AMERICAN UNIVERSITY OF BEIRUT

IMMUNE-BASED THERAPY FOR HOSPITALIZED PATIENTS WITH COVID-19 AND RISK OF SECONDARY INFECTIONS: SYSTEMATIC REVIEW AND META-ANALYSIS

by
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ABSTRACT
OF THE THESIS OF

Dima Marwan Kabbani for Master in Health sciences (SHARP)

Title: Immune-based Therapy for Hospitalized Patients with COVID-19 and Risk of Secondary Infections: A Systematic Review and Meta-analysis

Background: Some immune-based therapies are efficacious in the treatment of patients with COVID-19 requiring hospitalization. However, safety concerns related to the potential risk of secondary infections may limit their use.
Objectives: The objective of this study is to systematically review the evidence for the effect of immune-based therapy in patients hospitalized with COVID-19 on the risk of secondary infections.
Search Methods: A search was executed by an expert searcher/librarian on the following databases in October 2020, and updated in January 2021: OVID Medline, Ovid EMBASE, SCOPUS, Cochrane Library including Clinical trial.gov, PROSPERO, and using controlled vocabulary (eg: MeSH, Emtree, etc) and key words representing the concepts "Covid 19" and "immunotherapies" and "outcomes including secondary infections."
Registration: The protocol is registered with PROSPERO CRD4202122940
Eligibility criteria: We included randomized controlled trial (RCT) and non-randomized studies (NRS), in which adults, hospitalized with COVID-19 were treated with immunotherapy versus standard of care or placebo and had infectious complications as an outcome. We extracted data in duplicate an independent manner. We used RevMan 5.3 to conduct a meta-analysis for RCTs and NRS using the random effects models to calculate the pooled risk ratio (RR) with 95% confidence interval (CI) for the incidence of infection. Statistical heterogeneity was determined using the I^2 statistic. We assessed the risk of bias for all included studies and rated the certainty of evidence for each outcome using the GRADE approach. We conducted a meta-regression using the R package to meta-explore whether age, sex, and invasive mechanical ventilation modified the risk of infection with immune-based therapies.
Findings: We identified 74 eligible publications (16 RCT and 58 NRS). Due to high heterogeneity in NRS, we performed meta-analysis only for RCTs, which included 3403 participants (mean age 60 years and 63% male). Infection risk was lower with immune-based therapy (173/1906, 9.1% versus 210/1496, 14%; RR= 0.74 (95% CI, 0·58-0·96; p=0.02 and (I^2=26 %). Subgroup analysis did not identify any subgroup effect by type of immune-based therapies (p=0.41)**.** Meta-regression revealed no impact of age, sex or mechanical ventilation on the effect of immune-based therapies on the risk of infection. Pneumonia occurred in 65/1131 on immune-based therapy versus 99/998 with placebo; RR= 0.67 (95%CI 0·41-1·09; p=0.11) and (I^2= 44%).
Interpretation: We identified moderate certainty evidence that the use of immune-based therapies in COVID-19 reduces the risk of secondary infections as compared to standard of care in hospitalized patients with COVID-19.

TABLE OF CONTENTS

ILLUSTRATIONS

Figure

TABLES

Table

ABBREVIATIONS

AZM	Azithromycin
CAPA	COVID-19 associated pulmonary aspergillosis
CAR	Chimeric antigen receptor
CI	Confidence interval
COVID- 19	Coronavirus virus disease -19
CRS	Cytokine release syndrome
DM	Diabetes
HCQ	Hydroxychloroquine
IFI	Invasive fungal infection
IL-1	Interleukin-1
IL-6	Interleukin -6
IMV	Invasive mechanical ventilation
JAK	Janus Kinase
Lp/r	Lopinavir/ritonavir
MERS	*Middle East Respiratory Syndrome*
NRS	*Non-randomized studies*
RCT	*Randomized Clinical Trials*
RDV	*Remdesivir*
RR	*Relative Risk*
SARS-COV-2	Severe Acute Respiratory Syndrome- related Coronavirus-2
SOC	*Standard of Care*
Toci	*Tocilizumab*
WHO	World Health Organization

CHAPTER I

INTRODUCTION

A. Epidemiology of COVID-19

A global outbreak of a novel coronavirus has caused a widespread infectious syndrome called coronavirus 2019-associated disease (COVID-19). COVID-19 initially emerged in the city of Wuhan, the capital of Central China's Hubei province, in December 2019, when a cluster of patients were hospitalized with pneumonia of unknown etiology[1]. The initial cluster was epidemiologically linked to Huanan, a seafood wholesale market in Wuhan[2], and shortly afterwards the pathogen was identified as a novel Coronavirus. Due to the resemblance of Wuhan's patients cluster clinical picture with that caused by the Coronovaris SARS-CoV between 2002 to 2003, the virus was named severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2). On March 11 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic after the sharp increase of cases outside China and the increasing number of affected countries[3].

Coronaviruses are enveloped RNA viruses, found in humans, other mammals and birds. Seven species of coronavirus causing disease in humans have been identified, with 229E, OC43, NL63, and HKU1 causing bening "common cold-like" symptoms in non-immunocompromised individuals. The other three, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2, and are associated with severe respiratory infection that can lead to death [4, 5]. SARS-CoV, which originated from bats, was the pathogen responsible for the aforementioned SARS outbreak, which started in the Guangdong Province, China, causing fast spread

infection in 8000 individuals and the death of 774 persons in few months between 2002-2003.[5] MERS-CoV originated from camels, causing the outbreak in the Middle East in 2012 with 1879 laboratory-confirmed cases in humans in 27 countries and, at least, 659 related deaths. [4] As of April 29 2021, SARS-CoV-2 has spread to more than 192 counties, infected more than 149 million people, and killed three million individuals worldwide.[6, 7]

B. SARS-CoV-2 Transmission and Clinical Presentation

SARS-CoV-2 most commonly spreads by respiratory droplets during face-to-face exposure, especially when the distance between individuals is less than 1 meter, and less commonly through surface contamination [8-11]. There is increasing evidence supporting aerosol transmission (smaller droplets that remain suspended in air) [12-14]. COVID-19 is a syndrome with a wide range of clinical manifestations. A report from the CDC China back in February 2020, described a cohort of 44,672 confirmed cases with 81% of infected patients having mild manifestations, 14% categorized as severe requiring supplemental oxygen and 5% critically-ill requiring mechanical ventilation. In that cohort, the overall case fatality rate was 2.3% [15].

Asymptomatic persons seem to account for approximately one third of SARS-CoV-2 infections [16], but a significant proportion of them will develop symptoms in the following days, situation now known as pre-symptomatic state. As an example, in a long-term care facility SARS-CoV-2 outbreak, 77% of asymptomatic residents developed symptoms in the following 7 days [17]. Most of the infected individuals will develop upper respiratory tract symptoms and other less common symptoms (diarrhea and conjunctivitis among other). Loss of smell and/or taste are very typical initial

manifestations of the disease [18]. Most people with symptoms will improve with no sequela after 7 days but 20-30% will progress from the initial picture with shortness of breath secondary to bilateral pulmonary infiltrates and will require hospitalization [19]. The most common symptoms in hospitalized patients are fever, cough and shortness of breath [20-22]. Other symptoms include fatigue, weakness, and headache, gastrointestinal symptoms such as nausea/vomiting or diarrhea [22-24].

Several risk factors for complications (progression to respiratory failure, the need for mechanical ventilation, prolonged stay in intensive care, and death) have been described, including age more than 65 years, the presence of comorbidities (hypertension, diabetes (DM) , obesity, cardiovascular disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, malignancy), lymphopenia, elevated C-reactive protein and other inflammatory markers. [21, 24-26] Typically, patients with severe COVID-19 suffer from severe inflammation with increased levels of C-reactive protein, interleukin-6, CCL4, CCL2 and CXCL9 (among others) associated with activation of the C5a-C5aR1 axis [27].

While the upper respiratory tract symptoms occurring in the first week are associated with a high SARS-CoV-2 viral load and result from direct viral invasion, the clinical deterioration with pneumonia is mainly caused by an aberrant immune response to SARS-CoV-2. Patients with severe respiratory failure display either macrophage activation syndrome or very low HLA-DR expression accompanied by a profound depletion of CD4 lymphocytes, CD19 lymphocytes and NK cells [28]. This immune profile is distinct from that found in patients with sepsis and can be partially rescued with interleukin-6 blockage by tocilizumab, with restoration of HLA-DR expression on

monocytes [28]. The reduction of CD4 and CD8 T cells is accompanied by expression of exhaustion (PD-1 and TIM-3) T cell markers [29].

C. Stages of COVID- 19

While the initial upper respiratory tract symptoms occurring in the first week after infection are associated with a high SARS-CoV-2 viral load and result from direct viral invasion, the clinical deterioration with pneumonia is mainly caused by an aberrant immune response to SARS-CoV-2.

Siddiqui et al have proposed a 3-stage classification of the illness: Stage I or early infection, stage II or pulmonary phase and stage III or Hyper-inflammation phase [30]. During early infection, the SARS-CoV-2 replicates in the respiratory tract and binds to the angiotensin- converting enzyme 2 receptors found in the lungs, gastrointestinal tract and endothelial system [31]. This stage is characterized by mild symptoms of cough, malaise and fever. For those, with illness limited to this first stage, recovery is usually speedy. During stage II, the infection progress to the lungs with viral replication and inflammation; and the disease is characterized by fever, cough and, in some, hypoxia. Changes in the form of infiltrates and ground glass opacities are seen on lung imaging. Only a minority will progress to stage III, with systemic hyperinflamation syndrome, which is characterized by increased proinflammatory cytokines [32] and progressive respiratory failure, shock and cardiopulmonary collapse.

