular disease, CLD, Chronic bronchitis	Fever, Cough, Shortness of breath, Chest pain, Sore throat, Myalgia,	LPV/RTV, Corticosteroid, TCM, Fluoroquinolone or β-lactams, Lactobacillus Bifidus triple live bacteria tablets, Novaferon	M(Total(-41), Common(-41), Severe(-37) (of all cases n = 54), I (Total (31–51),	IFN-α-2b (5 mIU diluted with 2 ml sterile water) (common (18/37), data out of 40 cases

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Table 1 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Non-intervention treatments	Age[a]	Intervention
					further analysis		Headache, Dizziness, Fatigue, Nausea, Diarrhea, Phlegm, Anorexia, ARDS		Common (31–51), Severe (27.5–55.5) (of all cases n = 54))	comprising 37 common and 3 severe), Novaferon (Common(13/37)), data out of 40 cases comprising 37 common and 3 severe)
Wang et al. (2020a)	China	Randomized Clinical trial (LOE I)	SARS-CoV-2	Nasopharyngeal or oropharyngeal swab RT-PCR	236	HTN, Diabetes, Coronary heart disease	Fever	LPV/RTV, Corticosteroid, Antibiotic, Vasopressors, Renal replacement therapy	M(Rem+ IFN(-66), Placebo + IFN(-64) (in this study all data is for Remdesivir+ IFN vs. Placebo(with IFN)), I(Rem+ IFN (57–73), Placebo + IFN(53–70))	IFN-α-2b (76)
Lo et al. (2020)	China	Retrospective cohort (LOE II)	SARS-CoV-2	Nasopharyngeal swab RT-PCR	10	HTN, Dyslipidemia, Past Hep B infection	Fever, Cough, Shortness of breath, Runny nose, Sore throat, Myalgia, Dizziness, Nausea, Diarrhea, Abdominal pain	LPV/RTV, Methylprednisolone, Cephalosporins, Quinolones, Macrolides	M(54), I(27–64)	IFN-β-1b (250mcg) (3)
Wang et al. (2020a)	China	Retrospective cohort (LOE II)	SARS-CoV-2	Throat swab RT-PCR	80	HTN, Diabetes, CVD, Cerebrovascular disease, COPD, Renal disease, Liver disease	NI	LPV/RTV, ARB, Corticosteroid, Antibiotic	M(Total:-39, SARS2-Conf:-40, Clinically diagnosed:-39), I (Total:(32–48.5), SARS2-Conf 33–39, Clinically diagnosed: 32–48)	IFN-α (78)
Yu et al. (2020)	China	Retrospective case-series (LOE II)	SARS-CoV-2	Throat swab from the upper respiratory tract, Sputum, and Nasopharyngeal swab RT-PCR	7	Hypothyroidism, Polycystic ovary syndrome	Fever, Cough, Shortness of breath, Diarrhea, Manifestations of Obstetrics, Abdominal pain (labour, premonitory labour), increased fetal movement	Oseltamivir, ARB, Methylprednisolone, Jinyebaidu granules and Lianhuaqingwen capsules, Cephalosporins, Quinolones, or Macrolides, IV Ganciclovir	Patient 1:34, Patient 2: 30, Patient 3: 31, Patient 4: 33, Patient 5: 29, Patient 6: 34, Patient 7: 34	IFN (40 μg daily, atomization inhalation) (7)
Jin et al. (2020)	China	Retrospective cohort (LOE II)	SARS-CoV-2	Throat swabs and sputum RT-PCR	651	Diabetes, Chronic liver disease, Cancer, CKD, CVD, Pregnancy, COPD, Immunosuppression,	Fever, Cough, Shortness of breath, Phlegm, Runny nose, Sore throat, Myalgia, Headache, Fatigue, Nausea, Vomiting, Diarrhea, haemoptysis	LPV/RTV, ARB hydrochloride, Corticosteroid, Antibiotic	M(GI symptoms: 46.14, No GI symptoms: 45.09) I (GI symptoms: 14.19, No GI: 14.45)	IFN-α sprays, ARB hydrochloride capsules (two tab t. i.d. daily), LPV and RTV two tab (500 mg) b.i.d., via the oral route (546)

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Table 1 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Non-intervention treatments	Age[a]	Intervention
Fan et al. (2020)	China	Retrospective cohort (LOE II)	SARS-CoV-2	Swab and Sputum RT-PCR	55	Diabetes, Coronary artery disease, HTN	Fever, Cough, Shortness of breath, Sore throat, Myalgia, Fatigue, Nausea, Vomiting, Diarrhea	LPV/RTV, RBV, Oseltamivir, Arb, Corticosteroid, Antibiotic, Thymalfasin (Refer to Fig. 1 in original publication for more precise information)	M(46.8)	IFN-α-1b (19)
Sun et al. (2020)	China	Cohort (LOE II)	SARS-CoV-2	Nasopharyngeal swab RT-PCR	8		Fever, Cough, Myalgia, Headache, Fatigue, Nausea, Vomiting, Constipation, Polypnea	Oseltamivir, IVIG, Corticosteroid, TCM, Antibiotic, Voriconazole	R(2mon-15yr), Patient 1:8 y, Patient 2: 10 mon Patient3:1 y, 1 mon, Patient4: 2 mon, Patient 5: 2 y, 1 mon, Patient 6: 15 y, Patient7: 13 y, 11 mon, Patient 8: 13 y, 5 mon	Yes (8)
To et al. (2020)	China	Retrospective cohort (LOE II)	SARS-CoV-2	Nasopharyngeal or Throat swabs RT-PCR	23	HTN, Chronic heart disease, Chronic lung disease, Chronic kidney disease, Diabetes, Gout, Hyperlipidemia	Fever, Cough, Shortness of breath, Chest pain, Runny nose, Nose obstruction, Sore throat, Myalgia, Nausea, Diarrhea, Chills, Malaise	LPV, RTV	M (Severe(-66), Mild(-56)) I(Severe (39–75), Mild (37–75))	LPV/RTV with or without RBV or IFN-β-1b was given in (18)
Yuan et al. (2020)	China	Retrospective cohort (LOE II)	SARS-CoV-2	Nasal and Pharyngeal swab, sputum, and BALF RT-PCR	94	HBP, CHD, Diabetes	Fever, Cough, Sore throat, Fatigue, Diarrhea	LPV/RTV, RBV, ARB, Corticosteroid, Favipiravir, IVIG	M(Total(-40), Mild (-19) Moderate (-40), Severe(-63)) I (Total(1–78), Mild (7–39), Moderate (1–78), Severe (32–69))	IFN in combination with either LPV/RTV or RBV (59)
Pan et al. (2020)	China	Cross-Sectional (LOE III)	SARS-CoV-2	Throat swab from the upper respiratory tract RT-PCR	204	Respiratory system disease, Digestive 2, Critical 3)], Digestive system disease, CVD, Nervous system disease, Endocrine system disease, Malignant tumor	Fever, Myalgia, Fatigue, Vomiting, Diarrhea, Abdominal pain, loss of appetite	LPV/RTV, IVIG, Corticosteroid, Antibiotic, Antifungal	M(Total(52.91), no-Digestive symptoms(53.61), Digestive symptoms (52.21 [Mild(24), Moderate(47.91), Severe(60.00), Critical(60.87)]), S (Total(15.98), no-Digestive symptoms(16.10), Digestive symptoms(15.92 [Moderate(14.85), Severe(9.63), Critical(16.44)])	Nebulized IFN-α (96)
Jiang et al. (2020)	China	Clinical Trial[b] (LOE II)	SARS-CoV-2	RT-PCR	60	HTN, DM, COPD, CLD	Fever, Cough, Chest tightness, Sore throat, Headache,	LPV/RTV, Oseltamivir, ARB, IVIG, Corticosteroid, Antibiotics	M(Total(-41), non-Severe(40), Severe (-58)), R(Total (12–74), non-	IFN-β (60)

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Table 1 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Non-intervention treatments	Age[a]	Intervention
							Fatigue, Vomiting, Diarrhea		Severe(12–69), Severe(37–74))	

Abbreviations: ADE: adverse drug reaction, AF: atrial fibrillation, AKI: acute kidney injury, ARB: arbidol, ARDS: acute respiratory distress syndrome, b.i.d: 2 times a day, BALF: bronchoalveolar lavage fluid, BD: 2 times a day, CHB: chronic hepatitis B, CHD: coronary heart disease, CHF: congestive heart failure, CKD: chronic kidney disease, CLD: chronic liver disease, COPD: chronic obstructive pulmonary disease, CrCl: creatinine clearance, CRF: chronic renal failure, CVA: Cerebrovascular accident, CVD: Cardiovascular Disease, D: during, DM: diabetes mellitus, ESRD: end stage renal disease, F: female, G6PD: lucose-6-phosphate dehydrogenase, GI: gastrointestinal, GP: group, HBP: high blood pressure, HBV: hepatitis B virus, HCC: Hepatocellular carcinoma, HCQ: hydroxyl chloroquine, HSA: human serum albumin, HTN: hypertension, I: interquartile, IFN: interferon, IHD: Ischemic Heart Disease, IM: intramuscular, IU: international unit, IVIG: intravenous immunoglobulin, LOE: level of evidence, LPV: lopinavir, M(-number): median, M(number): mean, M: male, MERS: middle east respiratory syndrome, mg: milligram, mIU: milli-international unit q12h: every 12 h, mL: milliliter, NAC: N-acetyl cysteine, No.: number, OA: on admission, OD: on discharge, OF: other format, P: patient, PKD: Polycystic kidney disease, PO: per oral, q8h: every 8 h, QID: 4times a day, R: range, RAAS: renin-angiotensin-aldosterone system, RBV: ribavirin, REM: remdesivir, rhIFN: recombinant human interferon RT-PCR: real-time polymerase chain reaction, RTV: ritonavir, S: standard deviation, SARS-CoV: severe acute respiratory syndrome, SARS: severe acute respiratory syndrome, SC: subcutaneous, sec: second, SLE: systematic lupus erythematous, Tab: tablet, TB: tuberculosis, TCM: traditional Chinese medicine, TCMD: traditional Chinese medicine decoction, TDS: 3times a day, μg: microgram.

[a] Age of participants is reported as reported in each study. Estimated mean values may be found in (*supplementary material*).

[b] Randomization process not stated.

case-control analytic research, preferably from more than one center or study group;

Level II-3: Evidence acquired from multiple time series, both with or without the intervention. Dramatic outcomes in uncontrolled trials may also be taken as such kind of evidence;

Level III: Opinions of validated authorities, in accordance with clinical experience, descriptive research, or reports of expert groups.

2.4. Data synthesis

The protocol details methods used for narrative and quantitative syntheses (Supplementary Material) (College Station).

2.5. Risk of bias across studies

The tool developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (www.gradeworkinggroup.org) was selected for evaluation of bias across studies eligible for meta-analysis. GRADE enables consistent evaluation of the certainty of evidence. It also allows recommendations based on high-quality observational studies. GRADE initially ranks the evidence-based on study design. Studies are then promoted or downgraded according to criteria, including the risk of bias, indirectness, and imprecision (GradePro, 2020).

3. Results

3.1. Study selection

Our search strategy produced 2693 results from all six databases. Moreover, in addition to 42 initially included articles, our updated electronic search results identified 20 relevant results. An additional search yielded seven results. For five studies, full-text could not be obtained (Fig. 2) (Gao et al., 2003; Qing et al., 2005; Wu et al., 2003a, 2003b; Xu et al., 2008). Due to a lack of multilingual collaborators, we used online translators for foreign studies. All foreign articles that were sufficiently translatable via online translators were included (Rui et al., 2020; Xu et al., 2008).

3.2. Study characteristics

Fifty-five distinct publications were included in line with our eligibility criteria. Classified by aetiology, there were 29 eligible clinical studies for SARS-CoV2 (Cai et al., 2020; Fernández-Ruiz et al., 2020; Chen et al., 2020; Cheng et al., 2020; Du et al., 2020; Fan et al., 2020; ; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Pan et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhou et al., 2020b), 26 studies for MERS-CoV (24 distinct reports) (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2017, 2019; Cha et al., 2016; Choi et al., 2016, 2019; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2014, 2015, 2016; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2015, 2018; Sherbini et al., 2017), and seven studies for SARS-CoV1 from which two articles could be retrieved in full-text (Loutfy et al., 2003; Zhao et al., 2003). Three studies reported on a similar population of patients. There, they were merged (Arabi et al., 2017; Arabi et al., 2019; Shalhoub et al., 2018). More specifically, the report by Shalhoub et al. was based on a cohort of 32 cases derived from 330 cases previously described by Arabi et al. in 2017 in a conference paper (Arabi et al., 2017). The multi-center cohort by Arabi et al. (2019) is an extended version that includes 349 cases, most of whom were

Table 2
Characteristics of included MERS-CoV studies ($n = 26$[a]).

