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Interferon therapy in patients with SARS, MERS, and COVID-19: A 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-\(\alpha\) group compared with the LPV/RTV arm (\(P = 0.001\)). Also, nausea in patients receiving FPV + IFN-\(\alpha\) 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\(\alpha\) 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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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.

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.
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 (Rasoulnejad et al., 2020), cytokines, and IFNs which help to control viral disease and provide multi-system immunological protection (Kopitar-Jeral, 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 IFN-α-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-γ2b 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 CoV's 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 (Onabayo 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 treatment, 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 (Omran 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-MZ), 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., 2020b). 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
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

Fig. 2. PRISMA flow diagram.
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* | 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, | 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                | 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- α1b (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, Arthralgias. | Fever, Cough, Shortness of breath, Chest tightness, Myalgia, Dizziness, Fatigue, Nausea, Diarrhea, Pharyngalgia, Anorexia, Erythra Fever, Cough, Chest pain, Phlegm, Sore throat, Headache, Nausea, Anxiety | 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, Headache, Diarrhea, Expectation, Haemoptysis Fever, Cough, Myalgia, Headache, Diarrhea | 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, Hyperthyroidism, Kidney Stones, Arthralgias. | LPV, RT, ARB, IVIG, Corticosteroid, Quinolones, second generation of β-lactam (oral and IV), Flora therapy | M(41), I(32–52) | IFN-α2b inhalation 5000000U BD (33) |
| Huang et al. (2020b) | China   | SARS-CoV-2 | RT-PCR          | HTN, Cerebrovascular, Diabetes, CHD, COPD, Chronic | 36     | 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)
| Source                     | Country | Study design                  | Viral aetiology | Diagnosis                                             | Sample | Reported co-morbidities                                                                                                                                                                                                                                                                                                                                 | Symptoms on admission                                                                                      | Non-intervention treatments                                                                                                                                 | Age | Intervention |
|----------------------------|---------|-------------------------------|-----------------|-------------------------------------------------------|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|--------------|
| Chen/Zhang et al. (2020a)  | China   | Retrospective case-series (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                                                                                                                                   | Ganciclovir, umifenovir hydrochloride                                                                                                                                  | 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                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                      | Yes (OA(129), D(169))                                                                                                                                               | M(63), I(50–71) |
| 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: 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                                                                                                                                                                                                                                                                                                                                                             | LPV/RTV                                                                                                                                                              | IFN-α by aerosolization (b.i.d.) (36)                                                                       | M(8.3), S(3.5) |              |
| 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, Fever, Cough, Shortness of breath, Runny nose, Sore throat, Headache, Vomiting, Diarrhea                                                                                                                                                                      | LPV/RTV, Corticosteroid, TCM, Antibiotic                                                                                                                                  | IFN or Kaletra (135)                                                                                                                                               | M(47), I(36–55) |
| 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 | Intervention                        |
|-------------------------|---------|--------------------------------|-----------------|------------------------------------|--------|----------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------|------|-------------------------------------|
| 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), IFN: 35.5–59, LPV/RTV + IFN: 36–61) | IFN-a by aerosol inhalation (5 million U b.i.d.) | 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.) |
| Wang et al. (2020a)   | China   | Case reports (LOE III)           | SARS-CoV-2      | Throat swab RT-PCR                   | 2      | NI                                                                                     | Asymptomatic Couple                           | LPV/RTV, ARB, TCM                                   | M(Total(-41), Common(-41), Severe(-37) (of all cases n = 54), I (Total (31–51), IFN: 31–51)) | (80) |
| 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 apnea, 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)), IFN (31–61), LPV/RTV (33.5–62.5)) |
| 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: 31–51)) | IFN-α-2b (5 mIU diluted with 2 ml sterile water) (common (18/37), data out of 40 cases) | (continued on next page) |
| Source          | Country | Study design          | Viral aetiology            | Sample | Reported co-morbidities                        | Symptoms on admission                                      | Non-intervention treatments                                      | Age            | Intervention                                                                 |
|-----------------|---------|-----------------------|---------------------------|--------|-----------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------|
| Wang et al.     | 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 | 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 | IFN-α-2b (76)  |
| Lo et al. (2020)| China   | Retrospective cohort (LOE II) | SARS-CoV-2, Nasopharyngeal swab RT-PCR | 10     | HTN, Dyldipedemia, 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(Rem + IFN(-66), Placebo + IFN(-64)) (in this study all data is for Remdesivir vs. Placebo(with IFN)), I(Rem + IFN (57–73), Placebo + IFN(53–70)) | 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, Cerbrovascular disease, COPD, Renal disease, Liver disease | Fever, Cough, Shortness of breath, Diarrhea, Manifestations of Obstetrics, Abdominal pain (labour, premonitory labour), increased fetal movement | 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, Jinyeibaidu 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 | 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) |