Patients with severe respiratory failure display either macrophage activation syndrome or very low HLA-DR expression accompanied by a profound depletion of CD4 lymphocytes, CD19 lymphocytes and NK cell [33]. This immune profile is distinct to that found in patients with sepsis and can be partially rescued with interleukin-6 blockage by

Tocilizumab, with restoration of HLA-DR expression on monocytes[33]. The reduction of CD4 and CD8 T cells is accompanied by expression of exhaustion (PD-1 and TIM-3) T cell markers.[34].

D. Therapy for COVID-19

Different classes of drugs and therapeutics have been developed or deployed for the management of COVID-19 by two different approaches: 1) drugs with antiviral activity (e.g. remdesivir, favipiravir, hydroxycholoquine, lopinavir-ritonavir, ivermectin, SARS-CoV-2 neutralizing antibodies, convalescent plasma); and 2) medications targeting the aberrant immune response such as corticosteroids, monoclonal antibodies against interleukin-6 (IL-6) and -1 receptors, Janus kinases (JAK) inhibitors, colchicine and interferon.

Early during the pandemic, many therapeutic decisions were made with little scientific evidence. For example, the early and abundant use of hydroxycholoquine/chloroquine and lopinavir-ritonavir was later aborted after several trials showed not only lack of benefit, but also the possibility of harm with the use of hydroxychloroquine [35, 36].

Remdesivir is a prodrug of an adenosine nucleotide analogue with potent in vitro antiviral activity against a range of RNA viruses including MERS-CoV and SARS-CoV 1 & 2 [37]. Remdesivir, was previously under development for the treatment of Ebola virus disease but is no longer being developed for this indication as monoclonal antibodies outperformed remdesivir in a phase III clinical trial [38]. Despite the initial enthusiasm towards the use of remdesivir in severe COVID-19, several clinical trials have shown no impact on mortality and little effect in time to recovery [39-41].

Lopinavir has activity, both in vitro [42] and in an animal model [43], against Middle East respiratory syndrome coronavirus (MERS-CoV). Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450. Based on these previous data, lopinavir-ritonavir was also considered as a potential treatment for COVID-19. Unfortunately, no clinical benefit for lopinavir-ritonavir was observed in several clinical trials [40, 44, 45].

Both chloroquine [46] and hydroxychloroquine [47] inhibit SARS-CoV-2 replication in vitro. As hydroxychloroquine has a safer toxicity profile [48] it has been widely used to treat COVID-19. As for remdesivir and lopinavir-ritonavir, the use of hydroxychloroquine in COVID-19 shows no clinical benefit [35, 40, 49].

In November 2020, the FDA released an emergency authorization for the use authorizations of neutralizing monoclonal antibodies (bamlanivimab, combination of casirivimab and imdevimab and combination of bamlanivimab and etesevimab) against SARS-CoV-2. These neutralizing antibodies target the receptor-binding domain of SARS-CoV-2 spike protein and have been evaluated in hospitalized and outpatient settings with a diverse heterogeneity in the measured outcomes across these studies. So far, neutralizing antibodies have demonstrated a reduction in the SARS-CoV-2 viral load [50, 51] but with no clear impact on clinical outcomes [52].

It is not surprising that antivirals offer little clinical benefit for more severe patients, as this manifestation is secondary to an aberrant immune response. The only treatment that has demonstrated a mortality benefit in hospitalized patients with COVID-19 is dexamethasone at a dose of 6 mg daily for 10 days, with reduced number of deaths of hospitalized and ventilated COVID-19 patients by 1/3, by 1/5 in patients requiring oxygen only and no benefit in those not requiring respiratory support [53].

The use of corticosteroids has also been observed in outpatients with earlier disease. In line with our hypothesis, a recently published retrospective study from Brazil demonstrated the potential utility of prednisone in an outpatient setting in reducing hospitalization risk [54]. The COVID-19 patient cohort that received prednisone only (n=139; 14 hospitalizations [10.1%]) observed reduced hospitalization rates in comparison to those without prednisone only treatment (n=578; 100 hospitalizations [17.3%]). The efficacy of corticosteroids in COVID-19 patients is higher in those patients with associated inflammation (defined as C-reactive protein levels ≥ 20mg/dL) which reinforces the hypothesis that the inflammatory response is the main driver of morbidity and mortality in this disease [55].

Tocilizumab, a monoclonal antibody blocking the interleukin-6 receptor, was also estudied for the treatment of COVID-19 early in the course of the pandemic. Tocilizumab is FDA approved for the treatment of various autoimmune and inflammatory conditions (rheumatologic, neurologic, gastroenterology) as well as cytokine release syndrome (CRS) in patients receiving chimeric antigen receptor (CAR) T cell. Multiples observational and randomized clinical trials have assessed the use of tocilizumab in the management of patients with moderate to severe COVID ([56]). There is a significant variability in the inclusion criteria of tocilizumab clinical trials, with some including mechanically ventilated patients and other including lower disease severity. Some considered the inflammatory phenotype using blood levels of C-reactive protein higher than 75 mg/L or elevated interleukin-6 levels as an inclusion criterion, while other did not. This may account to some differences in patient's clinical response and outcome between trials. Two trials, RECOVERY (not yet accepted for publication) [57] and REMAP CAP [58], reported benefit of the use of tocilizumab and both were

designed to start treatment early in the course of the disease. In the RECOVERY trial [57], tocilizumab was started within 2 days of hospitalization and in the REMCAP trial [58], less than 24 hours after admission to ICU. Sarilumab, another IL-6 receptor antagonist that is FDA-approved for the treatment rheumatoid arthritis, did not show efficacy in hospitalized patients receiving supplemental oxygen when compared to placebo [59].

Janus kinase inhibitors are currently FDA-approved for the treatment of rheumatoid arthritis. Baricitinib, a Janus Kinase 1 and 2 inhibitor, was identified using artificial intelligence algorithms as a potential treatment for COVID-19 [60]. First, it inhibits clathrin-mediated endocytosis and thereby inhibits viral infection of cells [61]. Second, it inhibits cytokine intracellular signaling, with the potential to stop the inflammatory cascade associated with COVID-19 [62]. The clinical trial ACTT-2 compared the efficacy of the combination of baricitinib and remdesivir compared to remdesivir in hospitalized COVID-19 patients [63]. The baricitinib plus remdesivir arm showed a trend towards lower mortality than the remdesivir alone arm (4.7% vs. 7.1%; rate ratio: 0.65; 95%CI 0.39-1.09) with the maximum benefit for patients receiving supplemental oxygen or non-invasive ventilation [63]. However, it remains unclear if baricitinib would provide additional benefits beyond standard steroids since, steroids where not used as standard of care in this trial.

E. Secondary infections post COVID-19

Hospitalized patients with viral pneumonia, mainly influenza, are at increased risk of secondary bacterial and fungal infections [64-66]. Influenza virus infection breaches the natural barriers in the lungs, disrupting lung physiology, uncovering and

upregulating bacterial receptors and therefore promoting bacterial co-infection [67]. The incidence of bacterial co-infection in influenza is in the range of 20 to 30% and is associated with increased morbidity and mortality [64, 66, 68]. Some of these bacterial infections are community acquired but others are hospital acquired commonly secondary to prolonged ventilation and hospitalization. Although early community-acquired (within 48 hours of admission) bacterial co-infections in COVID-19 are much lower (8%) than that reported in influenza, there is a significant and widespread antibiotic use in hospitalized patients with COVID-19 reported in the literature [22, 69-74]. The rate of antibiotic use in hospitalized patients with COVID-19 ranges from 40-100% [22, 74-81]. The antibiotics prescribed were often broad-spectrum including respiratory fluoroquinolones, cephalosporins, and carbapenems.

Growing data shows an increased burden of secondary infections in hospitalized patients especially those with late ventilation associated pneumonia [71, 73, 82-85]. Rouze et al demonstrated that the incidence of ventilator associated pneumonia was significantly higher in SARS-CoV-2 patients (50.5%) as compared to influenza patients (30.3%), being Gram negative bacteria the most common pathogens [83]. COVID-19 associated pulmonary aspergillosis (CAPA) has also been described in ventilated patients with COVID-19, with up to one third of ventilated patients having putative aspergillosis in one study [86, 87].

In addition, medications given in the management of COVID 19 to dampen the immune system, such as steroids and monoclonal antibodies, may increase the risk of secondary infections as shown in patients with rheumatoid treated with these agents. [88-90]. Emerging data suggest increased secondary infections in critically-ill patients treated with IL-6 inhibitors [87, 91]. Kimming et al reported an increase of secondary

bacterial (48.1 vs. 28.1%; p = 0.029) and fungal (5.6 vs. 0%; p = 0.112) infections with tocilizumab use compared to standard of care, in hospitalized patient with COVID-19 [91]. However, in randomized clinical trial, the use of tocilizumab was associated with a decrease in infections rates (infections: 17.1% in control group and 8.1% in tociluzumab P=0.03) and a recent meta-analysis the use of tocilizumab did not show a higher risk of infections or adverse events [56, 92, 93]. Hence it is still unclear if the use of immune-based therapy in the management of COVID- 19 increases secondary infections, especially that some of these agents such as dexamethasone, tocilizumab, and baricitinib can be associated with improved survival, shortening hospital stay and avoiding the need of intubation. Prolonged ventilation and hospitalization are risk factors for nosocomial infections; therefore, by decreasing the duration with the use of some immunotherapy, we might see a decrease in infection rates.