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Age[b]	Intervention	Non-intervention treatments
Habib et al. (2019)	Saudi Arabia	Retrospective cohort study (LOE II)	MERS	PCR from respiratory tract samples	63	Diabetes, HTN, hepatitis C, chronic renal failure, and chronic heart disease	Fever, Diarrhea, Abdominal pain, Organ failure	M(59.7) S(18.2)	IFN- α (61)	RBV
Arabi et al. (2019)†	Saudi Arabia	Retrospective cohort study (LOE II)	MERS	Swab RT-PCR	349	DM, Malignancy, CPD, Moderate to severe liver disease, CKD, Chronic Cardiac, Chronic neurological disease, Rheumatological disease	NI	M(IFN and/or RBV (−57.5), No IFN and/or RBV (−58)) I(IFN and/or RBV (47–70), No IFN and/or RBV (41–70))	Combination of RBV and rIFN (117), rIFN alone (9), (rINF type: α 2a 73, α 2b 22, β-1a 31)	RBV, Oseltamivir, Corticosteroid, NO, Renal replacement therapy, Vasopressors, Neuromuscular blockade
Choi et al. (2019)	South Korea	Case report (LOE III)	MERS	Patient 1: RT-PCR of nasopharyngeal aspirate, Patients 2 and 3: RT-PCR	3	None	Fever, Cough, Shortness of breath, Phlegm, Sore throat, Myalgia, Headache, Diarrhea	Patient1 38, Patient 2 33, Patient 3 45	Patient 1: interferon α2a (180 μg/week), Patients 2 and 3: interferon-α2a	LPV, RTV, RBV
Alfaraj et al. (2019)	Saudi Arabia	Retrospective cohort study (LOE II)	MERS	RT-PCR of respiratory samples	314	NI	Fever, Cough, Shortness of breath, Sore throat	M(48.0), S(17.3)	Yes	RBV, Corticosteroid
Shalhoub et al. (2018)†	Mainly Saudi Arabia	Retrospective cohort study (LOE II)	MERS	RT-PCR from a respiratory tract sample (nasopharyngeal swab, sputum, deep tracheal aspirate or BAL	32	Diabetes, Chronic cardiac disease, CRD, CPD, Malignancies including leukemia, lymphoma or solid tumors	Fever, Cough, Shortness of breath, Chest tightness, Runny nose, Sore throat, Myalgia, Headache, Fatigue, Nausea, Vomiting, Diarrhea, Altered consciousness, Wheezing, Abdominal pain	M(-39), I(32–48)	Yes (13)	RBV, Oseltamivir, IVIG, Vasopressors, Renal replacement therapy
Garout et al. (2018)	Saudi Arabia	Retrospective Cohort (LOE II)	MERS	Swab RT-PCR	52	HTN, DM, CRF	NI	R(15–35) for (9), (35–55) for (24), (55–75) for (16), (75–85) for (3)	IFN-α (35)	RBV
Al-Tawfiq et al. (2014)	Saudi Arabia	Case report (LOE III)	MERS	Nasopharyngeal dacron-flocked swabs or sputum samples RT-PCR	3	Rheumatoid arthritis, DM, Dyslipidemia, Chronic HBV carrier	Fever, Cough, Dizziness, Fatigue, Nausea, Vomiting, Diarrhea,	Patient 1: 56, Patient 2: 52, Patient 3: 53	Patients 2 and 3: IFN-α 2b	Patients 2 and 3: RBV, Patient 2: Oseltamivir
Sherbini et al. (2017)	Saudi Arabia	Retrospective cohort (LOE II)	MERS	Swab RT-PCR	29	DM, CKD	Fever, Cough, Shortness of breath, Vomiting, Diarrhea	M(45), S(12)	Yes (19)	RBV, Corticosteroid, Levofloxacin, Meropenem, Linezolid, Piperacillin, Azithromycin
Lee et al. (2017)	South Korea	Retrospective case report (LOE III)	MERS	Swab RT-PCR	1	HTN, Dyslipidemia	Fever, Myalgia, Chills, Dyspnea, Malaise	Patient 1: 68	Pegylated IFN-α-2b 180 mcg Daily	RBV, Oseltamivir, IV ceftriaxone, azithromycin Vancomycin, and meropenem, Tigecycline, IV colistin, Amikacin, and Fluconazole
Kim et al. (2017)	South Korea	Retrospective case report (selected from a cohort) (LOE II)	MERS	RT-PCR for specimen from the lower respiratory tract (collected sputum and endotracheal aspirates)	23, 4 were included in further analysis	DM, HTN, CHD, CKD, Bronchiectasis, Malignancy, Psychiatric disorder, Ankylosing spondylitis	Fever, Cough, Shortness of breath, Myalgia, Headache, Nausea, Confusion	M(-46), I(27–46) Patient 1: 55, Patient 2: 43, Patient 3: 46, Patient 4: 38	Pegylated IFN α -2a S.C (180 μg/ week for 2 weeks) (23)	LPV, RTV, RBV, Ceftazidime, Teicoplanin, Meropenem, and Moxifloxacin, Patient2: Antiemetic, Antitussive, and

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Table 2 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Age[b]	Intervention	Non-intervention treatments
										Non-steroidal anti-inflammatory drugs
Arabi et al. (2017)[†]	Saudi Arabia	Retrospective cohort (LOE II)	MERS	RT-PCR	349	Diabetes, CKD, chronic liver disease	NI	RBV/rIFN M (−57.5) I (47.0–70.0), No RBV/rIFN M (−58.0) I (41.0–70.0)	rIFN α-2a (73) rIFN α-2b (22) rIFN-β-1a (31)	RBV
Rhee et al. (2016)	South Korea	Retrospective case-series (LOE II)	MERS	Oropharyngeal swab sputum, and tracheal aspiration RT-PCR	5	NI	Fever, Cough, Myalgia, Headache, Diarrhea, Abdominal pain, Loose stool	Patient 1: 46, Patient 2: 47, Patient 3: 65, Patient 4: 27, Patient 5: 35	Pegylated IFN α -2a SC 180 mg/ week for 2 weeks (2)	Patients 1, 2, 3, 4, and 5: LPV, Patients 1, 2, 3, 4, and 5: RTV, Patient 2: RBV, Patient 5: Corticosteroid, Patients 1, 2, 3, 4, and 5: Antibiotic, patient3: Ionotropic, Patient 5: Convalescent plasma
Malik et al. (2016)	UAE	Case report (LOE III)	MERS	Nasopharyngeal aspirate RT-PCR	1	32 week pregnant	Fever, Back pain	Patient 1: 32	Peg IFN-α (180 μg/week) (1)	RBV, Oseltamivir, Vancomycin, Meropenem
Kim et al. (2016)	South Korea	Case report (LOE III)	MERS	nasopharyngeal/ oropharyngeal, sputum RT-PCR	1	HTN, DM, Distal Pancreatectomy due to benign pancreatic neoplasm, Chronic dry cough, and Diagnosed with mycobacterium intracellulare	Fever, Cough, Weakness,	Patient 1: 64	IFN-α2a SC180 microg/0.5 ml (1)	LPV, RTV, RBV
Khalid et al. (2016)	Saudi Arabia	Retrospective cohort (LOE II)	MERS	Swab RT-PCR	32 (14 final inclusion in further analysis)	HTN, DM, Respiratory diseases, Obesity, CHF, CKD, Dialysis, IHD, Stroke, Immunosuppression	Fever, Cough, Shortness of breath, Chest pain, Sore throat, Myalgia, Headache, Nausea, Vomiting, Diarrhea, Hemoptysis, Abdominal pain	M(-54), R (23–79)	Peg IFN-α-2b (11)	RBV, Oseltamivir, Methylprednisolone, Antibiotic, NO, Neuromuscular Blockade, Renal replacement therapy, Vasopressor
Choi et al. (2016)	South Korea	Retrospective cohort (LOE II)	MERS	RT-PCR	186	HTN, DM, Malignancy, COPD, CHD, Cerebrovascular disease, CLD, CKD, Hematologic malignancy	Fever, Cough, Shortness of breath, Runny nose, Sore throat, Myalgia, Headache, Nausea, Vomiting, Diarrhea, Sputum, Abdominal pain, Decreased consciousness	M(-55), R (16–86)	Yes (183)	LPV/RTV,RBV, IVIG, Antibiotic, Convalescent serum
Cha et al. (2016)	South Korea	Case report (LOE III)	MERS	Urine, stool, and sputum RT-PCR	1	HTN	Fever, Cough, Shortness of breath, Myalgia, Weakness, Nausea, Vomiting	68	Pegylated IFN- α 180 μg (1)	RBV, Vancomycin, Tigecycline, Colistimethate
Al-Hameed et al. (2016)	Saudi Arabia	Prospective cohort (LOE II)	MERS	Swab RT-PCR	8	DM, HTN, CHF or IHD, Cirrhosis, G6PD deficiency	Fever, Cough, Shortness of breath, Chest pain, Myalgia, Headache, Diarrhea, Sputum production, Altered mental state	M(-56.5), R (26–94)	IFN- α-2b (8)	RBV, Oseltamivir, Corticosteroid, Antibiotic, Norepinephrine, Renal replacement therapy

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Table 2 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Age[b]	Intervention	Non-intervention treatments
Al Ghamdi et al. (2016)	Saudi Arabia	Retrospective cohort (LOE II)	MERS	PCR from clinical nasal swabs or nasopharyngeal aspirates	51	DM, HTN, End stage renal disease, Coronary artery disease, Immunosuppression, Pregnant	Fever, Cough, Runny nose, Sore throat, Vomiting, Diarrhea	M(-54), I (36.5–58)	IFN-β (23, 10 in combination with RBV, 11 IFN- β alone), IFN-α (8, 5 in combination with RBV, 2 IFN-α alone)	RBV, Oseltamivir, Antibiotic, Mycophenolate mofetil
Shalhoub et al. (2015)	Saudi Arabia	Sequential retrospective cohort study (LOE II)	MERS	RT–PCR from a respiratory tract sample	32, 24 included in further analysis (received IFN)	DM, HTN, Chronic renal impairment, Renal failure on hemodialysis, Low ejection fraction	Fever, Cough, Shortness of breath, Chest pain, Phlegm, Vomiting, Diarrhea, Abdominal pain, Confusion	M(IFNa (−65), IFNb (−67), I (IFNa (33–84), IFNb (25–84))	IFN-α-2a (180 mg S.C. once a week) combined with RBV (loading dose of 2 g orally followed by 600 mg orally q12 h): 13, IFN-b1a (44 mg S.C. three times a week) combined with RBV, dosed as above: 11	RBV
Oh et al. (2015)	South Korea	Case Report (LOE III)	MERS	RT–PCR on a sputum specimen	1	NI	Fever, Cough	Patient 1: 35	Pegylated IFN α-2a via S.C. injection at a dose of 180 μg per week for 2 weeks (1)	RBV, Antibiotic, IV Methylprednisolone 1
Khalid et al. (2015)	Saudi Arabia	Case Report (LOE III)	MERS	Patient 1: RT-PCR (UPE, ORF 1b) Patient 2: RT-PCR Patient Routine clinical laboratory tests for influenza, parainfluenza, respiratory syncytial virus, adenovirus, rhino- virus, enterovirus, Epstein–Barr virus, cytomegalovirus, human metapneumovirus, urinary Legionella antigen and serology for Mycoplasma pneumoniae and Chlamydia pneumoniae (no serological results for MERS-CoV)	2	NI	Shortness of breath	Patient 1:52, Patient 2: 42	Pegylated IFN α-2b (2)	RBV, Corticosteroid (Patient 1: IV methylprednisolone, Antibiotic (Patient 1: Broad-spectrum antibiotics like ceftriaxone and azithromycin), Patient 2: Cefuroxime and Azithromycin)
Al-Qaseer (2015)	Kuwait	Case Report (LOE III)	MERS	BAL endotracheal RT-PCR	3	DM, HTN, peptic ulcer, DM, HTN, IHD	Fever, Cough, Shortness of breath, Diarrhea, Night sweats, loss of appetite	Patient 1: 47, Patient 2: 52, Patient 3: 60	Patient 1: IFN-α-2a μg S.C., Patient 2: IFN-α-2b 1.5 μg/kg S.C.	RBV, Patient 1: Oseltamivir, Patient 2: IVIG, Patients 1 and 2: Corticosteroid, Patients 1, 2, and 3: Antibiotic
Omrani et al. (2014)	Saudi Arabia	Retrospective cohort (LOE II)	MERS	RT-PCR testing of respiratory tract samples	44	CHF, Dementia, COPD, Asthma, Rheumatological disease, CLD, DM, Hemiplegia, CKD, Malignant disorder	NI	M(IFN/RBV: 67·4, No IFN/RBV: 64·0) S(IFN/RBV: 18·5,	Pegylated IFN-α -2a S.C. (180 μg/ week for 2 weeks) (20 from treatment group)	RBV, Oseltamivir, Hydrocortisone, Antibiotics, Vasopressor Therapy, IVIG

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Table 2 (*continued*)