(continued on next page)
| Source                  | Country          | Study design          | Viral aetiology | Diagnosis                                   | Sample | Reported co-morbidities                                                                 | Symptoms on admission                                                                 | Non-intervention treatments                  | Age* | Intervention |
|------------------------|------------------|-----------------------|-----------------|---------------------------------------------|--------|----------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------|------|--------------|
| Fan et al. (2020)      | China            | Retrospective cohort  | 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, Polyneuropnea | Fever, Cough, Shortness of breath, Chest pain, Runny nose, Nose obstruction, Sore throat, Myalgia, Nausea, Diarrhea, Chills, Malaise | Oseltamivir, IVIG, Corticosteroid, TCM, Antibiotic, Voriconazole | R(2mon-15yr), Patient: 1 y, 1 mon, Patient: 2 y, 1 mon, Patient: 6: 15 y, Patient: 7: 13 y, 11 mon, Patient: 8: 13 y, 5 mon | Yes (8) | LPV/RTV with or without RBV or IFN-β-1b was given in (18) |
| To et al. (2020)       | China            | Retrospective cohort  | 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(Total(-41), non-Severe(-40), Severe(-58)), R(Total(12–74), non-Severe(40), Severe(-58)) | IFN in combination with either LPV/RTV or RBV (59) | Nebulized IFN-α (96) |
| Yuan et al. (2020)     | China            | Retrospective cohort  | 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) | IFN in combination with either LPV/RTV or RBV (59) | Nebulized IFN-α (96) |
| 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 [Mild24), Moderate(47.91), Severe(60.60)], Critical(60.87)], S (Total(15.98), no-Digestive symptoms(18.10), Digestive symptoms15.92 [Moderate(14.85), Severe(9.63), Critical(16.44)] | M(Total-41), non-Severe(40), Severe(-58)) | IFN-β (60) |
| Jiang et al. (2020)    | China            | Clinical Trial (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 | IFN-β (60) | (continued on next page) |
Table 1 (continued)

| Source | Study Design | Viral Diagnosis | Sample | Reported Co-morbidities | Symptoms on Admission | Intervention |
|--------|--------------|-----------------|--------|------------------------|----------------------|--------------|
|        |              |                 |        |                        |                      | Non-intervention treatments |
|        |              |                 |        |                        |                      | Severe(12-74) |
|        |              |                 |        |                        |                      | Severe|37|
|        |              |                 |        |                        |                      | Fatigue, Vomiting, Diarrhea, Severe |
|        |              |                 |        |                        |                      |                |

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, gastrointestinal, GP: group, HBP: high blood pressure, HBV: hepatitis B virus, HCC: Hepatocellular carcinoma, HCQ: hydroxy 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, RTV: ritonavir, S: standard deviation, SARS-CoV: severe acute respiratory syndrome, SARS: severe acute respiratory syndrome, SC: subcutaneous, sec: second, SLE: systematic lupus erythematos, Tab: tablet, TB: tuberculosis, TCM: traditional Chinese medicine, TCMD: traditional Chinese medicine decoction, TDS: 3 times a day, g: microgram.

a Supplementary material.

b Randomization process not stated.

c 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.

d 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.

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., 2020; Loutfy et al., 2003; Malini et al., 2020; Malik et al., 2016; Oh et al., 2015; Omrani et al., 2014; Rhee et al., 2016; Shin et al., 2017; 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; Shalhoub et al., 2018), 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 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.
Table 2: Characteristics of included MERS-CoV studies *(n = 26)*.