Although to date there are many meta-analyses, including network meta-analyses, for COVID -19 therapeutics, comparing the effects of different therapeutic agents on a variety of outcomes in patients with COVID-19, secondary infections are not always assessed. [92, 94-96]

We propose to conduct this systematic review, to assess if the rate of secondary infections in COVID-19 patients treated with immune-based therapy is increased compared to those that received standard of care.

F. Thesis objective

The objective of this systematic review is assessing whether the use of immune-based therapy in the management of adult patients (age ≥ 18) hospitalized with COVID 19, increases the risk of secondary infections compared to placebo or standard of care.

G. Thesis Hypothesis

Although the use of immunotherapy, such as steroids and monoclonal antibodies, increases the risk of secondary infections in general by supressing the immune system, we hypothesize that its use in the treatment of COVID 19 will mildly increase the risk of secondary infections. The use of steroids and some of these immune-based agents in COVID- 19 has shown to improve survival and other secondary outcomes such as ventilation days, need for ventilation and hospitalization; which are all well know risk factors for secondary infection in hospitalized patients. [97]

CHAPTER II

DATA AND METHODS

A. Protocol Registration

We developed the protocol of this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [97] and the protocol is published in the PROSPERO registry; protocol registration number PROSPERO CRD42021229406. Please refer to appendix B for the PRISMA item checklist

B. Eligibility criteria

1. Type of study

a. Inclusion

We included randomized controlled trial (RCT), non-randomized studies (NRS) published between January 2020 and January 2021. We elected to include NRS since we are not confident, that we would identify enough RCTs on immunotherapy that assessed secondary infections as an outcome to conduct the meta-analysis. No language restriction was applied to the search.

b. Exclusion

We excluded papers that are not peer reviewed yet, (ie: in pre-print form), meeting abstracts and dissertations of thesis.

2. Population

a. Inclusion

This study participants included adult (age 18 years and older) human patients, hospitalized and diagnosed with COVID-19 based on reverse transcriptase polymerase chain reaction (RT-PCR) testing or antigen testing.

b. Exclusion

We excluded pediatrics patients since the manifestations and the severity of illness is different in this age group. We excluded patients with COVID-19, that did not require hospitalizations since the severity of illness and the risk of infection in the outpatient setting is very different from patients hospitalized.

3. Intervention

a. Inclusion

We included studies where patients hospitalized with COVID 19 where treated with immune-based therapy; and this includes the following agent: Steroids, monoclonal antibodies suchinterleukin-6 (IL-6) inhibitors (tocilizumab, sarilumab, siltuximab), interleukin -1 inhibitors (IL-1)(anikinra), anti-CD147 (meplazumab), monoclonal antibody against C5 (eculizumab), Janus kinase (JAK) inhibitors (baricitinib ruxolitinib, fedratinib), bruton tyrosine kinase (BTK) inhibitor (acalabrutinib), pegylated interferon (IFN) or IFN alpha-2a or IFN alpha-2b, anti-tumor necrosisfactor (infliximab, etanercept, adalidumab) and colchicine. We did not limit to a specific dose or route or duration.

b. Exclusion

We excluded papers that assess the effect of interventions that do not act on the immune system and hence we excluded antivirals, vaccines, passive antibody, and traditional Chinese herbals; if used alone without immunotherapy. We also excluded studies, where infection was not collected according to the intervention given and studies where immunotherapy was used for the treatment of primary autoimmune disease or chronic inflammatory disease and not for management for COVID -19.

4. Comparators

We included no immunotherapy or placebo or standard of care in the control group as comparators.

5. Co-interventions

Any study with COVID-19 directed treatment, whether pharmacological or not, as long as it is delivered in the intervention and comparator groups was included.

6. Primary outcomes

Our primary outcome was secondary infections. Secondary infections are infections that occurred after immunotherapy or standard of care that is given for treatment of COVID-19 disease. Total infection was included as provided in each manuscript. In studies where they presented pathogens (bacterial, fungal, viral) or infectious syndrome (pneumonia, bacteremia, invasive fungal infections) without a total infections, we added the number of infections in each category to obtain total secondary infections. We did not include sepsis and septic shock when adding total infections

since infectious etiology is not always identified in these syndromes and could be secondary to SARS- Cov2 infection rather then superimposed infection. We presented sepsis and septic shock separately. We also presented each infection syndromes: pneumonia, bacteremia, fungal infections, sepsis and septic shock separately in the result sections. This was not planned in the original protocol, but we felt it would add granularity to the results.

C. Information sources

a) Search strategy: A search was executed by an expert searcher/librarian (SC) on the

following databases: OVID Medline, Ovid EMBASE, SCOPUS, Cochrane Library and clinicalTrial.gov using controlled vocabulary (eg: MeSH, Emtree, etc) and key words representing the concepts “Covid 19” and “immunotherapies” and “outcomes including secondary infections”. Prognostic hedges from the McMaster Health Information Research Unit were applied to the EMBASE and Medline searches .[98] Searches were adjusted appropriately for different databases. PROSPERO was also searched for previous systematic review on this topic. The initial search was in October, 2020 and updated on January 2021. No other limits were applied. Results were exported to to RefWorks and Covidence systematic review system and duplicates were removed. We also hand searched from references in manuscript identified by electronic database. Duplicates were removed in Covidence.

D. Search

Full electronic search can be found in appendix B

E. Study Selection

We reviewed references retrieved in the search strategy in duplicate and independently (DK, AS, KL, BW). We screened abstracts based on our eligibility criteria. We retrieved the full text of citations included by at least one reviewer. DK screened all studies and AS, KL, BW divided the studies between them. A calibration exercise was done on a sample of abstracts and full texts to make sure reviewers screening was standardized. We recorded the reasons for excluding studies. Using standardized data extract element, 5 reviewers ((DK, AS, KL, BW,MR) extracted data independently and in duplicate from each eligible study. DK extracted data from all while AS, KL, BS, MR divided the studies equally between them. To ensure consistency, we conducted a calibration exercise before starting the data extraction. Disagreements where resolved by discussion with an expert in this topic and thesis advisor CC who adjudicated unresolved disagreements.

F. Data items

Data abstracted included demographic information, methodology, intervention details, and all secondary infections reported in the outcomes. For demographic information extracted this included: country of the study, study size, year of the study, number of centers, funding source, trial registration numbers if applicable and the study design. The patient's characteristics (age, gender, DM, BMI, immunosuppression, setting, and severity of COVID (proportion with oxygen requirement, proportion with ventilation), diagnosis of COVID-19, intervention details (immune-based therapy used, including route, dosing, treatment duration, and concomitant immune-based therapies), and all secondary infections reported in the outcomes (proportion of patients with

bacteremia, pneumonia, urinary tract infection, sepsis, septic shock, invasive fungal infection, and viral infections). We did not collected time to infection since this data was missing from most studies.

G. Risk of Bias in individual studies

We used the Cochrane risk-of-bias tool for randomized controlled trial that covers the following six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[99] For NRS; we used key criteria proposed by the GRADE working group that include: 1. Failure to develop and apply appropriate eligibility criteria (inclusion of control population), 2.Flawed measurement of both exposure and outcome, 3. Failure to adequately control confounding, 4. Incomplete follow up.[100] Two reviewers independently assessed the study risk of bias with disagreements resolved by involving a third reviewer.

We also screened for the clinical trial registration at the international clinical trials registry platform of the World Health Organization (http://apps.who.int/trialssearch). We also evaluated publication biases using a funnel plot.

H. Data synthesis

Due to the heterogeneity among the studies in terms of study design and comparators, we used a random-effects model when conducting the meta-analyses. We analyzed RCTs and NRS separately. The primary analysis was the incidence of secondary infection in each group. Each outcome (including total infection, pneumonia, bacteremia, invasive fungal infection, sepsis, and septic shock) was analysed separately.

In studies that did not outline total infection in RCT we calculated the variable by adding different infectious syndrome with exception of sepsis and septic shock. The unit of analysis was based upon the aggregated outcome of secondary infections, as access to individual patient's data was unavailable. Dichotomous data was analysed using risk ratio (RR) with 95% confidence interval (CI). Non quantifiable data was narratively described. Statistical heterogeneity was determined using the I^2 statistic to assess appropriateness of performing a meta-analysis and categorized as: 1) 0% to 40%, might not be important; 2) 30% to 60%, moderate heterogeneity; 3) 50% to 90%, substantial heterogeneity; 75% to 100%, considerable heterogeneity. The statistical software RevMan 5·31 (Review Manager for MS Windows version 5·31, The Cochrane Collaboration, 2020) was used to calculate and combine each outcome.

In our protocol we predefined 3 subgroup analysis to try to explain the source of heterogeneity: 1) non critically ill vs critically ill (e.g., admitted to ICU) 2) Age (18-59) vs 60 and above, and immunosuppressed vs not. However, when we collected the data we realized that most do not separate based on critical illness but based need for oxygen, non-invasive ventilation and invasive mechanical ventilation so used that as surrogate of critical illness. We used meta-regression to explore the potential impact of age and invasive mechanical ventilation as a surrogate of severity of illness on the (log) RR of infection with immune-based therapies. For the meta-regression we conducted the analysis using the R package meta.[101] We could not perform a sub group analysis on immunosuppression, since most RCTs excluded these patients and very few observational studies included them.

We used sensitivity analysis to assess the impact on the overall outcome, for those studies

that have high rates of participant attrition, or other missing data and by omitting studies that are

judged to be at high risks of bias. In addition, since in few studies we calculated total infections we performed a sensitivity analysis by excluding these studies to ensure it did not affect the robustness of our outcome.