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Age[b]	Intervention	Non-intervention treatments
								No IFN/RBV: 18-1)		
Khalid et al. (2014)	Saudi Arabia	Case-series (LOE II)	MERS	Swab RT-PCR	6	IHD, heart failure, Right bundle branch block, Cardiomyopathy heart failure	NI	Patient 1: 74, Patient 2: 84, Patient 3: 76, Patient 4: 54, Patient 5: 48, Patient 6: 17	IFN-α-2b 180 μg S.C. once per weeks for 2 weeks in CrCl 20–50 ml/min (6)	RBV, Methylprednisolone pulse, Antibiotic
Al-Tawfiq et al. (2014)	Saudi Arabia	Case reports (LOE III)	MERS	Swab RT-PCR	5	HTN, DM, CKD, Dialysis, Asthma, Obstructive sleep apnea, Coronary artery disease, AF, ESRD	Fever, Cough, Shortness of breath, Respiratory failure	M(-62), R (24–81) Patient 1: 62, Patient 2: 58, Patient 3: 63, Patient 4: 81, Patient 5: 24)	IFN-α-2b 130 μg S.C. (1), 100 μg S.C.(3), 144 μg S.C. (1)	RBV, Oseltamivir, IV Methylprednisolone, Imipenem, Levofloxacin

Abbreviations: AF: atrial fibrillation, BAL: bronchoalveolar lavage, CHD: coronary heart disease, CKD: chronic kidney disease, CoV: coronavirus, CPD: cephalopelvic disproportion, CRD: chronic respiratory disease, CRF: chronic renal failure, DM: diabetes melitus, ESRD: end stage renal disease, G6PD: Glucose-6-phosphate dehydrogenase, g: grams, HBV: hepatitis B virus, HTN: hypertension, I: interquartile, IFN: interferon, IHD: ischemic heart disease, IVIG: intravenous immunoglobulin, LOE: level of evidence, M: mean, MERS: middle east respiratory syndrome, mL: milliliter, NI: not identified/indicated, NO: nitric oxide, ORF: open reading frame, q12h: every 12 h, RBV: ribavirin, rIFN: recombinant interferon, RT-PCR: reverse transcription polymerase chain reaction, S: standard deviation, SARS: severe acute respiratory syndrome, SC: subcutaneous, μg: microgram, upE: envelope gene.

[a] 24 distinct studies are listed. The three non-distinct studies are marked as †. Among the studies with common participants (2, 5, 11), Arabi et al. is considered the most complete, and was considered for analyses.

[b] Age of participants is reported as reported in each study. Estimated mean values may be found in (*supplementary material*).

previously described in earlier publications. As a result, the three studies were merged according to the 2019 report by Arabi et al. (2019). A sum of 3122 cases, 1665 (53.3%) males and (46.7%) 1457 females, with either suspected or confirmed COVID-19, was explored in 29 distinct reports. The mean age for COVID-19 patients was 47.12 ($n = 1046$) for 12 studies (Chen et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020b; Jin et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Qiu et al., 2020; Sun et al., 2020; Wang et al., 2020a; Yu et al., 2020; Zhou et al., 2020b). After calculating the point estimate of the mean for the rest of the studies, which did not report study setting (Weir et al., 2018), the mean age for all COVID-19 cases reached 51.26 ($n =$ 3122) (Cai et al., 2020; Chen et al., 2020; Cheng et al., 2020; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Pan et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhou et al., 2020b). In 24 distinct MERS publications, 1196 patients, including 587 males, 269 females, and 340 whose gender was not reported, were investigated (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2019; Cha et al., 2016; Choi et al., 2016, 2019; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2014, 2015, 2016; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2015; Sherbini et al., 2017). The mean age for patients with MERS was 53.58 ($n = 464$) for 17 studies (Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Cha et al., 2016; Choi et al., 2019; Habib et al., 2019; Khalid et al., 2014, 2015; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Sherbini et al., 2017), and after estimation of missing mean age reached 53.33 ($n = 1170$) for all eligible MERS studies (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2019; Cha et al., 2016; Choi et al., 2016; Choi et al., 2016, 2019; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2014, 2015, 2016; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2015; Sherbini et al., 2017). Two studies did not report the age of 18 (Khalid et al., 2016) and 8 cases (Shalhoub et al., 2015), respectively. A SARS study reported a mean age of 28.6 ($n = 190$) for one study (Zhao et al., 2003). The overall mean of both studies was 30.39 ($n = 212$) after calculating the mean for the other study (Loutfy et al., 2003; Zhao et al., 2003).

All studies used nucleic acid real-time polymerase chain reaction (RT-PCR) test to detect the presence of CoVs in respiratory (e.g., nasopharyngeal, throat, upper respiratory swab) or urinary specimen (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Cha et al., 2016; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2017; Arabi et al., 2019; Cai et al., 2020; Chen et al., 2020; Cheng et al., 2020; Choi et al., 2019; Choi et al., 2016; Du et al., 2020; Fan et al., 2020Fernández-Ruiz et al., 2020; Garout et al., 2018; Habib et al., 2019; Huang et al., 2020a; Huang et al., 2020b; ; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020Jin et al., 2020; Khalid et al., 2016; Khalid et al., 2015; Khalid et al., 2014; Kim et al., 2017; Kim et al., 2016; Lee et al., 2017; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Pan et al., 2020; Qiu et al., 2020; Rhee et al., 2016; Rui et al., 2020; Shalhoub et al., 2018; Shalhoub et al., 2015; Sherbini et al., 2017; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhou et al., 2020b), except for SARS-CoV1-infected patients who were included according to clinical inclusion criteria and IgG testing (Loutfy et al., 2003; Zhao et al., 2003). A both positive and clear contact history with suspected or confirmed

Table 3
Characteristics of included SARS-CoV studies *(n = 2)*.

Source	Country	Study design	Viral aetiology	Diagnosis	Sample	Reported co-morbidities	Symptoms on admission	Age[a]	Intervention	Non-intervention treatments
Zhao et al. (2003)	China	Randomized Clinical Trial	SARS-CoV-1	SARS clinical inclusion criteria	190	NI	Fever, Cough, Shortness of breath, Chest pain, Myalgia, Headache, Dizziness, Fatigue, Diarrhea, palpitation, Chills/ Rigor	M(28.6) (group A:(33.6), group B:(32.4), group C:(32.5), group D: (30.5)), S(10.3) (group A: (13.9), group B:(12.4), group C:(12.1), group D: (12.3)), R(16–84)	30 cases in group B: recombinant IFN-a, I.M. 3,000,000 U/day, Some cases in group C: IFN-a IM. 3,000,000 U/day), 45 cases in group D: IFN-a I.M. 3000000U/day	RBV, Methylprednisolone, Antibiotic
Loutfy et al. (2003)	Canada	Cohort	SARS-CoV-1	Clinical inclusion criteria and IgG sample testing	22	HTN	NI	M (IFN Alfacon-1 group (−48), Corticosteroids Alone group (−42), R(IFN Alfacon-1 (27–56), Corticosteroids Alone (16–86))	IFN- alfacon-1 (9)	IVIG, Corticosteroids, High-dose methylprednisolone, Antibiotics, OF (Maximum steroid dose, mg (IFN Alfacon-1 group 500 (50–500) Corticosteroids Alone group 70 (40–500)))

Abbreviations: CoV: coronavirus, IFN: interferon, igG: immunoglobulin G, IM: intramuscular, IVIG: intravenous immune globulin, M: mean, O: other formats, R: range, RBV: ribavirin, SARS: severe acute respiratory syndrome, U: unit.

[a] Age of participants is reported as reported in each study. Estimated mean values may be found in *(supplementary material)*.

Table 4
Critical appraisal for cross-sectional studies using the NIH tool.

Source	subject	Clarifying question	Clarifying population	50% eligible persons	Selection from similar population	size justification, power description, or variance and effect estimates provided	the exposure(s) of interest measured prior to the outcome(s) being measured	timeframe sufficient	study examine different levels of the exposure as related to the outcome	the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	the exposure (s) assessed more than once over time	outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	the outcome assessors blinded to the exposure status of participants	loss to follow-up after baseline 20% or less	key potential confounding variables measured	Final quality
Pan et al. (1)	SARS-CoV-2	yes	yes	yes	yes	no	NR	NR	yes	CD	NR	yes	no	no	no	Poor quality

Abbreviations: CD: Cannot be determined, NR: Not Reported, severe acute respiratory syndrome coronavirus.

1. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. The American journal of gastroenterology. 2020;115.

CoV cases or travelling to epidemic areas was reported in 20 (Cai et al., 2020; Chen et al., 2020; Du et al., 2020; Fan et al., 2020; Huang et al., 2020a; Huang et al., 2020b; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Lo et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; Wan et al., 2020; Wang et al., 2020a; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020), 16 (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Cha et al., 2016; Choi et al., 2016, 2019; Garout et al., 2018; Khalid et al., 2014, 2015; Kim et al., 2016, 2017; Malik et al., 2016; Oh et al., 2015; Rhee et al., 2016; Shalhoub et al., 2015; Sherbini et al., 2017), and 2 (Loutfy et al., 2003; Zhao et al., 2003) studies for COVID-19, MERS, and SARS infections, respectively. Moreover, a descriptive study divided COVID-19 patients into cases with "clear" and "unclear" contact history but did not determine whether the "clear" cases had a positive or negative contact history with a SARS-CoV2 patient or a high prevalence area (Pan et al., 2020).

At least one patient was treated with IFN in each selected study. Type of IFN and its combined treatments varied between studies. Additionally, IFN types in all CoV studies included pegylated or recombinant IFN-α2a, IFN-α2b, IFN-β1b, and IFN Alfacon-1 administered via inhalation, subcutaneous (SC) injection, or nebulization (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2017; Arabi et al., 2019; Cai et al., 2020; Cha et al., 2016; Chen et al., 2020; Cheng et al., 2020; Choi et al., 2019; Choi et al., 2016; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Garout et al., 2018; Habib et al., 2019; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Khalid et al., 2016; Khalid et al., 2015; Khalid et al., 2014; Kim et al., 2017; Kim et al., 2016; Lee et al., 2017; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Loutfy et al., 2003; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Pan et al., 2020; Qiu et al., 2020; Rhee et al., 2016; Rui et al., 2020; Shalhoub et al., 2018; Shalhoub et al., 2015; Sherbini et al., 2017; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020b,c; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhao et al., 2003; Zhou et al., 2020b). Non-IFN pharmacological treatments comprised antivirals such as Umifenovir, also called Arbidol (ARB), (Cheng et al., 2020; Du et al., 2020; Fan et al., 2020; Huang et al., 2020b; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liu et al., 2020a; Wang et al., 2020a; Wang et al., 2020b; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhou et al., 2020b), REM (Wang et al., 2020c), Oseltamivir (Du et al., 2020; Fan et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Liu et al., 2020b; Sun et al., 2020; Yu et al., 2020), Ganciclovir (Chen et al., 2020; Cheng et al., 2020; Yu et al., 2020), LPV and RTV (or Kaletra (LPV/RTV)) (Arabi et al., 2017; Cai et al., 2020; Chen et al., 2020; Cheng et al., 2020; Choi et al., 2019; Choi et al., 2016; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Kim et al., 2017; Kim et al., 2016; Liu et al., 2020a; Lo et al., 2020; Pan et al., 2020; Qiu et al., 2020; Rhee et al., 2016; Rui et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yuan et al., 2020), FPV (Yuan et al., 2020), and RBV (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2017; Arabi et al., 2019; Cha et al., 2016; Chen et al., 2020; Cheng et al., 2020; Choi et al., 2019; Choi et al., 2016; Du et al., 2020; Fan et al., 2020; Garout et al., 2018; Habib et al., 2019; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Khalid et al., 2016; Khalid et al., 2015; Khalid et al., 2014; Kim et al., 2017; Kim et al., 2016; Lee et al., 2017; Liu et al., 2020b; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2018; Shalhoub et al., 2015; Sherbini et al., 2017; Yuan et al., 2020; Zhao et al., 2003). Administered curatives also included IVIG (Al-Qaseer, 2015; Chen et al., 2020; Choi et al., 2016; Du et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020b; Jian-ya, 2020; Jiang et al., 2020; Liu et al., 2020a;

Table 5
a and b. Critical appraisal of clinical trials using ROBINS-I and RoB2 tools *(n = 1, 3)*.

Source	Aetiology	Randomization	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Cai et al. (1)	SARS-CoV-2	Non-randomized	low	moderate	NI	low	low	moderate	NI	Moderate risk of bias

Source	Aetiology	Randomization	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk of bias
Hung et al. (2)	SARS-CoV-2	Randomized	low	some concerns	NA	low	high	low	High risk of bias
Wang et al. (3)	SARS-CoV-2	Randomized	low	low	NA	low	low	low	Low risk of bias
Zhao (4)	SARS-CoV-1	Randomized	some concerns	high	NA	low	high	some concerns	High risk of bias

Abbreviations: CD: Cannot be determined, NA: Not applicable, NI: not indicated/identified, NR: Not Reported, SARS-CoV: severe acute respiratory syndrome coronavirus.