| Source               | Country       | Study design               | Viral aetiology | Diagnosis                                      | Sample | Reported co-morbidities                                           | Symptoms on admission                                      | Age(?) | Intervention | Non-intervention treatments                        |
|----------------------|---------------|----------------------------|-----------------|-----------------------------------------------|--------|-------------------------------------------------------------------|----------------------------------------------------------|---------|--------------|--------------------------------------------------|
| Habib et al. (2019)  | Saudi Arabia  | Retrospective cohort study | MERS            | PCR from respiratory tract samples            | 63     | Diabetes, HTN, pancreatitis, Chronic renal failure, and chronic heart disease | Fever, Diarrhea, Abdominal pain, Organ failure             | M(59.7) | IFN-α (61)  | RBV                                              |
| Arabi et al. (2019)  | Saudi Arabia  | Retrospective cohort study | MERS            | Swab RT-PCR                                   | 349    | DM, Malignancy, CPD, Moderate to severe liver disease, CKD, Chronic Cardiac, Chronic neurological disease | M(IFN and/or RBV (≥57.5), No IFN and/or RBV (≥58)) | M(IFN and/or RBV (47-70), No IFN and/or RBV (117), rIFN alone (9), rIFN 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                 | MERS            | RT-PCR of nasopharyngeal aspirate, Patients 1 and 3: RT-PCR | 3      | None                                                             | Fever, Cough, Shortness of breath, Phlegm, Sore throat, Myalgia, Headache, Diarrhea | M(48.0), | Patient 1: interferon α2a (180 μg/week), Patients 2 and 3: interferon α2a (117), rIFN | RBV, Corticosteroid                                    |
| Alfaraj et al. (2019)| Saudi Arabia  | Retrospective cohort study  | MERS            | RT-PCR of respiratory samples                 | 314    | None                                                             | Fever, Cough, Shortness of breath, Sore throat, Headache, Myalgia, Diarrhea | M(39), | Yes (13)     | RBV, Oseltamivir, IVIG, Vasopressors, Renal replacement therapy |
| Shalhoub et al. (2018)| Saudi Arabia  | Retrospective cohort study  | 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), | 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) | IFN-α (35)   | RBV                                              |
| Al-Tawfiq et al. (2014)| Saudi Arabia | Case report                 | 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 | M(45), | Patient 1: 56, Patients 2 and 3: interferon α2b S.C (180 μg/week) | RBV                                              |
| Sherbini et al. (2017)| Saudi Arabia  | Retrospective cohort study  | MERS            | Swab RT-PCR                                   | 29     | DM, CKD                                                          | Fever, Cough, Shortness of breath, Vomiting, Diarrhea     | M(45), | Yes (19)     | RBV, Oseltamivir, IV ceftriaxone, azithromycin, Vancomycin, and meropenem, Tigecycline, IV colistin, Amikacin, and Fluconazole |
| Lee et al. (2017)    | South Korea   | Retrospective case report   | MERS            | Swab RT-PCR                                   | 1      | HTN, Dyslipidemia                                                | Fever, Myalgia, Chills, Dyspnea, Malaise                    | M(45), | Pegylated IFN-α 2b 180 mcg Daily | Pegylated IFN-α 2a S.C (180 μg/week for 2 weeks) |
| Kim et al. (2017)    | South Korea   | Retrospective case report   | MERS            | RT-PCR for specimen from the lower respiratory tract (collected sputum and endotracheal aspirates) | 23, 4 | included in further analysis                                    | Fever, Cough, Shortness of breath, Myalgia, Headache, Nausea, Confusion | M(46), | Pegylated IFN-α 2a S.C (180 μg/week for 2 weeks) | Pegylated IFN-α 2a S.C (180 μg/week for 2 weeks) |

(continued on next page)
| Source                  | Country          | Study design                | Viral aetiology | Diagnosis                | Sample | Reported co-morbidities                                                                 | Symptoms on admission                                      | Age | Intervention                | Non-intervention treatments                                                                 |
|------------------------|------------------|----------------------------|-----------------|--------------------------|--------|----------------------------------------------------------------------------------------|-----------------------------------------------------------|-----|----------------------------|------------------------------------------------------------------------------------------|
| 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) (47.0–70.0), No RBV/rIFN M (-58.0) (41.0–70.0) |     | Non-steroidal anti-inflammatory drugs 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, patient: Ionotropic, Patient 5: Convalescent plasma RBV, Oseltamivir, Vancomycin, Meropenem |
| Malik et al. (2016)    | UAE              | Case report (LOE III)       | MERS            | Nasopharyngeal aspirate RT-PCR/ oropharyngeal, sputum RT-PCR | 1      | 32 week pregnant                                                                       | Fever, Back pain                                          | Patient 1: 32                                                                 | Peg IFN-α (180 μg/week) (1) |                                                                       |
| Kim et al. (2016)      | South Korea      | Case report (LOE III)       | MERS            | Nasopharyngeal aspirate RT-PCR/ oropharyngeal, sputum RT-PCR | 1      | HTN, DM, Distal Pancreatectomy due to benign pancreatic neoplasm, Chronic dry cough, and Diagnosed with mycobacterium intracellular | Fever, Back pain                                          | Patient 1: 64                                                                 | IFN-α2a SC 180 μg/0.5 ml (1) |                                                                       |
| 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, Decreased consciousness | M(54), R (23–79)                                                                 | Peg IFN-α2b (11) | RBV, Oseltamivir, Methylprednisolone, Antibiotic, NO, Neurumuscular 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, Chest pain, 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-α2b (8) | RBV, Oseltamivir, Corticosteroid, Antibiotic, Norepinephrine, Renal replacement therapy |