Based on screening of the literature, we expected some degree of heterogeneity in our study population and in the frequency and definitions of secondary infections. Heterogeneity may limit the interpretation of our results. We also presented the information in text and tables explaining the findings of the studies.

I. Confidence in cumulative evidence

The Grading of Recommendations Assessment, Development and Evaluation working group methodology was used to assess the certainty of evidence for primary outcomes. We assessed the quality of evidence across the domains of risk of bias, consistency, directness, precision and publication bias. [100] The evidence of whether use of immunotherapy in the treatment of COVID-19 increases the risk of secondary infection was presented and the Quality was graded.

CHAPTER III

RESULTS

The search strategy identified 7539 citations (Figure 1). After duplicate removal, we were left with 4989 citations for title and abstract screening. We identified 378 citations as eligible, for which we retrieved and screened the full text. After excluding 304 articles, we identified 74 papers that fulfilled our inclusion criteria. The most common reasons for exclusion were: no outcome of interest which is infection (137), outcomes was not assessed by immunotherapy given (42), abstract only (35), no comparator group without immunotherapy (30), duplicates (17), no outcome of interest in control group (15), wrong study design(8), letter to editor(11) , editorials(2), protocol or Prospero only (2), in two we did not have information on denominator for immunotherapy, preprint 1 and one no immunotherapy used for management of COVID-19 (Figure 1). Appendix B lists the excluded studies and the specific reason for exclusion of each one.

Our systematic review included the following randomized controlled studies (Table 1)

The immune-based therapies used in the RCTs consisted of corticosteroids in six studies [102-107], tocilizumab in five [56, 108-111], interferon in two [112, 113] ,baricitinib in one [114], ruxolitinib[115] in one and vilobelimab in one[116].

Most trials were registered online (15/16, 94%). A total of 3403 subjects were randomized (1906 to immunotherapy and 1496 to standard of care or placebo). The mean age in these trials was 60 years with a standard deviation of 3.7 and range 55 to 70; 63 % were male. In 14 trials (Angus, Cao, CorralGudino, Davoudi-Monfared,

Dequin, Hermine, Jeronimo, Edalatifard, Rahmani, Salama, Salvarani, Tomazini, Veiga, and Vlaar) the participants included had moderate to severe COVID-19, while in 2 trials (Kalil, Stone) , patients with mild disease were also included. At the time of randomization, 2.5 % did not require oxygen supplementation, 60 % were on oxygen, 10.5% required non-invasive ventilation, 25 % required invasive mechanical ventilation with and without extracorporeal membrane oxygenation (ECMO) (table 1, 2). Concurrent treatment with steroids and antivirals varied between trials (table 1).

We included fifty-eight NRS in our systematic review (table 3).[91, 93, 117-173] The following immunotherapy were used in treatment of COVID-19: Steroids, tocilizumab with and without steroids, anakinra with and without steroids, interferon, ruxolitinib, eculizumab, sarilumumab, baricitinib, mavrilimumab, interleukin-7. Table 3 describe the characteristics and outcomes in theses studies.

A. Risk of total infections with immune-based therapy

Out of the 16 RCTs included in this systematic review, 12 collected total infection as secondary outcomes or adverse effect (Salama, Stone, Veiga, Salvarini, Dequin, Edalatifard, Tomazini, Vlaar, Rahmani, Davoudi, Khalil and Cao). Hermine et al presented infection outcomes as bacterial sepsis, fungal sepsis and viral sepsis that we combined to get total infection. Angus et al presented only invasive fungal infection that we included as total infection. In the trial by Jerenimo et al, we included bacteremia as total infection and analyzed sepsis separately. Finally for the trial by Corral-Gudino et al we combined pneumonia and invasive fungal infections as total infection. There were 173 infections identified in 1906 patients receiving immunotherapy and 210 infections in 1496 receiving placebo or standard of care. The risk of infection with immunotherapy

was 9.1% vs 14 % with placebo. Based on a random effect meta-analysis, the summary RR was 0.74 (95 % CI, 0.58-0.96; p= 0.02). There was little inconsistency between the trial results (I^2= 26 %) (Figure 2).

Despite separating the NRS by drug type, considerable heterogeneity I2 remained (I^2 74% for steroids and 76% for Tocilizumab) between studies (supplementary A figures) and hence it was felt that a meta-analysis was not appropriate and we described the findings in table 3 and 4. In the majority of observational studies, there was an increase in infections in those treated with immunotherapy.

B. Influence of drug type, age, sex and need for invasive mechanical ventilation in RCTs

We explored subgroup analysis by immunotherapeutic agent and found no significant difference (p=0.41 and I^2 = 0.8%) (Figure 3)**.** Meta-regression revealed no impact of age (p= 0.86956), % females (p=0.87946) or % patients on mechanical ventilation, (p = 0.25275), on the effect of immune-based therapy on the risk of infection (Figure 6A, B, and C).

C. Risk of Bias in included studies

For the RCTs, 5 studies were judged low risk in all domains (Dequin, Jerenimo, Kalil, Salama, Stone); 6 studies were open label so were judged high risk in the domains of blinding (Angus, Cao, Corral-Gudino, Salvarani, Tomazini, Veiga); 5 had high risk of bias in several domains (Davoudi, Edalfirrad, Hermine, Rahmani, Vlaar). (Table 4 and Figure 7) In the observational studies, majority were judged as high risk

due to failure to adequately control confounding factors and flawed measurement of exposures and outcomes (Table 5 and figure 8)

D. Sensitivity Analysis

By omitting studies with high rates of participant attrition, or other missing data or studies that were judged to be at high risks of bias. (Davoudi, Edalfirrad, Hermine, Rahmani, Vlaar) the summary RR remained in favor of immunotherapy RR= 0.71 CI 95% (0.56- 0.90; p= 0.005) (Figure 9). Moreover by omitting studies where the total number of infections was calculated (Angus, Corral-Gudino, Jerenimo, Hermine) the results were not altered RR= 0.74 CI 95% (0.59- 0.92; p= 0.007). (Figure 10).

E. Risk of pneumonia, bacteremia, IFI, sepsis and septic shock with immune-based therapy in RCTs

Eight trials assessed the risk of secondary pneumonia in hospitalized patients with COVID treated with immunotherapy. (Corral, Sequin, Kalil, Rahmani, Salama, Tomazini, Vlaar, Veiga). (Figure 5A). The risk of pneumonia was 65/1131 with immunotherapy versus 99/998 with placebo. Based on a random effect meta-analysis, the summary RR was 0.67 (95 % CI, 0.41-1.09; p= 0.11). There was moderate inconsistency between the trial results (I^2= 44%). Six trials assessed bacteremia secondary to immune-therapy (Dequin, Jeronimo, kalil, Rahmani, Tomazini, Veiga). The risk of bacteremia was 34/946 with immunotherapy vs 39/295 with placebo. Based on a random effect meta-analysis, the summary RR was 0.83 (95 % CI, 0.53-1.31; p= 0.43). There was low inconsistency between the trial results (I^2= 0%) (Figure 5B). Four trials assessed the risk of invasive fungal infections post immune-therapy (Angus,

Corral-Gudino, Hermine, kalil). The risk of IFI was 3/891 (0.3%) participants on immune-based therapy versus 4/715 (0.6%) with placebo (Figure 5C). Based on a random effect meta-analysis, the summary RR was 0·68 (95%CI 0.16-2.85; p= 0.59) with low inconsistency between the trial results (I^2=0%). Seven trials assessed the risk of sepsis (Cao, Corral-Gudino, Hermine, Jerenimo, kalil, Salvarani, Vlaar) and four septic shock (Davoudi, kalil, Rahmani, Salama) after immune-based therapy. The risk of sepsis and septic shock with immunotherapy compared to placebo was 81/894 versus vs 104/903 and 23/832 versus vs 24/708 respectively. Based on a random effect meta-analysis, the summary RR for sepsis and septic shock was 0.52 (95 % CI, 0.25-1.09; p= 0.73) and 0.88 (95 % CI, 0.50-1.55; p= 0.67) respectively. There was low inconsistency between the trial results (sepsis: I^2= 38% and septic shock: I^2= 0%; for heterogeneity) (Figure 5D, and E).

F. Certainty of evidence using GRADE

We rated the certainty of evidence to assess the risk of infection with immune-based therapy compared to control in adults hospitalized with moderate to severe COVID -19, using GRADE, , as moderate (Table 6). Although the evidence derived from randomized controlled trials is considered as high quality of evidence, it was downgraded because of the high risk of bias in five trials. Although we included different immunotherapeutic agents, we considered the indirectness low, since all these agents work of the aberrant immune system caused by SARS-CoOV-2

CHAPTER IV

DISCUSSION

A. Review of findings

In this systematic review and meta-analysis of 16 randomized clinical trials that included adult patients with COVID-19 requiring hospitalization, the use of immune-based therapies was associated with lower risk of secondary infections from the time of randomization as compared to standard of care. The decrease risk of infection is not dependent on age, sex or mechanical ventilation at inclusion.