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Liu et al., 2020b; Loutfy et al., 2003; Pan et al., 2020; Rui et al., 2020; Shalhoub et al., 2018; Sun et al., 2020; Xiao-Wei et al., 2020), thymopentin (Jian-ya, 2020), corticosteroids (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2017; Arabi et al., 2019; Chen et al., 2020; Cheng et al., 2020; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; ; Huang et al., 2020b; Hung et al., 2020Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Khalid et al., 2016; Khalid et al., 2015; Khalid et al., 2014; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Loutfy et al., 2003; Oh et al., 2015; Omrani et al., 2014; Pan et al., 2020; Rhee et al., 2016; Rui et al., 2020; Shalhoub et al., 2018; Sherbini et al., 2017; Sun et al., 2020; Wan et al., 2020; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhao et al., 2003), antibiotics such as imipenem, meropenem, cilastatin, quinolones, cephalosporins, and macrolides (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq et al., 2014; Cha et al., 2016; Choi et al., 2016; Du et al., 2020; Fan et al., 2020; Huang et al., 2020a; Hung et al., 2020; Jiang et al., 2020; Jin et al., 2020; Khalid et al., 2014, 2015, 2016; Kim et al., 2017; Lee et al., 2017; Lo et al., 2020; Loutfy et al., 2003; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Pan et al., 2020; Rhee et al., 2016; Sherbini et al., 2017; Sun et al., 2020; Wan et al., 2020; Wang et al., 2020b, 2020c; Yu et al., 2020; Zhao et al., 2003; Zhou et al., 2020b), albumin (Jian-ya, 2020; Liu et al., 2020a), and traditional Chinese medicine (TCM) (Huang et al., 2020a; Jian-ya, 2020; Sun et al., 2020; Wan et al., 2020; Wang et al., 2020a). Non-drug interventions included ventilation (both invasive and non-invasive) (Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq et al., 2014; Arabi et al., 2017; Arabi et al., 2019; Cha et al., 2016; Chen et al., 2020; Cheng et al., 2020; Choi et al., 2016; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Habib et al., 2019; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Khalid et al., 2016; Khalid et al., 2015; Khalid et al., 2014; Kim et al., 2017; Lee et al., 2017; Liao et al., 2020; Liu et al., 2020b; Loutfy et al., 2003; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2018; Shalhoub et al., 2015; Sherbini et al., 2017; Sun et al., 2020; Wan et al., 2020; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Zhao et al., 2003), continuous renal replacement therapy (CRRT) (Arabi et al., 2017, 2019; Khalid et al., 2014; Omrani et al., 2014), hemodialysis (Choi et al., 2016), Continuous Positive Airway Pressure (CPAP) (Fernández-Ruiz et al., 2020; Zhao et al., 2003), nutrition therapy (Jian-ya, 2020), extracorporeal membrane oxygenation (ECMO) (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Alfaraj et al., 2019; Arabi et al., 2017, 2019; Chen et al., 2020; Choi et al., 2016; Fan et al., 2020; Garout et al., 2018; Khalid et al., 2014; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2018; Wan et al., 2020; Wang et al., 2020b, 2020c), electrolyte correction (Cai et al., 2020), oral or IV rehydration (Cai et al., 2020), prone positioning (Arabi et al., 2017; Khalid et al., 2014; Omrani et al., 2014; Shalhoub et al., 2018), blood transfusion (Al-Qaseer, 2015; Arabi et al., 2017; Omrani et al., 2014; Shalhoub et al., 2018), NO therapy (Arabi et al., 2019; Shalhoub et al., 2018), tracheostomy (Cha et al., 2016; Khalid et al., 2016; Lee et al., 2017; Shalhoub et al., 2018), intubation (Al-Hameed et al., 2016; Loutfy et al., 2003), and oxygen therapy (e.g., via nasal cannula) (Al-Hameed et al., 2016; Cai et al., 2020; Cha et al., 2016; Fernández-Ruiz et al., 2020; Huang et al., 2020b; Hung et al., 2020; Khalid et al., 2015; Liu et al., 2020a; Lo et al., 2020; Qiu et al., 2020; Rhee et al., 2016; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Yu et al., 2020). Several studies reported patients' initial symptoms on admission, including fever, cough, shortness of breath, sputum or phlegm production, runny nose, nose obstruction, sore throat, myalgia, headache, dizziness, asthenia, and GI symptoms (e.g., diarrhea, nausea, and vomiting) (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Cha et al., 2016; Chen et al., 2020; Cheng et al., 2020; Choi et al., 2019; Choi et al., 2016; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Habib et al., 2019; Huang et al.,

Table 6
Critical appraisal for case-series using NIH tool.

Source	Subject	Clarifying question	Clarifying population	cases consecutive	Comparability of subjects	Clarifying interventions	Clarifying outcome	Length of follow up	Statistical method	Result	Final quality
Wan et al. (1)	SARS-CoV-2	yes	yes	no	no	yes	yes	yes	yes	yes	Good
Du et al. (2)	SARS-CoV-2	yes	yes	yes	no	no	yes	yes	yes	yes	Fair
Ruiz et al. (3)	SARS-CoV-2	yes	yes	no	no	yes	yes	yes	yes	yes	Good
Huang et al. (4)	SARS-CoV-2	yes	yes	no	no	yes	yes	yes	yes	yes	Good
Yu et al. (5)	SARS-CoV-2	yes	yes	no	no	yes	yes	yes	yes	yes	Good
Rui et al. (6)	SARS-CoV-2	yes	yes	yes	no	yes	CD	No/CD	no	CD	Poor
Jian-ya (7)	SARS-CoV-2	yes	yes	yes	CD	yes	yes	yes	yes	yes	Good
Liu et al. (8)	SARS-CoV-2	yes	yes	yes	yes/CD	No/NA	yes	no	yes	yes	Fair
Liao et al. (9)	SARS-CoV-2	yes	yes	No/NR	yes/CD	No/NA	yes	yes	yes	yes	Fair
Liu et al. (10)	SARS-CoV-2	yes	yes	yes	yes/CD	yes	yes/no	no	yes	yes	Good
Xu et al. (11)	SARS-CoV-2	yes	yes	yes	yes	yes	yes	no	yes	yes	Good
Chen/ Zhang et al. (12, 13)[a]	SARS-CoV-2	yes	yes	yes	CD	yes/no	yes	yes	yes	yes	Fair
Khalid et al. (14)	MERS-CoV	yes	yes	yes	yes	yes	yes	yes	no	yes	Good
Rhee et al. (15)	MERS-CoV	no	yes	yes	yes/CD	yes	yes	yes	yes	yes	Good

Abbreviations: CD: Cannot be determined, MERS-CoV: Middle-Eastern respiratory syndrome coronavirus, NA: Not applicable, NR: Not Reported, SARS-CoV: severe acute respiratory syndrome coronavirus.

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[a] This paper was published as Zhang et al. (13) with 134 cases, and comparative study design. Please refer to results section of the manuscript for quality assessment of the extended version of this study.

2020a; Huang et al., 2020b; Hung et al., 2020; Jiang et al., 2020; Jin et al., 2020; Khalid et al., 2016; Kim et al., 2017; Kim et al., 2016; Lee et al., 2017; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Malik et al., 2016; Oh et al., 2015; Pan et al., 2020; Qiu et al., 2020; Rhee et al., 2016; Rui et al., 2020; Shalhoub et al., 2018; Shalhoub et al., 2015; Sherbini et al., 2017; Sun et al., 2020; To et al., 2020; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhao et al., 2003; Zhou et al., 2020b). COVID-19, MERS, and SARS studies mentioned 20 (Fan et al., 2020; Liao et al., 2020; Liu et al., 2020a; Lo et al., 2020; Qiu et al., 2020; Rui et al., 2020; Wang et al.,

Table 7
Critical appraisal for included Cohorts via the NOS tool.

Source	Aetiology	Selection 1-representativeness	Selection 2-non exposed	Selection 3-Ascertainment of exposure	Selection 4-outcome of interest	Comparability	Outcome 1-assessment	Outcome 2-length of follow up	Outcome 3-adequate length of following	Final quality
Zhou et al. (1)	SARS-CoV-2	1(b)	1(a)	1(a)	Yes(a)	2(a-b)	1(a)	1(a)	0(d)	Good quality
Qui et al. (2)	SARS-CoV-2	1(a)	1(a)	0(e)	1(a)	1(b)	1(b)	1(a)	0(d)	Poor quality
Lo et al. (3)	SARS-CoV-2	1(b)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	0(d)	Poor quality
Wang et al. (4)	SARS-CoV-2	1(b)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	0(d)	Poor quality
Jin et al. (5)	SARS-CoV-2	1(a)	1(a)	1(a)	0(b)	0(c)	1(b)	1(a)	1(b)	Good quality
Fan et al. (6)	SARS-CoV-2	1(a)	1(a)	1(a)	0(b)	0(c)	1(a)	1(a)	1(a)	Fair quality
Sun et al. (7)	SARS-CoV-2	1(a)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	0(d)	Fair quality
To et al. (8)	SARS-CoV-2	1(a)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	0(d)	Poor quality
Yuan et al. (9)	SARS-CoV-2	1(a)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	0(d)	Poor quality
Cheng et al. (10)	SARS-CoV-2	1(a)	1(a)	1(a)	1(a)	2(a-b)	1(a)	1(a)	1(a)	Good quality
Huang et al. (11)	SARS-CoV-2	0(c)	0(c)	1(a)	1(a)	0(c)	1(a)	1(a)	0(d)	Poor quality
Habib et al. (12)	MERS-CoV	0(c)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	1(a)	Poor quality
Arabi et al. (13)	MERS-CoV	1(a)	1(a)	1(a)	1(a)	2(a-b)	1(b)	1(a)	1(a)	Good quality
Alfaraj et al. (14)	MERS-CoV	0(d)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	1(a)	Poor quality
Garout et al. (15)	MERS-CoV	0(d)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	1(a)	Poor quality
Sherbini et al. (16)	MERS-CoV	0(d)	1(a)	1(a)	1(a)	0(c)	1(a)	1(a)	1(a)	Poor quality
Khalid et al. (17)	MERS-CoV	0(d)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	1(a)	Poor quality
Choi et al. (18)	MERS-CoV	0(d)	1(a)	1(a)	1(a)	0(c)	1(a)	1(a)	1(a)	Poor quality
Al-Hameed et al.(19)	MERS-CoV	1(b)	0(c)	1(a)	1(a0	0(c)	0(c)	1(a)	1(a)	Poor quality
Al-Ghamdi et al.(20)	MERS-CoV	0(d)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	1(a)	Poor quality
Shalhoub (2015) et al. (21)	MERS-CoV	1(a)	1(a)	1(a)	1(a)	2(a-b)	1(b)	1(a)	1(a)	Good quality
Omrani et al. (22)	MERS-CoV	1(a)	1(a)	1(a)	1(a)	0(c)	1(b)	1(a)	1(a)	Poor quality
Loutfy et al. (23)	SARS-CoV-1	1(a)	1(a)	1(a)	1(a)	2(a-b)	1(b)	1(a)	1(a)	Good quality

Abbreviations: CD: Cannot be determined, MERS-CoV: Middle-Eastern respiratory syndrome coronavirus, NA: Not applicable, NR: Not Reported, SARS-CoV: severe acute respiratory syndrome coronavirus.

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Table 8
Critical appraisal for case-reports via the tool recently suggested by Murad et al. (1).

Source	Aetiology	Selection	Ascertainment	Causality	Reporting	Final quality
Wang et al. (2)	SARS-CoV-2	unclear	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Choi et al. (3)	MERS-CoV	unclear	Yes/no	No/no/no/yes	yes	High Risk of Bias
Al-Tawfiq et al. (4)	MERS-CoV	unclear	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Kim et al. (5)	MERS-CoV	Yes	Yes/yes	Yes/no/no/yes	yes	Low risk of bias
Malik et al. (6)	MERS-CoV	unclear	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Kim et al. (7)	MERS-CoV	unclear	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Cha et al. (8)	MERS-CoV	unclear	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Oh et al. (9)	MERS-CoV	Yes	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Khalid et al. (10)	MERS-CoV	Yes	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Lee et al. (11)	MERS-CoV	Yes	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Al-Tawfiq et al. (12)	MERS-CoV	unclear	Yes/yes	No/no/no/yes	yes	High Risk of Bias
Tawalah et al. (13)	MERS-CoV	unclear	Yes/yes	No/no/no/yes	yes	High Risk of Bias

Abbreviations: CD: Cannot be determined, MERS-CoV: Middle-Eastern respiratory syndrome coronavirus, NA: Not applicable, NR: Not Reported, SARS-CoV: severe acute respiratory syndrome coronavirus.