(continued on next page)
| Source                    | Country       | Study design                  | Viral aetiology | Diagnosis                                      | Sample | Reported co-morbidities                                                                 | Symptoms on admission                                                                 | Age | 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                               | 54   | 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 | IFNa (65), IFNb (67), IFNa (33–84), IFNb (25–84) | RBV |                                                                            |                                               |
| Oh et al. (2015)         | South Korea   | Case Report (LOE III)         | MERS            | RT–PCR on a sputum specimen                   | 1      | NI                                                                                      | Fever, Cough                                                                           | 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 | 2      | NI                                                                                      | Shortness of breath                                                                    | 52, 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, IBD                                                   | Fever, Cough, Shortness of breath, Diarrhea, Night sweats, loss of appetite            | 47, 52, 30 | Patient 1: IFN-α-2a µg S.C., Patient 2: IFN-α-2b 1.5 µg/kg S. C, Patient 3: IFN-α-2b (8 from treatment group) | RBV, Patient 1: Oseltamivir, Patient 2: IVIG, Patients 1 and 2: Corticosteroid, Patients 1, 2, and 3: Antibiotic RBV, Oseltamivir, Hydrocortisone, Antibiotics, Vasopressor Therapy, IVIG |
| 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                                                                                     | 67–4, 64–0 | Pegylated IFN-α-2a S.C. (180 µg/week for 2 weeks) (20 from treatment group) |                                               |

(continued on next page)
Table 2 continued

| Source                  | Country | Study design | Viral aetiology | Sample | Reported co-morbidities | Symptom on admission | Diagnosis | RT-PCR | Interventions |
|-------------------------|---------|--------------|-----------------|--------|------------------------|---------------------|-----------|--------|--------------|
| Khalid et al. (2016)    | Saudi   | Case-series  | CoV-2            | Patient 1: 74 | No IFN/RBV: 18         | Age: 65, R          | bundle branch block, Coronary artery disease | Case reports | No IFN/RBV: 18 | 1) Khalid et al. (2014)  
|                         |         |              |                 | Patient 2: 84 | IFN-αμ (2014)          | Age: 70 (4-41) Patient 5: 24) | No IFN/RBV: 18 | 2) Al-Tawfiq et al. (LOE III) |
|                         |         |              |                 | Patient 3: 76 | IFN-αμ (2014)          | Age: 62 (4-41) Patient 5: 24) | No IFN/RBV: 18 | 2) Al-Tawfiq et al. (LOE III) |
|                         |         |              |                 | Patient 4: 54 | IFN-αμ (2014)          | Age: 58 (4-41) Patient 5: 24) | No IFN/RBV: 18 | 2) Al-Tawfiq et al. (LOE III) |
|                         |         |              |                 | Patient 5: 48 | IFN-αμ (2014)          | Age: 48 (4-41) Patient 5: 24) | No IFN/RBV: 18 | 2) Al-Tawfiq et al. (LOE III) |
|                         |         |              |                 | Patient 6: 17 | IFN-αμ (2014)          | Age: 17 (4-41) Patient 5: 24) | No IFN/RBV: 18 | 2) Al-Tawfiq et al. (LOE III) |

**Abbreviations:** 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.

bAge of participants is reported as reported in each study. Estimated mean values may be found in (supplementary material).
### 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<sup>a</sup> | 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)      | 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                                                                                   | M (IFN Alfacon-1 group (48), Corticosteroids Alone group (42), R(IFN Alfacon-1 (27–56), Corticosteroids Alone (16–86))) | M (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.