B. Comparison of findings of secondary infection in non-COVID-19 literature

The protective effect of immune-based therapies for secondary infections in severe COVID-19 in RCTs seems initially as a surprise, considering previously published data showing increased risk of infections when these agents are used. [89, 90] The use of short-course corticosteroids, generally prescribed for upper respiratory tract infections, acute spinal conditions, and allergies, was associated with 5.3-fold increase in the risk of sepsis within 30 days of drug initiation in a large, population-based study in the United States [174]. When corticosteroids are used as adjunctive treatment for influenza requiring hospitalization, a pooled analysis of 7 studies from systematic review and meta-analysis including 1 RCT and 29 observational studies showed a 2.7-fold increased risk of hospital-acquired infection [175]. In a meta-analysis including 6 RCTs from a systematic review on the use of tocilizumab for rheumatoid arthritis, only the combination of tocilizumab at 8 mg/kg with methotrexate mildly (OR 1.3) increased the risk of infection ([176]). Sarilumab, another monoclonal antibody targeting the

interleukin-6 receptor, has also shown no increased risk of infections in patients with rheumatoid arthritis with and inadequate response to conventional disease-modifying antirheumatic drugs [177]. Baricitinib, a Janus Kinase (JAK) inhibitor, at a dose of 4 mg, increased the risk for infections (RR, 1.28; 95% CI, 1.12 to 1.45) compared to placebo in a meta-analysis of 6 RCTs including 3520 patients with rheumatoid arthritis ([177]). Ruxolitinib, another JAK Janus kinase inhibitor, increases the risk of opportunistic and non-opportunistic infections [178]. For vilobelimab, a chimeric monoclonal IgG4 antibody binding C5a, the information is limited to a single-arm study in 12 participants with hidradenitis suppurativa, six of whom experienced nine adverse events, three being infectious [179].

C. Hypothesis for decreased risk of infection

We hypothesize that there are two main reasons that can explain the decreased risk of infections in treating hospitalized COVID-19 patients treated with immune-based therapies. First, the use of corticosteroids and tocilizumab have shown better clinical outcomes such as the need for invasive mechanical ventilations, shorter hospitlization and, in the case of corticosteroids definitively, survival [92, 94] [180]. Both corticosteroids and tocilizumab decreased the risk for mechanical ventilation (OR 0.74 and OR 0.71, respectively) in a meta-analysis including 3 studies and 6,873 patients for corticosteroids, and 6 studies and 771 patients for tocilizumab ([181]; [92]). Therefore, by decreasing hospitalization rates, ICU admissions and need for ventilations, this might explain the lower rates of infection. In addition as the protective effect conferred by immune-based therapy for COVID-19 is highest for secondary pneumonia, we hypothesize can infer that lesser or no time on mechanical ventilation

may decrease prevent the occurrence of ventilator-associated pneumonia. Second, patients with severe COVID-19 display either macrophage activation syndrome or very low HLA-DR expression accompanied by a profound depletion of CD4 lymphocytes, CD19 lymphocytes and NK cells. Therefore by partially rescuing this immune profile with interleukin-6 blockage by tocilizumab, there is restoration of HLA-DR expression on monocytes [33]. It is reasonable to believe that other drugs targeting different pathways of the inflammatory response may also partially revert the consequences of this aberrant immune response and restore optimal immune responses against other pathogens.

It is important to emphasize the significant discrepancy between the observational and the randomized clinical trials of this systematic review on the risk of secondary infections in hospitalized patients with COVID-19. While randomized controlled trials showed a protective effect, in the observational studies, comparing tocilizumab to standard of care or corticosteroids to standard of care showed that treatment with tocilizumab or corticosteroids increased the risk of secondary infections. The heterogeneity between these studies was very high, with I^2 values over higher than 70%, and the risk of bias was high, driven in large part by especially because of failure to adequately control for confounding. In addition, we should also emphasize that meta-regression analysis did not identify changes in the protective effect according to age, sex or and requirement for mechanical ventilation.

Immune-based therapies for severe COVID-19 have been the only treatments demonstrating survival benefit to dates so far. According to the results of this meta-analysis also demonstrate, the use of corticosteroids, anti-interleukin 1 and 6 monoclonal antibodies, anti-C5 and -C5a monoclonal antibodies, JAK inhibitors and

interferon are associated with lower rates of secondary infections compared to standard of care. These treatments should not be delayed when indicated including in older or mechanically ventilated patients where there was no increase in the risk of secondary infections observed.

Guidelines on the treatment of severe COVID-19 should reflect our findings and make appropriate recommendations about the use of preventive antibiotics and antifungals. In the absence of data to support their use, the potential for adverse effects and our findings in this meta-analysis, and no additional antibiotic or antifungal prophylaxis should be administered in patients receiving these immunomodulating drugs. In addition, its use in older or mechanically ventilated patients should not increase the risk of secondary infections. Guidelines on the treatment of severe COVID-19 should reflect our findings and make appropriate recommendations about the use of preventive antibiotics and antifungals.

D. Limitations and Strengths

This study has several limitations. First, the definitions and reporting of infectious adverse events were not consistent across the trials. While this lack of consistency precludes estimating the rates of infectious complications for each immune-based therapy compared to standard of care, there is no reason to believe that will impact on the protective association measures.

Second, although there is little missing outcome data, no follow up was done after hospital discharge in most trials and the rates of secondary infection after hospital discharge are not evaluated. The potential immunosuppressive effects for some of the evaluated drugs may persist in time. For instance, short term use of corticosteroids

increases the rates of sepsis by 2.5-folds between 31-90 days after discontinuation [174] and tocilizumab and sarilumab both have both a half life of around 10 days [182],[183]

Third, some trials allowed combining the study drug with other immune-based therapies. All RCTs evaluating tocilizumab allowed the concomitant use of corticosteroids ranging from 11-80% of all participants included in the interventional arm and 1 participant received at least tocilizumab plus anakinra. In one RCT evaluating hydrocortisone, 1 participant in the interventional arm received tocilizumab and 3 eculizumab. In the 2 RCTs evaluating interferon β, 15% and 62% of the participants randomized to interferon received corticosteroids. Seventy percent of the participants assigned to ruxolitinib received concomitant treatment with corticosteroids. Finally, 17% of the participants randomized to receive baricitinib plus remdesivir received corticosteroids. Despite the obvious limitation in the accuracy of the estimations, it is important to highlight that the high frequent co-administration reinforces the hypothesis of using immune-based therapies as the first-line therapy for severe COVID-19.

Fourth, we used mechanical ventilation as a surrogate marker for the severity of the disease. There are reasons to use mechanical ventilation in COVID-19 other than the severity of the disease. As an example, early intubation has been suggested by some authors to interrupt the progressive lung deterioration mediated by tissue stress, raise pulmonary transvascular pressures, vascular flows and fluid leakage [184]. Although mechanical ventilation may not accurately reflect the severity of COVID-19, stratifying the risk according to this variable is highly relevant as orotracheal intubation is a major risk factor for hospital-acquired pneumonia. .

Finally, the protective effect of immune-based therapies may not be generalized to all populations. The RCTs included in this meta-analysis were mostly done in high income countries, in adults, in individuals without concomitant infections (or without previous specific infections such as tuberculosis) and those not previously on exogenous without immunosuppression. More information is required to evaluate the protective effect of immune-based therapies for secondary infections in specific populations such as children and immunocompromised patients.

Strengths

This is the first systematic review and meta-analysis evaluating the risk of secondary infections using immune-based therapies in patients hospitalized with COVID-19. We had enough RCTs included that we performed meta-analysis without having to include NRS that are lower level of evidence and associated with increased bias

E. Conclusion

This systematic review and meta-analysis provides an evidence base review that could be used to support future guidelines on the management of hospitalized patients with COVID-19 treated with immune-based therapy