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2020a), 42 (Alfaraj et al., 2019; Choi et al., 2016; Khalid et al., 2014), and no asymptomatic patients, respectively. Among MERS studies, one excluded the symptomatic cases ($n = 38$) from further analysis (Alfaraj et al., 2019).

Furthermore, study characteristics including country, study design, age of participants, comorbidities, symptoms on admission, and type,

dosage, and administration route of both IFN and non-IFN treatments have been summarized (Tables 1–3).

3.3. Assessment of risk of bias

29 COVID-19 studies (Cai et al., 2020; Chen et al., 2020; Cheng et al., 2020; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Pan et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhou et al., 2020b) were included, four of which were clinical trials (Cai et al., 2020; Hung et al., 2020; Jiang et al., 2020; Wang et al., 2020c). Among trials, two were randomized (Hung et al., 2020; Wang et al., 2020c). An RCT was of a high risk of bias; due to that, the assessors were aware of the intervention, and no efforts to resolve the possibility of bias were discussed (Hung et al., 2020). The other was of low risk of bias (Wang et al., 2020c). Also, there were two non-randomized trials (Cai et al., 2020; Jiang et al., 2020), which had a moderate risk of bias (Cai et al., 2020), and one was not assessed due to no statement on the randomization process (in the protocol or the publication) (Jiang et al., 2020). A poor quality cross-sectional study was also included (Pan et al., 2020). 11 cohorts of COVID-19 cases were critically appraised (Cheng et al., 2020; Fan et al., 2020; Huang et al., 2020a; Jin et al., 2020; Lo et al., 2020; Qiu et al., 2020; Sun et al., 2020; To et al., 2020; Wang et al., 2020b; Yuan et al., 2020; Zhou et al., 2020b). Of those, three had good quality (Cheng et al., 2020; Jin et al., 2020; Zhou et al., 2020b), two had a fair quality (Fan et al., 2020; Sun et al., 2020), and others had a poor quality (Cai et al., 2020; Huang et al., 2020a; Lo et al., 2020; To et al., 2020; Wang et al., 2020b; Yuan et al., 2020). 12 case-series (Chen et al., 2020; Du et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Jian-ya, 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Rui et al., 2020; Wan et al., 2020; Xiao-Wei et al., 2020; Yu et al., 2020) were also assessed. Results showed seven to be of good quality, while four had a fair quality (Du et al., 2020; Liao et al., 2020; Liu et al., 2020b; Xiao-Wei et al., 2020), and one was of poor quality (Jian-ya, 2020). Importantly, a case-series was pre-printed (Chen et al., 2020), but was later published with a comparator group. The published version showed poor quality due to a lack of comparability according the NOS tool (Zhang et al., 2020a). The only included case report was of a high risk of bias (Wang et al., 2020a) (Tables 4–8).

From 26 studies of MERS (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2017, 2019; Cha et al., 2016; Choi et al., 2016, 2019; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2014, 2015, 2016; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2015, 2018; Sherbini et al., 2017), two were good quality case-series (Khalid et al., 2014; Rhee et al., 2016). There were 11 cohorts (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Alfaraj et al., 2019; Arabi et al., 2019; Choi et al., 2016; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2016; Omrani et al., 2014; Shalhoub et al., 2015; Sherbini et al., 2017), two of which were good quality (Arabi et al., 2019; Shalhoub et al., 2015), while the other nine were of poor quality, mostly due to low comparability scores and not adjusting for confounding factors (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Alfaraj et al., 2019; Choi et al., 2016; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2016; Omrani et al., 2014; Sherbini et al., 2017). From 11 case reports in MERS (Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Cha et al., 2016; Choi et al., 2019; Khalid et al., 2015; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015), ten were of a high risk of bias, mainly because of lacking any description of suitable selection processes (Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Cha et al., 2016; Choi et al., 2019; Khalid et al., 2015; Kim et al., 2016; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015). Furthermore, only one study had a low risk of bias (Kim et al., 2017).

Two studies were included in SARS (Loutfy et al., 2003; Zhao et al., 2003). One was a randomized clinical trial (Zhao et al., 2003) with a high risk of bias, and the other was a cohort study of good quality (Loutfy et al., 2003).

Finally, we provided the results for the quality of evidence by the LOE tool (Tables 1–3). For COVID-19 studies, only one study declared a conflict of interest (Wang et al., 2020c), and others did not have any competing interests to declare. For MERS studies, two studies declared the existence of a conflict of interest (Arabi et al., 2020; Omrani et al., 2014). Finally, SARS studies declared no conflict of interest. A few studies did not mention whether competing interests were present (Table S2).

3.4. Mortality

3.4.1. COVID-19

Out of 29 clinical COVID-19 studies, three did not specify mortality (Cai et al., 2020a; Fan et al., 2020; Zhou et al., 2020b). A total of 414 cases expired in 26 studies (Chen et al., 2020; Cheng et al., 2020; Du et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Pan et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020). Interestingly, 14 studies reported no mortality (Huang et al., 2020a; Hung et al., 2020; Jiang et al., 2020; Liao et al., 2020; Liu et al., 2020a, 2020b; Lo et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; Wang et al., 2020a; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020), and all cases in three studies died (Chen et al., 2020; Du et al., 2020; Huang et al., 2020b). This was, in part, due to that some studies strictly sampled cases with a fatal outcome or survivors. Interestingly a study of 101 non-survivors was published with 134 cases, comprising a new comparator group of 33 survivors (Zhang et al., 2020a).

A recent open-label RCT showed no mortality in both LPV/RTV + RBV + IFN-β ($n = 86$) and LPV/RTV groups ($n = 41$) (P = 1.00) (Hung et al., 2020). A double-blind, placebo-controlled, multicenter RCT included 158 and 78 cases as intention-to-treat population in REM + IFN and Placebo + IFN groups, respectively. Results showed a 28-day Mortality of 22 (14%) in REM group (for REM + IFN: 29 (18%)) and 10 (13%) in the placebo group (for placebo + IFN: 15 (19%)) (risk difference = 1·1%, 95% CI: (−8·1,10·3)) (Wang et al., 2020c).

3.4.2. MERS

A total of 494 patients expired in all 24 studies (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Arabi et al., 2019; Cha et al., 2016; Choi et al., 2016, 2019; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2014, 2015, 2016; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shalhoub et al., 2015; Sherbini et al., 2017). A multi-center study, after adjusting for diabetes with chronic complications, liver disease, renal disease, any malignancy, SOFA score on day 1, source of infection, and year, indicated an increased day 90 mortality in the group receiving rIFN vs. the no rIFN group (logistic regression adjusted OR = 2.53, 95% CI: (1.32,4.85) (P = 0.005)) (Arabi et al., 2019). The combination therapy of IFN/RBV was not associated with death in a recent cohort (Alfaraj et al., 2019). Another study reported a CFR of 31.5% in patients who received IFN treatments, and a CFR of 40% in patients who did not receive IFN (P = 0.698) (Sherbini et al., 2017).

Table 9
Summary of findings for COVID-10 severity and IFN administration.

IFN compared to No IFN for COVID-19						
Patient or population: COVID-19 Setting: Observational studies Intervention: IFN Comparison: No IFN						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No IFN	Risk with IFN				
Severity	318 per 1000	**145 per 1000** (33–453)	**OR 0.363** (0.074–1.778)	168 (3 observational studies)	⨁⨁⨁x̂ MODERATE	(Lo et al., 2020), (Fan et al., 2020), (Pan et al., 2020)

*__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; **COVID-19:** coronavirus 2019; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **IFN:** interferon **OR:** Odds ratio

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

3.4.3. SARS

In two studies, 12 (5.67%) patients died (Loutfy et al., 2003; Zhao et al., 2003). A randomized trial of 190 patients treated SARS cases with the following regimens: Group A (n = 40): RBV and Cefoperazone/Sulbactam, and oxygen therapy; Group B: fluoroquinolone, rIFN-α and restricted steroid use (n = 30); Group C (n = 60): quinolone, azithromycin, rIFN-α for some patients, and steroids when symptoms worsened; and Group D (n = 60): levofloxacin, azithromycin, 45 patients were given rIFN-α, high-dose methylprednisolone was given when infiltrates affected more than one pulmonary segment or when consolidation was expanded, and broad-spectrum antibiotics if a bacterial infection was confirmed after culture. In four groups, 2 (5%), 2 (6.67%), 7 (11.67%), and 0 (0%) patients died, respectively (Zhao et al., 2003). In the other SARS study, 1 (7.7%) patient in the corticosteroid group (n = 13) died, while all patients in the corticosteroid + IFN-Alfacon-1 group (n = 9) survived (Loutfy et al., 2003).

3.5. Discharge

3.5.1. COVID-19

953 hospital discharges were reported in 24 studies (Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Pan et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Wang et al., 2020c; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhou et al., 2020b). A RCT using a six-category ordinal scale previously defined by the authors showed that at the first level of the scale, day 28 discharge (alive) was 92 (61%) in the REM + IFN group compared to 45 (58%) in the placebo + IFN group (OR = 1·15, 95% CI: (0·67,1·96)) (Wang et al., 2020c).

3.5.2. MERS

A total of 33 cases were discharged in 18 studies (Al Ghamdi et al., 2016; Al-Hameed et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Cha et al., 2016; Choi et al., 2016, 2019; Garout et al., 2018; Khalid et al., 2014, 2015, 2016; Kim et al., 2016, 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Rhee et al., 2016). However, six studies did not report a clear discharge outcome (Alfaraj et al., 2019; Arabi et al., 2019; Habib et al., 2019; Omrani et al., 2014; Shalhoub et al., 2015; Sherbini et al., 2017). A recent observation, in which all cases were either discharged or deceased by the end of the study period, showed a discharge rate of 20% in the RBV + IFN-α (n = 35) group vs. 35.2% in the no RBV + IFN-α group (n = 17) (Garout et al., 2018).

3.6. Chest imaging and X-ray presentations

3.6.1. COVID-19

Consolidation of pneumonia was indicated in six studies (Cai et al., 2020a; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Jian-ya, 2020; Liao et al., 2020; Liu et al., 2020a), and local or diffuse infiltrates were reported in two studies (Fan et al., 2020; Hung et al., 2020). Some publications reported ground glassy shadows (Chen et al., 2020; Du et al., 2020; Huang et al., 2020a; Jian-ya, 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a). Blurred edges were also reported by one study (Rui et al., 2020). Speckles and patchy shadows were observed in nine studies (Chen et al., 2020; Huang et al., 2020a; Liao et al., 2020; Liu et al., 2020a; Lo et al., 2020; Rui et al., 2020; Sun et al., 2020; Wan et al., 2020; Wang et al., 2020a). Thickening or disorder of textures was observed in three distinct reports (Huang et al., 2020a; Jian-ya, 2020; Rui et al., 2020). Other reported categories included unilateral or bilateral CXR involvement, pleural effusion, pneumothorax, white lung appearance, lung streak shadow, single lobe lesions, multiple solid nodules, visible band shadows, and bronchial shadow with air (Cai et al., 2020a; Cheng et al., 2020; Du et al., 2020; Fan et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Liu et al., 2020b; Lo et al., 2020; Pan et al., 2020; ; Rui et al., 2020; Sun et al., 2020Qiu et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020b; Xiao-Wei et al., 2020; Yu et al., 2020; Zhou et al., 2020b).

A recent non-randomized open-label trial investigated the efficacy of combination therapy of IFN with FPV, and included a total of 80 patients, who received IFN-α1b in two arms of the study (FPV + IFN group (n = 35), LPV/RTV + IFN (n = 45). The results showed that CT scan scores (median, range) were 12 (4.0–14.0) for FPV + IFN group, and 10 (4.5–13.5) for the LPV/RTV + IFN group (P = 0.78). Chest CT changes showed improvement in 32 cases (91.43%) vs. 28 (62.22%) cases, deterioration in 1 case (3.23%) vs. 9 (20.00%) cases, and was constant in 2 cases (6.45%) vs. 8 (17.78%) cases in FPV + IFN group and LPV/RTV + IFN group after 2 weeks, respectively (P = 0.004) (Cai et al., 2020a).

3.6.2. MERS

Of 24 distinct reports, lung consolidation was present in 12 studies (Al Ghamdi et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Arabi et al., 2019; Choi et al., 2016, 2019; Kim et al., 2017; Lee et al., 2017; Malik et al., 2016; Oh et al., 2015; Rhee et al., 2016; Sherbini et al., 2017), while 11 studies showed infiltrates (Al Ghamdi et al., 2016;

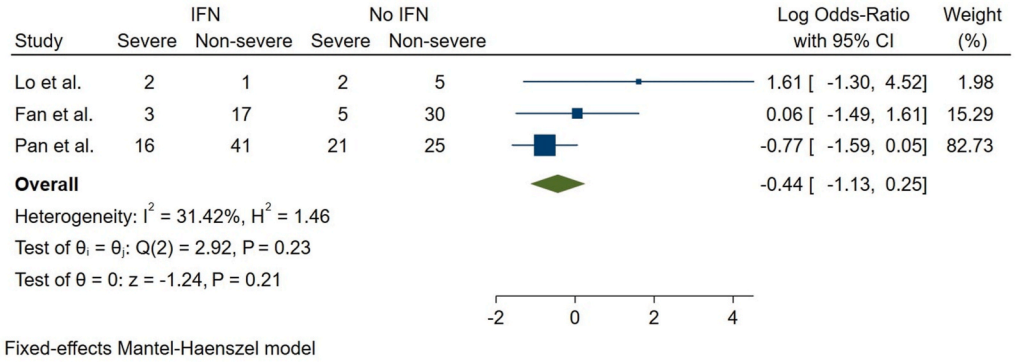

Fig. 3. Quantitative analysis for COVID-19 severity and IFN administration vs. placebo.