<sup>a</sup> 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 the outcome(s) | Exposure measures | Follow-up time | Final quality |
|--------|---------|---------------------------|-------------------|---------------|--------------|
| Pan et al. (1) | yes | yes | yes | yes | Poor quality |
| Pan et al. (1) | yes | yes | yes | yes | Poor quality |

Pan L, Hu M, Yang P, Sun Y, Wang R, Yan J, et al. Clarifying the outcome(s) of interest. The American Journal of Gastroenterology. 2020;115.

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-β1b, and IFN Alfacon-1 administered via inhalation, subcutaneous (SC) injection, or nebulization (Al Ghaddi et al., 2016; Al-Hameed 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; 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; Jing et al., 2020; Jin et al., 2020; Kang et al., 2016; Khalid et al., 2016; 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., 2020a; To et al., 2020; Wan et al., 2020; Wang et al., 2020b,c; Wang et al., 2020d; Wang et al., 2020e; 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., 2020a; Jiang-yu, 2020; Jiang-yu, 2020; Jin et al., 2020; Jin et al., 2020; Liu et al., 2020a; Wang et al., 2020b; Wang et al., 2020b; 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., 2020a; Jiang-yu, 2020; Jiang-yu, 2020; Jin et al., 2020; Jin et al., 2020; Liu et al., 2020a; Wang et al., 2020b; Wang et al., 2020b; 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., 2020a; Jiang-yu, 2020; Jiang-yu, 2020; Jin et al., 2020; Jin et al., 2020; Liu et al., 2020a; Wang et al., 2020b; Wang et al., 2020b; 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., 2020a; Jiang-yu, 2020; Jiang-yu, 2020; Jin et al., 2020; Jin et al., 2020; Liu et al., 2020a; Wang et al., 2020b; Wang et al., 2020b; Xiao-Wei et al., 2020; Yu et al., 2020; Yuan et al., 2020; Zhao et al., 2003; Zhou et al., 2020b).
Table 5

| 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.    | SARS-CoV-2    | Non-randomized| low                      | moderate                                        | NI                                     | low                                              | low                      | low                                | moderate                                             | Moderate risk of bias |
| Hung et al.   | SARS-CoV-2    | Randomized    | low                      | some concerns                                   | NA                                     | high                                             | high                     | low                                | Low risk of bias                                        | Low risk of bias |
| Zhao et al.   | SARS-CoV-1    | Randomized    | high                     | some concerns                                   | high                                  | high                                             | high                     | high                                | High risk of bias                                        | 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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| 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 | yes | yes | yes | yes | yes | yes | Good |
| Jian-ya (7) | SARS-CoV-2 | yes | yes | yes | yes | yes | yes | yes | yes | yes | Good |
| Liu et al. (8) | SARS-CoV-2 | yes | yes | yes | yes | No/NA | yes | yes | 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 | yes | Good |
| Rui et al. (12, 13)* | 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 | 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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* 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.
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.     | SARS-CoV-2       | 1(b)                             | 1(a)                      | 1(a)                                   | Yes(a)                          | 1(b)          | 1(a)                 | 1(a)                          | 0(d)                                  | Good quality |
| Qui et al.      | SARS-CoV-2       | 1(a)                             | 1(a)                      | 0(c)                                   | 1(a)                            | 1(b)          | 1(a)                 | 1(a)                          | 0(d)                                  | Poor quality |
| Lo et al.       | SARS-CoV-2       | 1(b)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 0(d)                                  | Poor quality |
| Wang et al.     | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 0(b)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(b)                                  | Poor quality |
| Jin et al.      | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 0(b)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(b)                                  | Poor quality |
| Fan et al.      | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 0(b)                            | 0(c)          | 1(a)                 | 1(a)                          | 1(a)                                  | Good quality |
| Sun et al.      | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 0(d)                                  | Fair quality |
| To et al.       | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 0(d)                                  | Poor quality |
| Yuan et al.     | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 0(d)                                  | Poor quality |
| Cheng et al.    | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 2(a-b)        | 1(a)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Huang et al.    | SARS-CoV-2       | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Habib et al.    | MERS-CoV         | 0(c)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Arabi et al.    | MERS-CoV         | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 2(a-b)        | 1(b)                 | 1(a)                          | 1(a)                                  | Good quality |
| Alfaraj et al.  | MERS-CoV         | 0(d)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Garout et al.   | MERS-CoV         | 0(d)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Sherbini et al. | MERS-CoV         | 0(d)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Khalid et al.   | MERS-CoV         | 0(d)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Choi et al.     | MERS-CoV         | 0(d)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(a)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Al-Hamed et al. | MERS-CoV         | 1(b)                             | 0(c)                      | 1(a)                                   | 1(a)                            | 0(c)          | 0(c)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Al-Ghamdi et al.| MERS-CoV         | 0(d)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Shallhoub (2015)| MERS-CoV         | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 2(a-b)        | 1(b)                 | 1(a)                          | 1(a)                                  | Good quality |
| Omri et al.     | MERS-CoV         | 1(a)                             | 1(a)                      | 1(a)                                   | 1(a)                            | 0(c)          | 1(b)                 | 1(a)                          | 1(a)                                  | Poor quality |
| Loutfy et al.   | 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-2: severe acute respiratory syndrome coronavirus.