Figure 1: PRISMA Flow diagram of Systematic Review

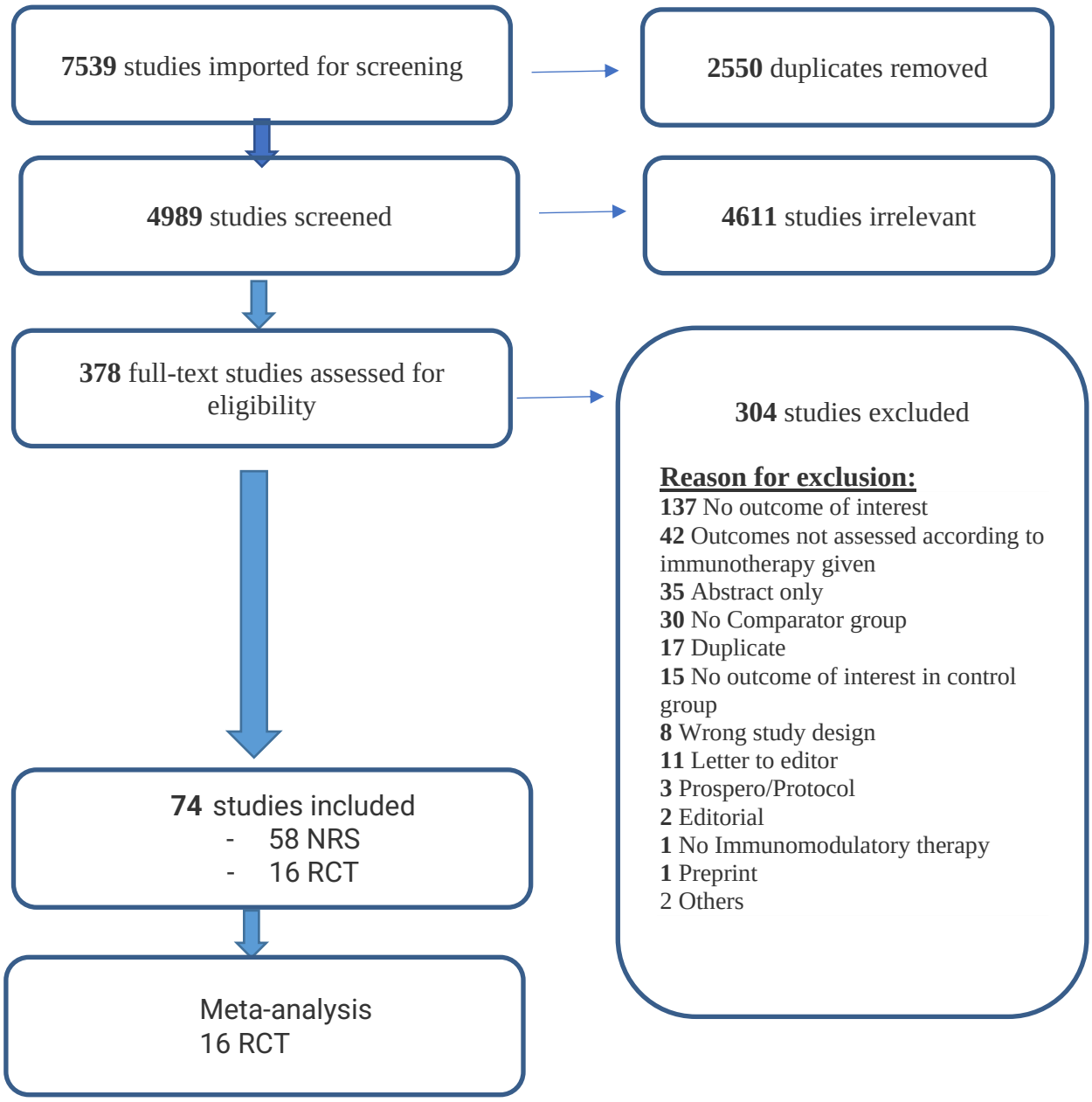

Figure 2: Risk of infection with immune-based therapy in randomized controlled trials.

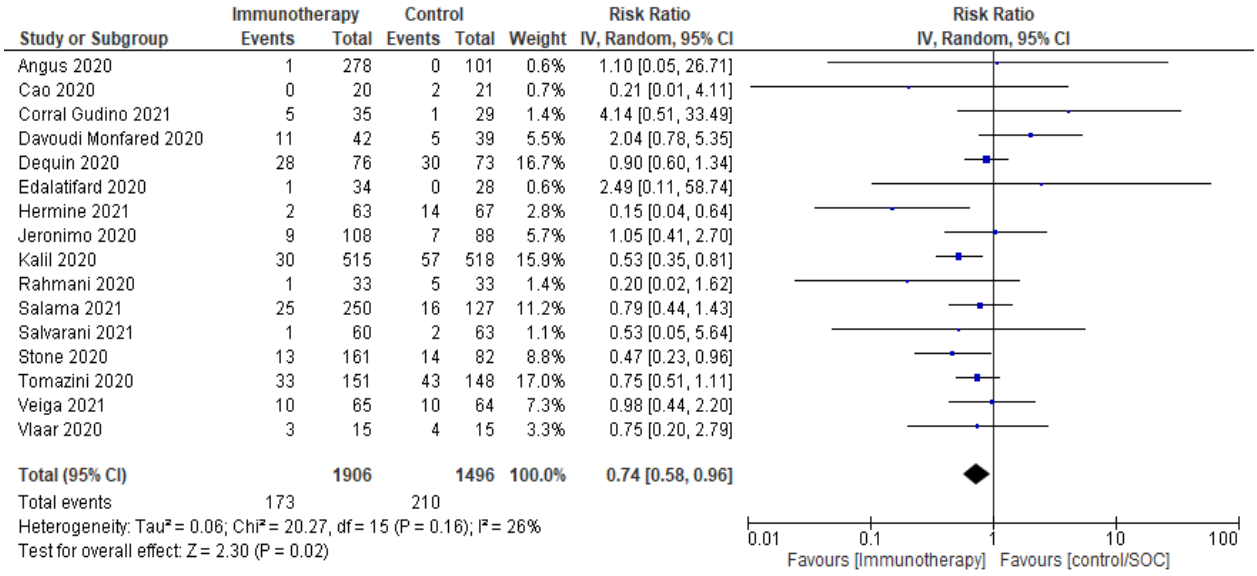

Figure 3: Risk of infection with different immune-based drugs in randomized controlled trials.

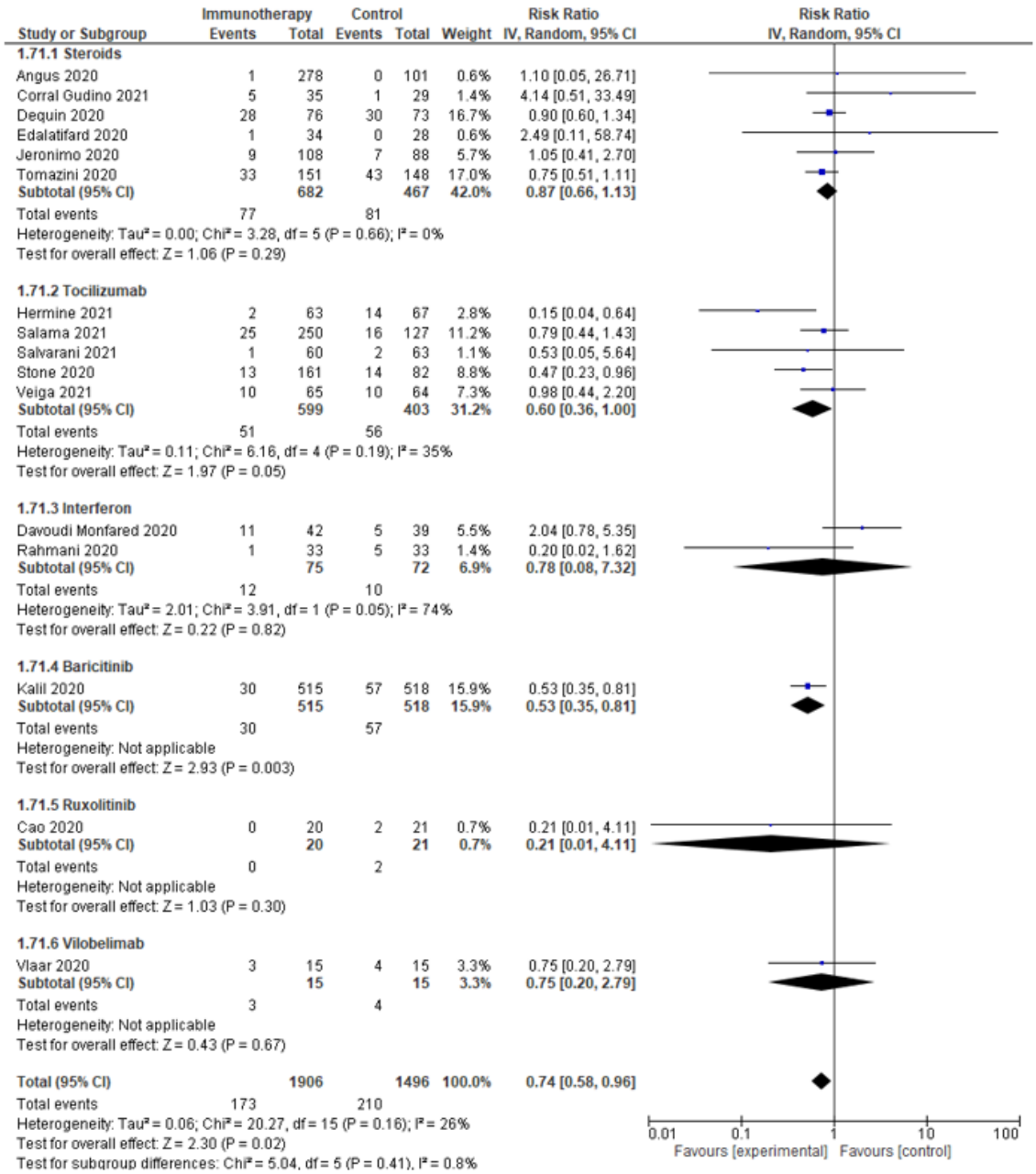

Figure 5A: Risk of pneumonia with immune-based therapy in randomized controlled trials

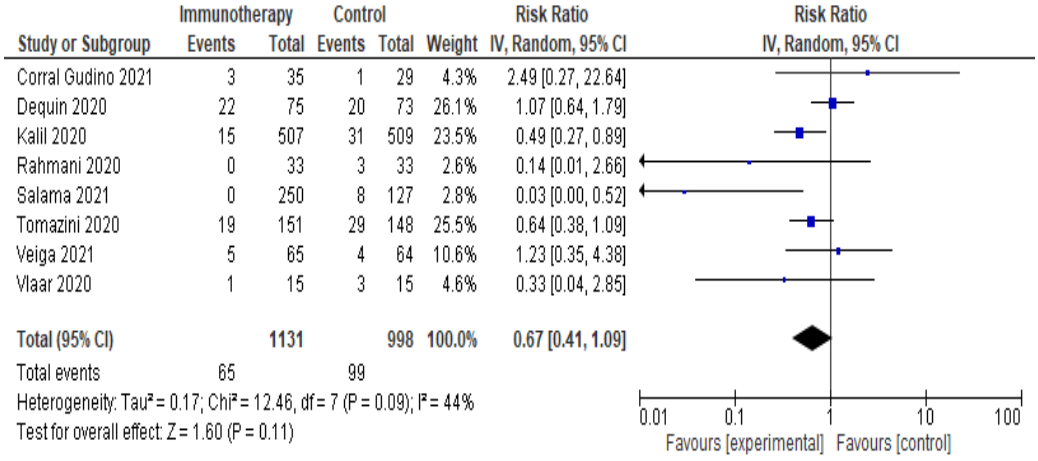

Figure 5B: Risk of bacteremia with immune-based therapy in randomized controlled trials.