Table 10
Summary of Findings table for MERS-CoV mortality and IFN/RBV administration.

Bias across studies for mortality in MERS studies						
Patient or population: MERS-CoV patients Setting: Observational studies Intervention: RBV/IFN Comparison: No RBV/IFN						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	References
	Risk with No RBV/IFN	Risk with RBV/ IFN				
Mortality	580 per 1000	**552 per 1000** (211–852)	**OR 0.891** (0.194–4.168)	708 (6 observational studies)	⨁⨁x̄x̄ LOW [a]	(Habib et al., 2019), (Arabi et al., 2019), (Omrani et al., 2014), (Garout et al., 2018), (Khalid et al., 2016), (Choi et al., 2016)

*__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; **CoV:** coronavirus; **IFN:** interferon; **MERS:** middle east respiratory syndrome; **OR:** Odds ratio; **RBV:** ribavirin.

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

Explanations.

References.

[a] Many did not control for age, sex, and disease severity.

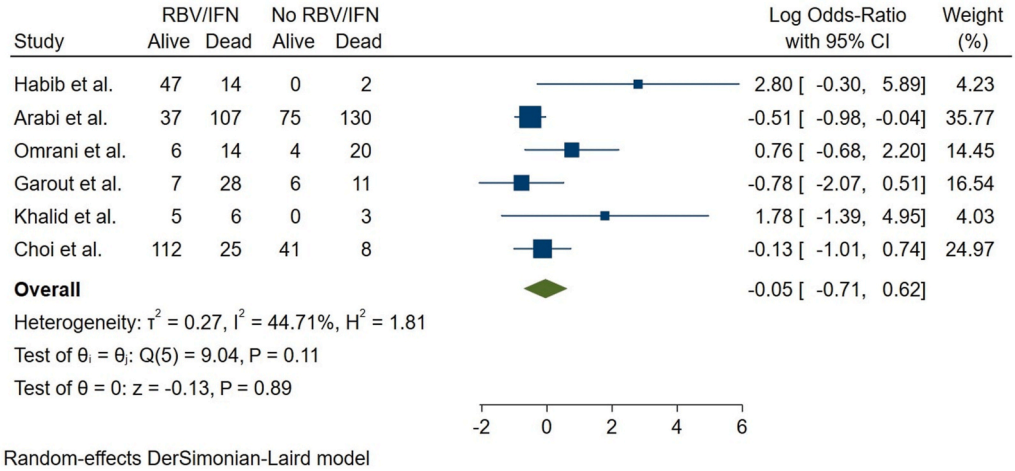

Fig. 4. Quantitative analysis for MERS-CoV mortality and IFN/RBV administration vs. no IFN/RBV.

Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Arabi et al., 2019; Cha et al., 2016; Khalid et al., 2014, 2015; Kim et al., 2016; Lee et al., 2017; Oh et al., 2015; Rhee et al., 2016). Eight studies reported ground glass shadows (Cha et al., 2016; Choi et al., 2016; Khalid et al., 2015; Kim et al., 2017; Lee et al., 2017; Oh et al., 2015; Rhee et al., 2016; Sherbini et al., 2017). Patchy shadows were observed in two studies (Al-Tawfiq

Table 11
GRADE assessment for narrative synthesis outcomes in COVID-19 studies.

Summary of findings:			
Combination or non-combination IFN treatment compared to No IFN/A different treatment protocol including IFN for COVID-19 Patient or population: COVID-19 Setting: RCTs, non-randomized trials, and observational studies Intervention: Combination or non-combination IFN treatment Comparison: No IFN/A different treatment protocol including IFN			
Outcomes	Impact	Studies	Certainty of the evidence (GRADE)
Mortality	Both studies did not report a remarkable difference in total mortality. Considerable variations were present among study designs.	(2 RCTs)	⨁⨁⨁◯ MODERATE[a]
	Comparative assessments are lacking.	(2 non-randomized trials)	–
	Comparative assessments are lacking.	(25 observational studies)	⨁⨁◯◯ LOW
Discharge	*Wang* et al. showed higher discharge rate in IFN + REM group compared to IFN + Placebo.	(2 RCTs)	⨁⨁⨁⨁ HIGH
	Comparative assessments are lacking.	(2 non-randomized trials)	–
	Comparative assessments are lacking.	(25 observational studies)	–
Chest X-ray	Comparative assessments are lacking.	(2 RCTs)	–
	Cai et al. showed FPV + IFN-α was significantly linked to improvement in CXR compared with LPV/RTV + IFN-α treatment (p = 0.004).	(2 non-randomized trials)	⨁⨁⨁⨁ HIGH
	Comparative assessments are lacking.	(25 observational studies)	–
Severity	Meta-analysis conducted.	(2 RCTs)	-[b]
	Jiang et al. showed cases treated with IFN-β + LPV/RTV, 39 (80%) were non-severe and 3 (38%) were severe ($p = 0.045$). Also, among cases treated with IFN-β + LPV/RTV + ARB, 10 (19%) were non-severe and 5 (63%) were severe ($p = 0.019$)	(2 non-randomized trials)	⨁⨁⨁◯ MODERATE[c]
	A cohort by Yuan et al. showed IFN treatment durations varied significantly among severe, moderate, and mild cases (p = 0.01).	(25 observational studies)	⨁◯◯◯ VERY LOW[d]
Inflammatory profile	Hung et al. did not find any significant difference in inflammatory profile.	(2 RCTs)	⨁⨁⨁◯ MODERATE[e]
	In a study with FPV + IFN-α and LPV/RTV + IFN-α arms, Cai et al. did not show a significant different in IL-6 and CRP.	(2 non-randomized trials)	⨁⨁⨁◯ MODERATE[e]
	Zhou et al. showed a higher efficacy for IFN and its combination therapies vs. therapy without IFN in reducing inflammatory elements.	(25 observational studies)	⨁◯◯◯ VERY LOW[e]
Hospital durations	Comparative assessments are lacking.	(2 non-randomized trials)	–
	Hung et al. showed LPV/RTV + RBV + IFN-β group had a reduced hospitalization time compared to LPV/RTV. Wang et al. included two arms both of which used IFN, and detected no difference in hospitalization duration.	(2 RCTs)	⨁⨁⨁⨁ HIGH
	No significant effects were detected in 3 studies. Xu et al. 15 (45.5%) cases with symptoms lasting longer than ten days and 19 (65.5%) cases with symptoms lasting shorter than or equal to 10 days received IFN alone or in combination with ARB, RBV, or LPV/RTV. In the study by Zhou et al. IFN, IFN + ARB, and ARB arms were not significantly different in regards to symptom onset to hospital admission (p = 0.87). Yuan et al. showed that the duration of hospitalization was significantly correlated with PCR negative conversion durations in the IFN-α + LPV/RTV + RBV group ($p = 0.0215$), as well as the IFN-α + LPV/RTV group ($p = 0.012$)	(25 observational studies)	⨁◯◯◯ VERY LOW[f,g]
ADEs	Significant and clear association was not established.	(2 RCTs)	⨁⨁⨁◯ MODERATE[h]
	Cai et al. showed FPV + IFN-α was significantly linked to less total ADEs compared with LPV/RTV + IFN-α treatment (p = 0.001).	(2 non-randomized trials)	⨁⨁⨁⨁ HIGH
	Comparative assessments are lacking.	(25 observational studies)	–

*__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).

ADEs: adverse drug events, **ARB:** arbidol, **CI:** Confidence interval, **FPV:** favipiravir, **IL:** interleukin, **LPV:** lopinavir, **RCT:** randomized controlled trial, **REM:** remdesivir, **RTV:** ritonavir.

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

Explanations.
[a] Different study designs with considerably different combination or non-combination IFN treatments may introduce inconsistency.
[b] For GRADE assessment of meta-analysis refer to Tables 9 and 10.
[c] No explanation of randomization process both in trial document and the article.
[d] IFN durations are indirectly related to our question. Our question is whether IFN use vs. a different treatment therapy is linked to COVID-19 severity. Duration of therapy is related but may not provide a direct answer.
[e] All important inflammatory elements, such as major inflammatory cytokines are required for proper assessment of inflammatory state.
[f] Different hospital durations have been comparatively described in different arms of 2 studies, which can not be assessed with consistency.
[g] Hospital durations and IFN use is the main question. However, Xu et al. synthesized IFN use by duration of symptoms. Although related, this might be seriously indirect in answering the research question.
[h] Assessment depending on specific ADEs, serious ADEs, or any ADEs could result in different interpretations of the same study.

Table 12
GRADE assessment for narrative synthesis outcomes in MERS studies.

Summary of findings:			
Combination or non-combination IFN treatment compared to No IFN/A different treatment protocol including IFN for MERS Patient or population: MERS Setting: Observational studies Intervention: Combination or non-combination IFN treatment Comparison: No IFN/A different treatment protocol including IFN			
Outcomes	Impact	Studies	Certainty of the evidence (GRADE)
Mortality	Meta-analysis conducted. Also, 2 additional studies for narrative synthesis detected the use of IFN therapy was possibly of no use (Alfaraj *et al* and Sherbini et al.).	(26 observational studies)	⨁x̂x̂x̂ VERY LOW[a]
Discharge	Garout et al. showed a discharge rate of 20% in the RBV + IFN-α ($n = 35$) group vs. 35.2% in the no RBV + IFN-α group ($n = 17$).	(26 observational studies)	⨁x̂x̂x̂ VERY LOW[a]
Chest x-ray	Comparative assessments are lacking.	(26 observational studies)	–
Inflammatory profile	A study compared IFN-α with IFN-β, and found the difference in CRP levels was not significant (p = 0.61) (Shalhoub et al.).	(26 observational studies)	⨁x̂x̂x̂ VERY LOW[b]
Severity	Al Ghamdi et al. showed a negative relation with severity for IFN-α but not IFN-β. Precisely, Univariable analysis of the influence of severity of disease on medications administered showed a significant negative risk association of – 4.62, 95% CI: (−8.40,−0.84) ($p = 0.018$) for IFN-α, and a negative but non-significant risk association of – 1.24, 95% CI: (−6.71,4.24) ($p = 0.652$) for IFN-β. Moreover, a multivariable analysis, which included a biomarker of disease severity, showed a strong association between disease severity and decreased survival, and no association between treatment with IFN-β and mortality (OR = 0.68, 95% CI: (0.04,10.28)) ($p = 0.778$)	(26 observational studies)	⨁⨁x̂x̂ LOW
Hospital durations	The length of hospital stay in RBV/IFN vs no RBV/IFN was not significantly different (p = 0.48) (Arabi et al.).	(26 observational studies)	⨁⨁x̂x̂ LOW
ADEs	In 7 studies, ADEs were recorded while using regimen containing IFNs, including multi-organ damage, adverse change in blood profile, thrombocytopenia, kidney disease, fever, and pancreatitis (Al-Tawfiq et al., Rhee et al., Kim et al., Cha et al., Al-Qaseer et al., Omrani et al., Khalid et al.).	(26 observational studies)	⨁x̂x̂x̂ VERY LOW[a,c]
*__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).			
__ADEs:__ adverse drug events, __CI:__ Confidence interval, __CRP:__ C-reactive protein, __IFN:__ interferon, __MERS:__ Middle-Eastern respiratory syndrome, __RBV:__ ribavirin.			
__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			

Explanations.
[a] Different IFN-based regimen were used, and were compared to varied treatment options. Results should be taken as speculative, rather than as for net efficacy of IFN.
[b] All important inflammatory elements, such as major inflammatory cytokines are required for proper assessment of inflammatory state.
[c] Combination therapies of IFN as well as lack of a comparator group makes it difficult to determine whether such adverse events are a direct result of IFNs administration.

and Hinedi, 2018; Oh et al., 2015). Other reported categorizations included atelectasis, hilar vascular shadow, bronchovascular marking, acute pulmonary embolism, multiple solid nodules, single or multiple lobe lesion, and pleural effusion (Al-Qaseer, 2015; Cha et al., 2016; Choi et al., 2016; Khalid et al., 2014, 2015, 2016; Kim et al., 2016, 2017; Malik et al., 2016; Rhee et al., 2016; Sherbini et al., 2017).