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### Table 8

| 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 | No/no/yes | No/no/yes | Yes/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 | No/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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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., 2020a; Huang et al., 2020a; Lo et al., 2020; To et al., 2020; Wang et al., 2020b; Yuan et al., 2020). 12 case-series (Cheng 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; 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., 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; 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)) (Hung et al., 2020c).

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 (Hung et al., 2020a; Hung et al., 2020; Jiang 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; 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)) (Hung 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 and Hinedi, 2018, 2019). A meta-analysis of 131 patients (Al-Qaseer, 2015; Al-Tawfiq and Hinedi, 2018; Al-Tawfiq and Hinedi, 2018, 2019; Alfaraj et al., 2019; Arabi et al., 2019; Cha et al., 2016; Choi et al., 2016, 2019; 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) showed a significant decrease in mortality rates in the IFN group compared to the placebo group (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 did not receive IFN treatments, and a CFR of 40% in patients who did not receive IFN (P = 0.698) (Sherbini et al., 2017).
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, azithromycin, rIFN-α, and restricted steroid use; Group C (n = 60): quinolone, azithromycin, rIFN-α for some patients, and steroids when symptoms worsened; and Group D (n = 60): levofoxacin, 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., 2020; Liu et al., 2020b; 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). 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% (33–453) in the REM + IFN group compared to 45% (58%) in the placebo + IFN group (OR = 1–1.5, 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). According to the authors, 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., 2020a; 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., 2020; 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; Liu et al., 2020; Liao et al., 2020; 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., 2020a; Huang et al., 2020a; Huang et al., 2020b; Hung et al., 2020; Jian-ya, 2020; Jiang et al., 2020; Liao et al., 2020; Qiu et al., 2020; Sun et al., 2020; To et al., 2020; Wang et al., 2020a). 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;
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 et al., 2018; Arabi et al., 2019).

**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                                   |
| Mortality                                    |
| Risk with No RBV/IFN                         |
| Risk with RBV/IFN                            |
| Anticipated absolute effects*                 |
| (580 per 1000)                               |
| (552 per 1000)                               |
| OR 0.891                                     |
| (0.194–4.168)                                |
| 708 (6 observational studies)                |
| 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).

**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.**

- Many did not control for age, sex, and disease severity.
Table 11

| Outcome                  | 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. Comparative assessments are lacking. | (2 RCTs)                                                                 | MODERATE*                          |
| Discharge                | Wang et al. showed higher discharge rate in IFN + REM group compared to IFN + Placebo. Comparative assessments are lacking. | (2 RCTs)                                                                 | MODERATE*                          |
| Chest X-ray              | Cai et al. showed FPV + IFN-α was significantly linked to improvement in CXR compared with LPV/RTV + IFN-α treatment (p = 0.004). Comparative assessments are lacking. | (2 RCTs)                                                                 | MODERATE*                          |
| Severity                 | Meta-analysis conducted.                                                | (2 non-randomized trials)                                               | MODERATE*                          |
| Inflammatory profile     | Hung et al. did not find any significant difference in inflammatory profile. | (2 RCTs)                                                                 | MODERATE*                          |
| Hospital durations       | Comparative assessments are lacking.                                    | (2 RCTs)                                                                 | MODERATE*                          |
| ADEs                     | Cai et al. showed FPV + IFN-α was significantly linked to less total ADEs compared with LPV/RTV + IFN-α treatment (p = 0.001). Comparative assessments are lacking. | (2 non-randomized trials)                                               | MODERATE*                          |

*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. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be substantially different from the estimate of 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 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.