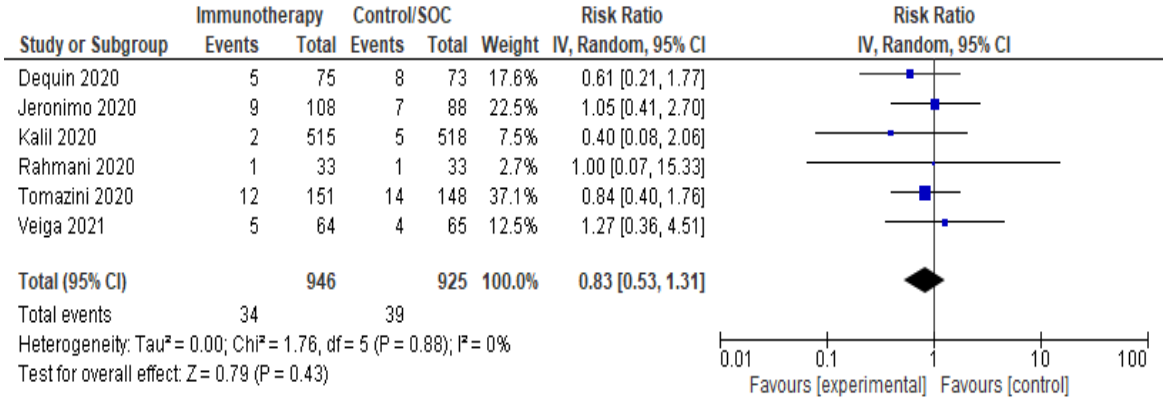

Figure 5C: Risk of invasive fungal infection with immune-based therapy in randomized controlled trials.

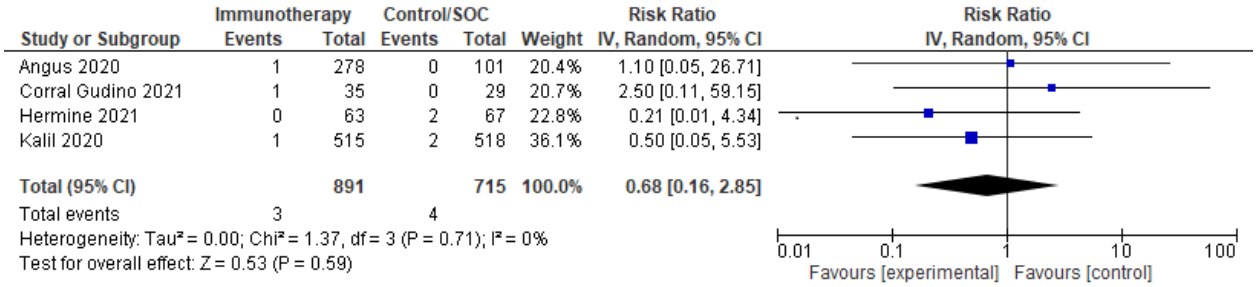

Figure 5D: Risk of sepsis with immune-based therapy in randomized controlled trials.

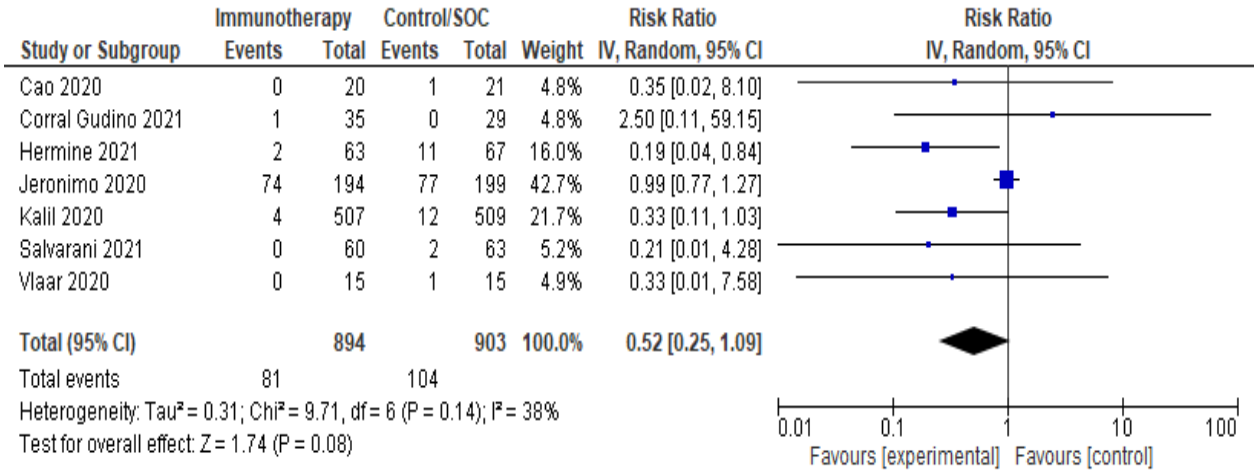

Figure 5E: Risk of septic shock with immune-based therapy in randomized controlled trials.

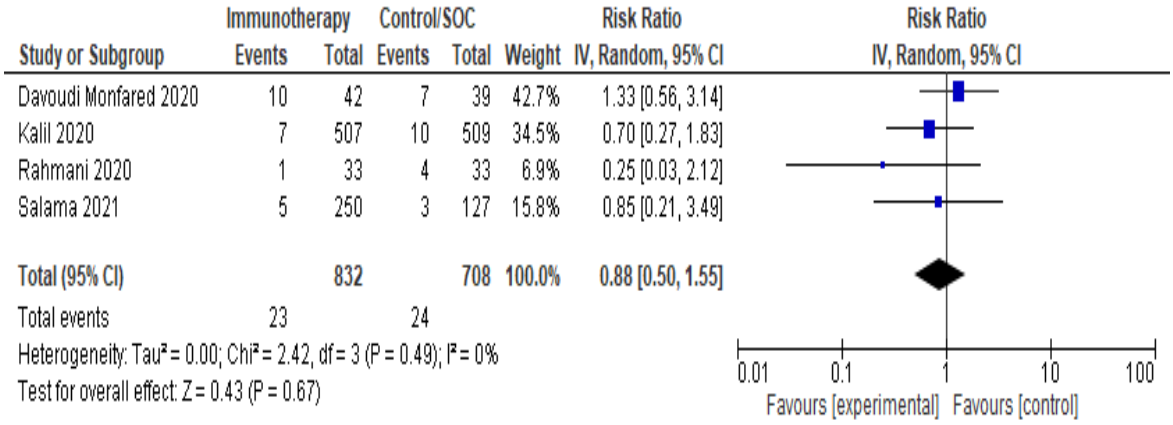

Figure 6A: Meta-regression: Age on (log)RR of infection with immune-based therapies

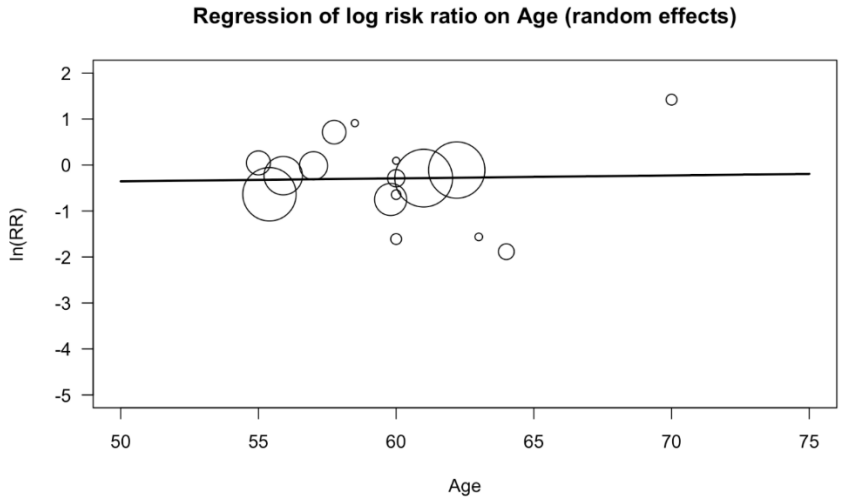

Figure 6B: Meta-regression: Percentage of female sex on (log)RR of infection with immune-based therapies.

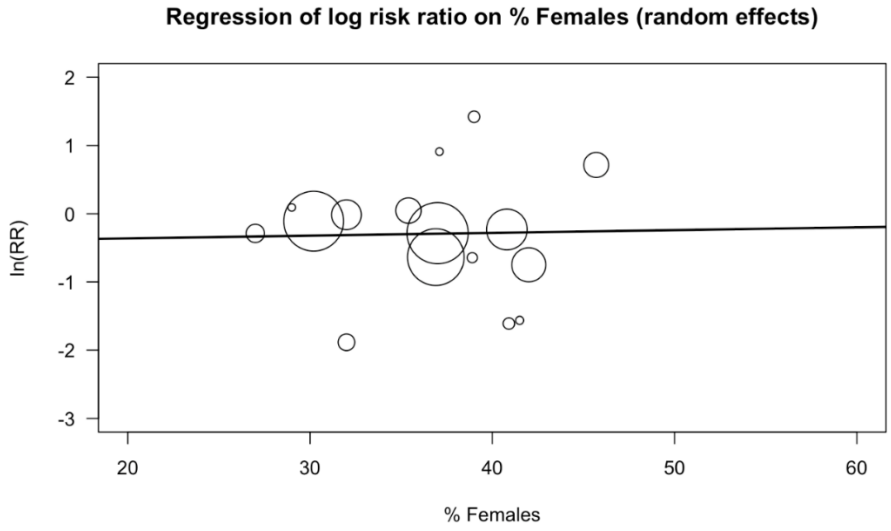

Figure 6C: Meta-regression: Percentage of invasive mechanical ventilation on (log)RR of infection with immune-based therapies.