3.6.3. SARS

In a randomized trial with four treatment groups (described in the SARS mortality section), the number of cases with unabsorbed pulmonary infiltrates was 12, 11, 13, and 4 for groups A, B, C, and D, respectively. Moreover, the difference between groups was significant (P = 0.003). This study also reported infiltrates localized in one pulmonary segment, signs in one pulmonary field, the involvement of both lungs, diffuse damage, as well as reported cases with only interstitial changes (Zhao et al., 2003). In a recent preliminary study, patients were treated with IFN-Alfacon-1 + corticosteroid or corticosteroid alone. In this study, all cases in both groups showed abnormal chest imaging (P > 0.99). Eighteen patients did not show a full resolution of CXR abnormalities. Interestingly, the IFN-Alfacon-1 treatment group showed a reduced duration to 50% resolution of lung imaging abnormalities. The median for this duration was 4 in the IFN-Alfacon-1 + corticosteroid group vs. 9 in the corticosteroid only group (P = 0.001) (Loutfy et al., 2003).

3.7. Disease severity

3.7.1. COVID-19

Seven studies that did not report the number of severe and non-severe cases (Chen et al., 2020; Fernández-Ruiz et al., 2020; Huang et al., 2020b; Liu et al., 2020b; Wang et al., 2020b; Xiao-Wei et al., 2020; Yu et al., 2020) were excluded. 22 distinct reports, including 766 severe and 2007 non-severe cases, were studied (Cai et al., 2020a; Cheng et al., 2020; Du et al., 2020; Du et al., 2020; Fan et al., 2020; Huang et al., 2020a; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Jin et al., 2020; Liao et al., 2020; Liu et al., 2020a; Lo et al., 2020; Pan et al., 2020; Qiu et al., 2020; Rui et al., 2020; Sun et al., 2020; To et al., 2020; Wan et al., 2020; Wang et al., 2020a; Wang et al., 2020c; Yuan et al., 2020; Zhou et al., 2020b).

A retrospective cohort reported mean IFN treatment durations (days) in various levels of COVID-19 severity were 10.88, 95% CI: (8.00,13.75) in the mild group ($n = 8$), 14.24, 95% CI: (13.45,15.03) in the moderate group ($n = 75$), and 15.55, 95% CI: (13.84,17.25) in the severe group ($n = 11$), which were significantly different (one-way ANOVA, P = 0.01) (Yuan et al., 2020). The number of non-severe ($n = 52$) and severe ($n = 8$) patients receiving various combination IFN regimens were reported in a trial. Among cases treated with IFN-β + LPV/RTV, 39 (80%) were non-severe and 3 (38%) were severe (P = 0.045). Also, among cases treated with IFN-β + LPV/RTV + ARB, 10 (19%) were non-severe and 5

Table 13
GRADE assessment for narrative synthesis outcomes in SARS studies.

Summary of findings:			
Combination or non-combination IFN treatment compared to No IFN/A different treatment protocol including IFN for SARS Patient or population: SARS Setting: RCTs and observational studies Intervention: Combination or non-combination IFN treatment Comparison: No IFN/A different treatment protocol including IFN			
Outcomes	Impact	No. of participants (studies)	Certainty of the evidence (GRADE)
Mortality	One randomized trial study was included, that gives a good idea of effect of specific regimen used in the study, However, assessment of efficacy of IFN therapies, and in particular the role of IFN is not feasible in such settings. Precisely, in a trial In four groups, 2 (5%), 2 (6.67%), 7 (11.67%), and 0 (0%) patients died, respectively (Zhao et al.). (See explanation for regimens in each group.)[a]	(1 RCT)	⨁⨁⨁⨁ HIGH[b]
	In the other SARS study, 1 (7.7%) patient in the corticosteroid group ($n = 13$) died, while all patients in the corticosteroid + IFN-Alfacon-1 group ($n = 9$) survived (Loutfy et al.).	(1 observational study)	⨁⨁x̂x̂ LOW
Discharge	Comparative assessments are lacking.	(1 RCT)	–
	Comparative assessments are lacking.	(1 observational study)	–
Chest x-ray	Regimen (A, B, C, and D) are could be linked to unabsorbed infiltrates ($p = 0.003$) (Zhao et al.). However, this may be of little help for a broad range of IFN regimen due to that regimen given in the study are combinations of numerous agents.	(1 RCT)	⨁⨁⨁⨁ HIGH
	Addition of IFN-Alfacon-1 to corticosteroid regimen may enhance its therapeutic efficacy. In a cohort, IFN-Alfacon-1 treatment group showed a reduced duration to 50% resolution of lung imaging abnormalities (p = 0.001) (Loutfy et al.).	(1 observational study)	⨁⨁x̂x̂ LOW
Inflammatory profile	Comparative assessments are lacking.	(1 RCT)	–
	Comparative assessments are lacking.	(1 observational study)	–
Severity	Comparative assessments are lacking.	(1 RCT)	–
	Comparative assessments are lacking.	(1 observational study)	–
Hospital durations	No significant difference was detected in time to discharge (Zhao et al.).	(1 RCT)	⨁⨁⨁⨁ HIGH
	Comparative assessments are lacking.	(1 observational study)	–
ADEs	Comparative assessments are lacking.	(1 RCT)	–
	A cohort revealed several adverse effects while treatment. However, it may not be feasible to attribute these, merely to IFN administration. Fever, neutropenia with an absolute neutrophil count (ANC) of less than 1000/μL on the last day of treatment, a minor transient decrease in ANC, and elevation of serum transaminase levels were reported during IFN therapy in both IFN-Alfacon-1 and corticosteroid alone groups (Loutfy et al.).	(1 observational study)	⨁⨁x̂x̂ LOW
* **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). **ANC:** absolute neutrophil count, **CI:** Confidence interval, **IFN:** interferon, **RCT:** randomized controlled trial, **SARS:** severe acute respiratory syndrome. **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		

Explanations.

[a] The randomized trial of 190 patients by Zhao et al. treated SARS cases with the following regimens: Group A (n = 40): RBV and Cefoperazone/Sulbactam, and oxygen therapy; Group B: fluoroquinolone, rIFN-α and restricted steroid use (n = 30); Group C (n = 60): quinolone, azithromycin, rIFN-α for some patients, and steroids when symptoms worsened; and Group D (n = 60): levofloxacin, azithromycin, 45 patients were given rIFN-α, high-dose methylprednisolone was given when infiltrates affected more than one pulmonary segment or when consolidation was expanded, and broad-spectrum antibiotics if a bacterial infection was confirmed after culture.

[b] Different IFN-based regimen were used, and were compared to varied treatment options. Results should be taken as speculative, rather than as for net efficacy of IFN.

(63%) were severe (P = 0.019) (Jiang et al., 2020).

3.7.2. MERS

454 severe cases were reported in 10 studies (Al-Hameed et al., 2016; Al-Qaseer, 2015; Arabi et al., 2019; Cha et al., 2016; Choi et al., 2016, 2019; Kim et al., 2017; Lee et al., 2017; Omrani et al., 2014; Rhee et al., 2016). The rest of studies had an unclear number of severe cases (Al Ghamdi et al., 2016; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2014, 2015, 2016; Kim et al., 2016; Malik et al., 2016; Oh et al., 2015; Shalhoub et al., 2015; Sherbini et al., 2017). In total, 9 non-severe cases were also reported in 10 studies (Al-Hameed et al., 2016; Arabi et al., 2019; Cha et al., 2016; Choi et al., 2016, 2019; Khalid et al., 2015; Kim et al., 2017; Lee et al., 2017; Omrani et al., 2014; Rhee et al., 2016), and the rest of studies had an unclear number of non-severe cases (Al Ghamdi et al., 2016; Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq et al., 2014; Alfaraj et al., 2019; Garout et al., 2018; Habib et al., 2019; Khalid et al., 2014, 2016; Kim et al., 2016; Malik et al., 2016; Oh et al., 2015; Shalhoub et al., 2015, 2018; Sherbini et al., 2017).

Univariable analysis of the influence of severity of disease on medications administered showed a significant negative risk association of – 4.62, 95% CI: (−8.40,−0.84) (P = 0.018) for IFN-α, and a negative but non-significant risk association of – 1.24, 95% CI: (−6.71,4.24) (P = 0.652) for IFN-β. Moreover, a multivariable analysis, which included a biomarker of disease severity, showed a strong association between disease severity and decreased survival, and no association between treatment with IFN-β and mortality (OR = 0.68, 95% CI: (0.04,10.28)) (P = 0.778) (Al Ghamdi et al., 2016). However, another study that did not discuss the severity of included patients showed a reduction in mortality was significantly associated with IFN-α (OR = 0.16, 95% CI:

(0.02,1.38)) (P = 0.09). The lower mortality did not reach statistical significance for IFN-β (OR = 0.28, 95% CI (0.03,2.33)) (P = 0.24) (Shalhoub et al., 2015).

3.8. Inflammatory cytokines

3.8.1. COVID-19

A cohort study showed that during the time interval of day 0–20 (upon onset of symptoms), on average, cases receiving the ARB only regimen had higher CRP levels than cases treated with IFN alone or both IFN and ARB, by 25.7 mg/l. Also, over the time interval between day 12 and day 42 (upon onset of symptoms), on average, cases receiving the ARB only regimen showed higher IL-6 levels than the cases who received IFN alone or both IFN and ARB, by 33.5 pg/ml. These effects were not influenced by co-morbidities for IL-6 (P = 0.456), or CRP (P = 0.420) levels (Zhou et al., 2020b). In a recent phase II trial, IL-6 levels (log10 pg/ml, median, (Q1,Q3)) were 1·4, (1·0–1·4) in LPV/RTV + RBV + IFN-β group (n = 86), and 1·4, (1·0–1·6) in LPV/RTV group (n = 41). These results did not show any significant differences between the trial arms (P = 0.43). Also, in this trial, TNF-α levels were measured for both trial arms (P = 1.00) (Hung et al., 2020). In another clinical study, CRP (mg/dl, median, (Q1,Q3) level was 18.6 (5.0–20.0) for all patients (n = 80). CRP levels were 15.0, (3.0–19.2) and 21.4, (5.0–23.2) in the FPV + IFN-α (n = 35) and LPV/RTV + IFN-α arm (n = 45) of the study, respectively (P = 0.33). IL-6 (ng/l, median, (Q1,Q3)) was 13.4, (4.4–16.2) in all patients. IL-6 levels were 14.0, (3.5–11.0) and 12.9, (5.3–16.8) in FPV + IFN-α and LPV/RTV + IFN-α arm, respectively (P = 0.77) (Cai et al., 2020).

3.8.2. MERS

There were higher CRP levels (mg/l, median, (Q1,Q3)) in cases treated with IFN-α (n = 13) (86.5, (25,226)) compared to cases treated with IFN-β (80, (19.3346)); However, this difference did not reach statistical significance (P = *0.*61) (Shalhoub et al., 2015).

3.9. Hospitalization duration

3.9.1. COVID-19

In a recent cohort, duration from the symptom onset to hospital admission (days, median, (Q1,Q3)) was 8.0, (5.5, 15.5), 6.5, (3.0, 10.0), and 10.0, (4.5, 19.5) for IFN, IFN + ARB, and ARB groups, respectively. This difference, however, was not statistically significant (P = 0.087) (Zhou et al., 2020b). A placebo-controlled RCT of IFN therapy in combination with REM showed a similar duration of hospitalization (days, median, (Q1,Q3)) in the two arms of the trial 25·0, (16·0,38·0) in intention-to-treat populations of REM group (for REM + IFN: 29 (18%)) vs. 24·0 (18·0,36·0) in placebo group (for placebo + IFN: 15 (19%)) (risk difference = 0·0, 95% CI: (−4·0,4·0)) (Wang et al., 2020c). A lately surfaced cohort indicated that the duration of hospitalization was significantly correlated with PCR negative conversion durations in the IFN-α + LPV/RTV + RBV group (P = 0.0215), as well as the IFN-α + LPV/RTV group (P = 0.012) (Yuan et al., 2020). A recent study divided the cohort of study into patients who experienced symptoms for more or less than ten days; Furthermore, 15 (45.5%) cases with symptoms lasting longer than ten days and 19 (65.5%) cases with symptoms lasting shorter than or equal to 10 days received IFN alone or in combination with ARB, RBV, or LPV/RTV (Xiao-Wei et al., 2020). In a recent phase II RCT, the duration of hospital stay (days, median (Q1,Q3)) was significantly lower in the LPV/RTV + RBV + IFN-β 9·0, (7·0–13·0), compared with 14·5, (9·3–16·0) in the LPV/RTV (control) group (P = 0·016) (Hung et al., 2020).

3.9.2. MERS

The length of hospital stay (days, median, (Q1,Q3)) in a recent multicenter study was reported 17 (10, 28) in RBV/IFN group compared to 20 (10, 36) in the no RBV/IFN group (P = 0.48) (Arabi et al., 2019).

3.9.3. SARS

In a randomized trial of 4 treatment groups (regimens were described in SARS mortality section), time to discharge (days, (S.D.)) was 24·8, (5·5) in group A, 24·8, (6·4) in group B, 22·4, (5·9) in group C, and 20·7, (4·6) in group D. Also, the difference between groups was not reported significant (Zhao et al., 2003).