1 Different study designs with considerably different combination or non-combination IFN treatments may introduce inconsistency.
2 For GRADE assessment of meta-analysis refer to Tables 9 and 10.
3 No explanation of randomization process both in trial document and the article.
4 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.
5 All important inflammatory elements, such as major inflammatory cytokines are required for proper assessment of inflammatory state.
6 Different hospital durations have been comparatively described in different arms of 2 studies, which cannot be assessed with consistency.
7 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.
8 Assessment depending on specific ADEs, serious ADEs, or any ADEs could result in different interpretations of the same study.
Table 2
GRADE assessment for narrative synthesis outcomes in MERS studies.

| Outcomes          | Impact                                                                 |
|-------------------|------------------------------------------------------------------------|
| 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.). |
| 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). |
| Chest x-ray       | Comparative assessments are lacking.                                    |
| Inflammatory profile | A study compared IFN-α with IFN-β, and found the difference in CRP levels was not significant (p = 0.61). |
| 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) (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). |
| Hospital durations | The length of hospital stay in RBV/IFN vs no RBV/IFN was not significantly different (p = 0.48) (Arabi et al.). |
| 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-Qaaser et al., Omran et al., Khalid et al.). |

*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).

Explanations:

- 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.
- All important inflammatory elements, such as major inflammatory cytokines are required for proper assessment of inflammatory state.
- Combination therapies of IFN as well lack of a comparator group makes it difficult to determine whether such adverse events are a direct result of IFNs administration.

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 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-α: cortisol 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-α treatment group showed a reduced duration to 50% resolution of lung imaging abnormalities. The median for this duration was 4 in the IFN-α 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., 2020; 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., 2020b, 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...
the rest of studies had an unclear number of non-severe cases (Al-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., 2014, 2015, 2016; Kim et al., 2016; Malik et al., 2016; Oh et al., 2015).

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.).

Comparative assessments are lacking. (1 RCT)

Severity
Comparative assessments are lacking.

Comparative assessments are lacking.

Hospital durations
No significant difference was detected in time to discharge (Zhao et al.).

Comparative assessments are lacking.

ADEs
Comparative assessments are lacking.

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.).

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.

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): quinoline, 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.

Different IFN-based regimens were used, and were compared to varied treatment options. Results should be taken as speculative, rather than as for net efficacy of IFN.
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 levels (Zhou et al., 2020b). In a recent phase II trial, IL-6 levels (log10 levels (log10), 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 levels (Zhou et al., 2020b). In a recent phase II trial, IL-6 levels (log10

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%)) (Fig. 3). A late 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).
administration of RBV/IFN treatment vs. no RBV/IFN (log OR = −0.05, 95% CI: (−0.71,0.62), F = 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, 2020; 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; Pakni et al., 2020; Sahghazadeh and Rezaei, 2020; Sarzaeim and Rezaei, 2020; Yazdanpanah et al., 2020b). Such an unpleasant event is orchestrated by genetic and environmental factors that make individuals susceptible to develop hyper inflammatory responses (Darbehesht and Rezaei, 2020; Yousefzadeh 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 it. However, there are sporadic reports of death in patients with combined immunodeficiency (Abanchian 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., 2020; Fathi and Rezaei, 2020; Jahanshahlu and Rezaei, 2020; Mansourabadi et al., 2020; Pashaei and Rezaei, 2020; Pourahmad et al., 2020; Sahghazadeh 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 unfavorable 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 CXR in FFV + 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 anti-viral 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 (Anchanchian et al., 2020b; Fathi and Rezaei, 2020; Lotfi et al., 2020; Mansourabadi et al., 2020; Rabiei et al., 2020; Rezaei, 2020b; Saghzadhe 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 management of comorbid diseases (Moazzami et al., 2020; Sahu et al., 2020) 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. A.S. conceptualized the study, designed the project, and performed data curation. M.G. conceptualized the study and performed data curation. E.H. conceptualized the study and performed data curation, and prepared the initial draft. M.B. conceptualized the study, performed data curation, and prepared the initial draft. M.B. conceptualized the study, performed data curation, and prepared the initial draft. M.B. conceptualized the study, performed data curation, and prepared the initial draft. M.B. conceptualized the study, performed data curation, and prepared the initial draft. M.B. conceptualized the study, performed data curation, and prepared the initial draft.
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