3.10. Unfavorable drug events in CoV infections

3.10.1. COVID-19

The total number of ADEs were significantly lower in the FPV + IFN-α (4) compared to the LPV/RTV arm of the trial (25) (P = 0.001); Also, nausea in patients in the FPV + IFN-α group was lower significantly in the FPV + IFN-α (0) compared to the LPV/RTV arm of the trial (6) (P = 0.03) (Cai et al., 2020). In another study, self-limited nausea and diarrhea were similar between the two groups. Furthermore, in this study, ADEs were reported by 41 (48%) of cases in the LPV/RTV + RBV + IFN group and 20 (49%) of cases in the LPV/RTV group (Hung et al., 2020). A placebo-controlled multi-center trial for the efficacy of REM + IFN compared with placebo + IFN found that ADEs were reported in 102 (66%) of REM receivers compared to 50 (64%) of placebo receivers. Importantly, REM was stopped early because of ADEs in 18 (12%) cases compared to 4 (5%) patients who discontinued placebo early (Wang et al., 2020c). Finally, ADEs have been provided (Table S2).

3.10.2. MERS

MERS patients showed several ADEs during treatment with IFNs and other drugs. ADEs also included pancreatitis, which was reported in one patient (Al-Tawfiq et al., 2014), kidney injuries (e.g., AKI) in 5 cases (Khalid et al., 2016), and renal failure in 3 cases (Khalid et al., 2014). Hepatic jaundice occurred in one patient during therapy (Choi et al., 2019). Changes in laboratory data were mentioned in some studies. Alterations in the laboratory profile of patients included increased amylase and lipase in seven patients who were treated with IFN (Al-Tawfiq et al., 2014; Rhee et al., 2016), increased bilirubin (Kim et al., 2016), decrease in Hb in 45 cases (Al-Tawfiq et al., 2014; Omrani et al., 2014), Scr and AST-ALT elevation in one patient with IFN therapy (Al-Tawfiq et al., 2014), thrombocytopenia in 2 patients (Al-Tawfiq et al., 2014; Cha et al., 2016), anemia in 46 cases (Al-Qaseer, 2015; Omrani et al., 2014), and hemodynamic instability in 3 patients during treatment with IFN and other drugs were reported as ADEs (Khalid et al., 2014). Fever was mentioned in one IFN receiver (Cha et al., 2016). Also, multi-organ damage as a severe side effect was reported in 5 cases treated with IFN (Omrani et al., 2014).

3.10.3. SARS

In SARS patients, fever, neutropenia with an absolute neutrophil count (ANC) of less than 1000/μl on the last day of treatment, a minor transient decrease in ANC, and elevation of serum transaminase levels were reported during IFN therapy in both IFN-Alfacon-1 and corticosteroid alone groups (Loutfy et al., 2003).

3.11. Quantitative analysis

Three observational COVID-19 investigations were eligible for meta-analysis of IFN treatment and severity. The studies showed moderate certainty (Table 9). Fixed-effects (Mantel-Haenszel) (I^2 <35%) approach was employed. Results showed the relation between receiving IFN and severity to be inconclusive. Effect size in all three studies crossed the line of no effect, indicating inconclusiveness of the current data (log OR = −0.44, 95% CI: (−1.13,0.25), I^2 = 31.42%) (Fig. 3).

Six MERS-CoV cohorts were included in the quantitative synthesis. Evaluation of the risk of bias across studies via GRADE showed the evidence was low certainty, indicating that further research could change our estimation (Table 10). Random-effects (DerSimonian-Laird) (I^2 >35%) approach was selected. Mortality was not clearly affected by the

administration of RBV/IFN treatment vs. no RBV/IFN (log OR = −0.05, 95% CI: (−0.71,0.62), I^2 = 44.71%) (Fig. 4). Publication bias was not analyzed due to the insufficient number of studies (n < 10). Finally, summary of findings table for GRADE assessments for narrative synthesis outcomes were conducted according to a new study (Murad et al., 2017), and results were provided in Tables 11–13 for COVID-19, MERS, and SARS, respectively.

4. Discussion

SARS-CoV, MERS-CoV, and SARS-CoV2 are human CoVs (hCoVs) that have been the cause of three outbreaks during the last two decades (Jabbari et al., 2020). All of them have shown the potential to manifest as multisystem difficult to treat infections (Goudarzi et al., 2020; Heidarpour et al., 2020; Jahanshahlu and Rezaei, 2020a; Jenab et al., 2020; Nejadghaderi et al., 2020; Rahmani et al., 2020; Sadeghmousavi and Rezaei, 2020; Yazdanpanah et al., 2020b). In particular, multisystem involvement in COVID-19 has been associated with anti-viral immunity paralysis on the one hand, and on the other hand release of pro-inflammatory cytokines, e.g., interleukin-6, and hyperinflammatory shock (Bahrami et al., 2020; Fathi and Rezaei, 2020; Mojtabavi et al., 2020; Nasab et al., 2020; Rokni et al., 2020; Saghazadeh and Rezaei, 2020a; Sarzaeim and Rezaei, 2020; Yazdanpanah et al., 2020a). Such an unpleasant event is orchestrated by genetic and environmental factors that make individuals susceptible to develop hyper inflammatory responses (Darbeheshti and Rezaei, 2020; Yousefzadegan and Rezaei, 2020). Supporting this, inborn errors of immunity have not been shown to increase the risk of developing severe COVID-19 and dying from that. However, there are sporadic reports of death in patients with combined immunodeficiency (Ahanchian et al., 2020a, 2020b; Babaha and Rezaei, 2020). For this, anti-inflammatory and immunomodulatory treatments along with monoclonal antibodies appear as potential candidates (Basiri et al., 2020b; Fathi and Rezaei, 2020; Jahanshahlu and Rezaei, 2020b; Mansourabadi et al., 2020; Pashaei and Rezaei, 2020; Pourahmad et al., 2020; Saghazadeh and Rezaei, 2020b; Seyedpour et al., 2020; Shojaeefar et al., 2020).

The ongoing COVID-19 pandemic has led the scientific community to consider repurposing previously approved treatments such as convalescent plasma, antivirals like IFN, and LPV/RTV, and the clinical reapplication of the experience learned from previous global epidemics caused by hCoVs (Guy et al., 2020). The present research has systematically investigated the efficacy of combinational or mere IFN therapy. We have reviewed the clinical literature regarding the clinical efficacy of IFN for three deadly human CoVs by analyzing the mortality, discharge, CXR presentations, onset-to-treatment duration, ADEs, and other clinically essential outcomes.

Understandably, mortality is of high clinical interest. Mortality in COVID-19 and SARS cases was not significantly affected by IFN therapy, as studies reported no mortality in all study subgroups of similar mortality. Moreover, a poor-quality cohort of SARS patients showed lower mortality and faster CXR improvement in patients receiving IFN-Alfacon-1 compared to IFN-Alfacon-1 + corticosteroids group. However, the results of this uncontrolled study should be taken with its small sample size and lack of randomization in mind. The higher discharge was indicated in a high-quality trial for combinational IFN therapy with REM vs. IFN alone in COVID-19. However, lower discharge rates for taking RBV/IFN were indicated in a poor-quality cohort. In addition to a lack of high-quality evidence backing up the use of RBV/IFN for COVID-19 patients, the calculated effect size for six MERS-CoV studies shows that IFN/RBV treatment did not prove beneficial compared with no RBV/IFN in terms of mortality. Cytokine storm in COVID-19 cases has been known for inducing a destructive immune response and is possibly responsible for unfavored clinical outcomes in COVID-19 (Nile et al., 2020). For COVID-19, inflammatory cytokines (e.g., IL-6, TNF-α, and CRP) were lower in patients who received IFN with or without ARB. The quality of this study was good. Moreover, a randomized trial of a high risk of bias indicated no difference between inflammatory cytokine levels. Furthermore, our results should be interpreted in light of competing interests of included literature.

Also, a comparison between the anti-inflammatory potential of two IFN types was not significant in MERS patients. A wide range of chest radiography presentations was found in both COVID-19 and MERS patients. Interestingly, a moderately biased trial by Cai et al. showed a significant improvement in CXRs in FPV + IFN-α group vs. LPV/RTV +IFN-α group (P = 0.004), while also showing significantly fewer ADEs (P < 0.001). The median for onset-to-treat times was mostly under two weeks for both MERS and COVID-19. Interestingly, combination ARB + IFN treatment was clinically effective in a cohort via reducing inflammatory cytokines despite the relatively long onset-to-treatment interval (days, median (Q1,Q3)) 17.0 (10.0, 22.0). ADEs were mostly reported for IFN in combination with other antivirals. Therefore, despite that some studies showed certain combinations are less likely to result in ADEs, they were inconclusive for the use of IFN.

Studies strictly including patients according to a strictly fatal or non-fatal outcome do not help compare drug effects. In general, we indicate that although IFN has been commonly given in combination with antiviral therapies (e.g., with RBV in MERS cases), most studies have not reported a definitive benefit for the inclusion of IFN in administered regimens. Therefore, we suggest that more placebo-controlled RCTs with larger populations are required to clarify further the efficacy of IFN for a reduction in improving clinical status, and more importantly, mortality in COVID-19 patients. Also, we recommend that in order to reduce bias and increase usability in practice, comparative observational studies should control for confounding factors, especially severity.

The major restriction in our synthesis was the high risk of bias in many observational studies. Also, most articles were observational studies, many of which were case reports or case series, and did not include a control group. Also, many cohort studies did not control any confounders, resulting in a high risk of bias. Most studies used a combination of pharmacological and non-pharmacological treatments, and utilized highly varied administration protocols along with IFN therapy or did not report outcomes classified by receiving IFN, complicating the distinguish of IFN-related harms or benefits from other interventions. MERS studies mostly reported RBV/IFN treatment groups, which does not assess the net effect of IFN therapy. Despite calling authors, six of SARS studies could not be retrieved due to the unavailability of the full-text. A limitation in SARS studies was using solely clinical criteria for inclusion rather than confirmed laboratory results. This may lead to the dampening of any actual treatment effects of antiviral therapeutics. We highlighted our assessments in light of lessons that can be learned from past CoVs, as they share principal similarities with the novel SARS-CoV2 (Gilbert, 2020; Peeri et al., 2020). However, though IFN treatments may hold significant potential for the management of hospitalized COVID-19 patients, it is challenging to approximate their worldwide acceptance in regards to evidence of this treatment, irrespective of the efficacy of such therapeutics in past outbreaks.

5. Conclusion

In conclusion, the present systematic review reveals that the efficacy of IFN alone has not been investigated sufficiently for three deadly human CoVs. Still, we found that combination therapy of IFN with antivirals such as FPV, ARB, REM, or corticosteroids can have potential benefits (e.g., faster CXR improvement, lower level of inflammatory cytokines). These potentials need to be tested in larger RCTs. Also, the data regarding mortality, a crucially determining clinical outcome, seem insufficient for assessing treatment efficacy. Further investigation considering potential benefits and harms (e.g., ADEs) discussed in the present research can shed light on the path, leading to more successful conclusive trials in the strict time researchers possess during rapidly evolving outbreaks.

It is notable that many of the available therapeutic options are not

specific to the COVID-19 condition and the death tolls are rising (Mohamed and Rezaei, 2020). This lack of specificity has brought about numerous efforts towards understanding the origin of the virus (Lundstrom et al., 2020; Sharifkashani et al., 2020) and discovering more targeted approaches for treatment of the disease (Ahanchian et al., 2020b; Fathi and Rezaei, 2020; Lotfi et al., 2020; Mansourabadi et al., 2020; Rabiee et al., 2020; Rezaei, 2020b; Saghazadeh and Rezaei, 2020b; Seyedpour et al., 2020; Sharifkashani et al., 2020), and the management of comorbid diseases (Moazzami et al., 2020; Sahu et al., 2020). Definitely, such efforts need great scientific collaborations to occur and get presented (Mohamed et al., 2020b; Momtazmanesh et al., 2020; Moradian et al., 2020; Rzymski et al., 2020). During this pandemic in which people are at risk of infection and re-infection (Jabbari and Rezaei, 2020; Rezaei, 2020a) and social distancing is the most important method of prevention, utilization of hybrid methods for holding scientific events might help the data to be shared and the information to be exchanged (Hanaei et al., 2020; Samieefar et al., 2020).

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have read and approved the final version of the manuscript.

Availability of data and materials

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Authors' contributions

K.S. conceptualized the study, performed data curation and analysis, and prepared the initial draft. S.Y. conceptualized the study, performed data curation, and prepared the initial draft. M.B. conceptualized the study and performed data curation. E.H. conceptualized the study and performed data curation. M.G. conceptualized the study and performed data curation. A.S. conceptualized the study, designed the project, and prepared the final draft. N.R. conceptualized the study, supervised the project, and critically appraised the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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