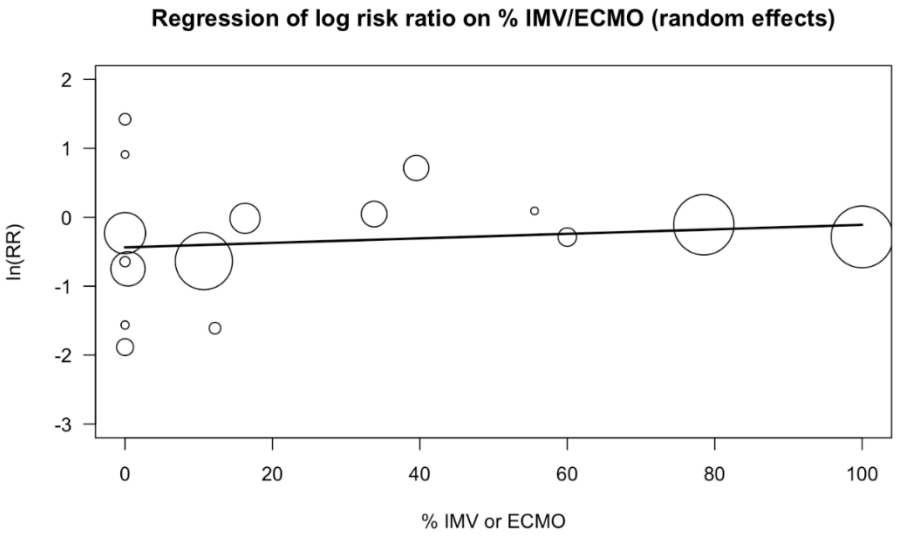

Figure 7: Risk of bias in randomized clinical trials

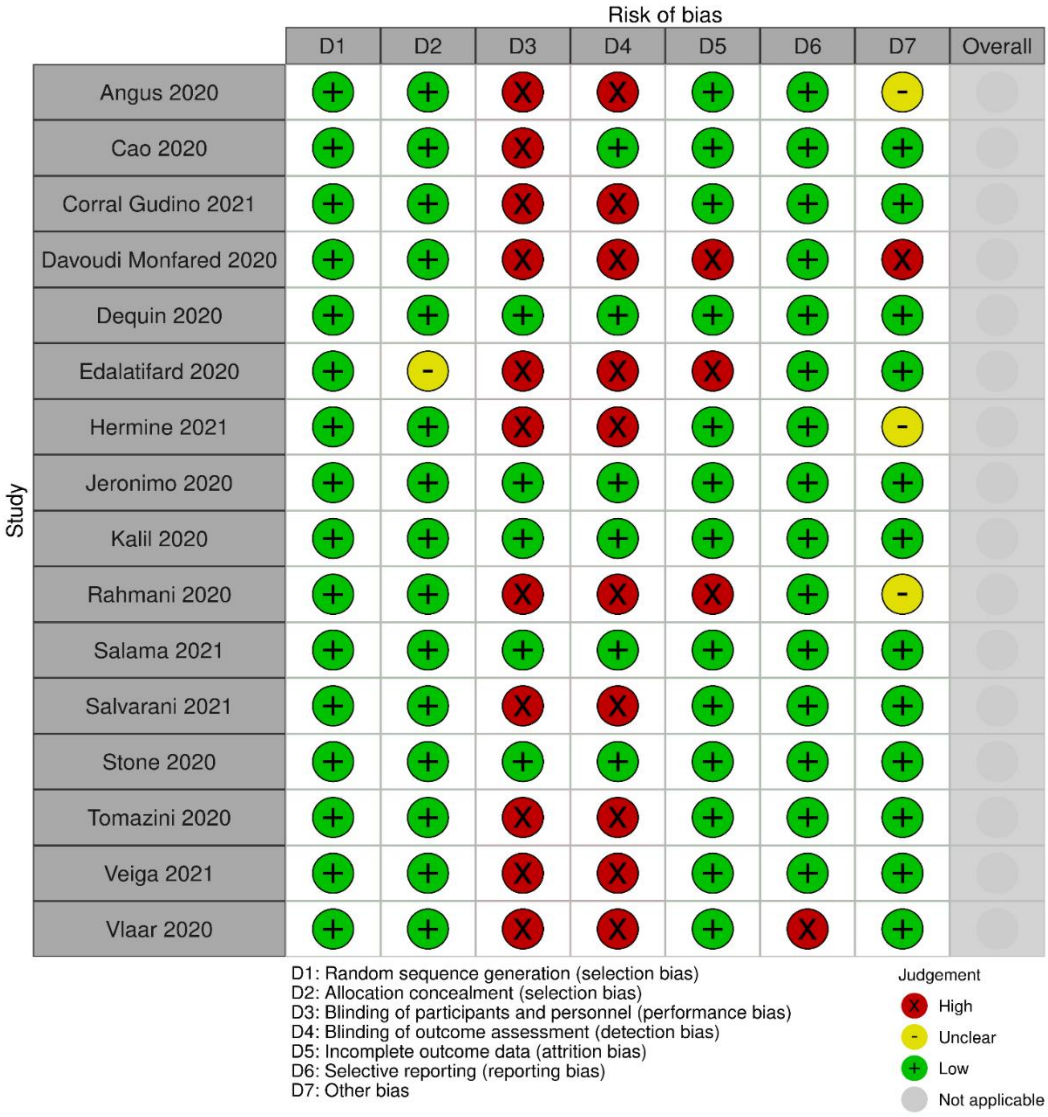

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Figure 8: Risk of bias in non-randomized studies

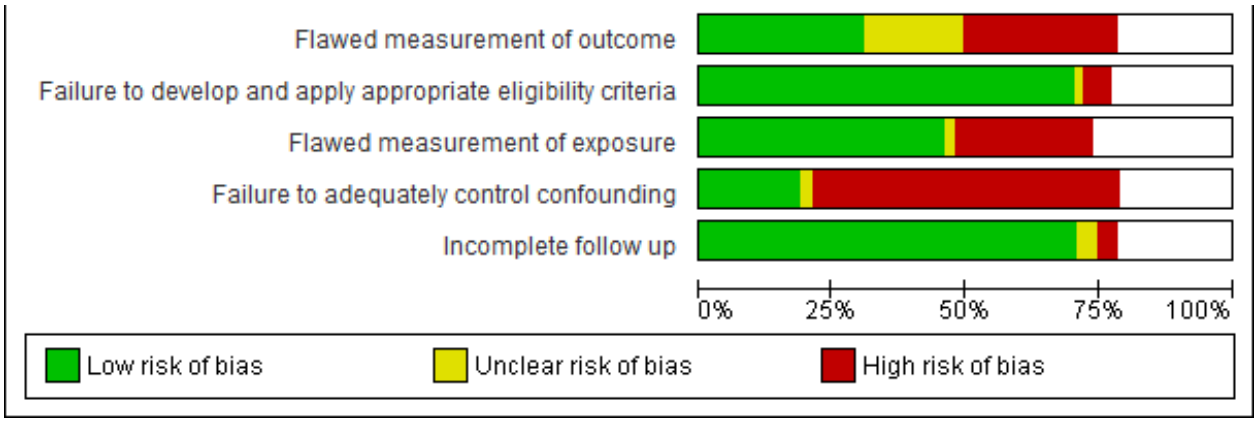


Figure 9: Sensitivity Analysis

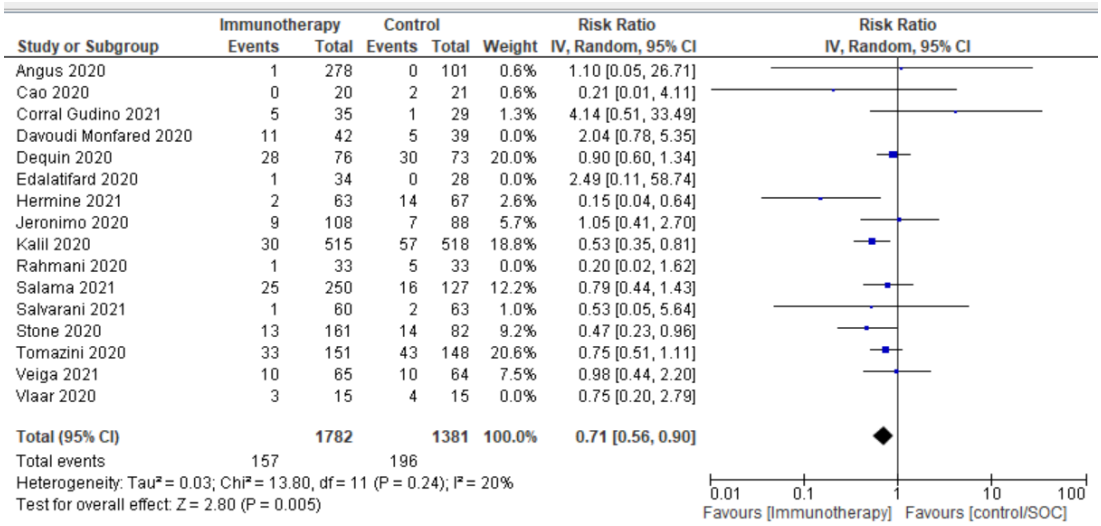


Figure 10: Sensitivity Analysis (omitting studies with calculated total infection)

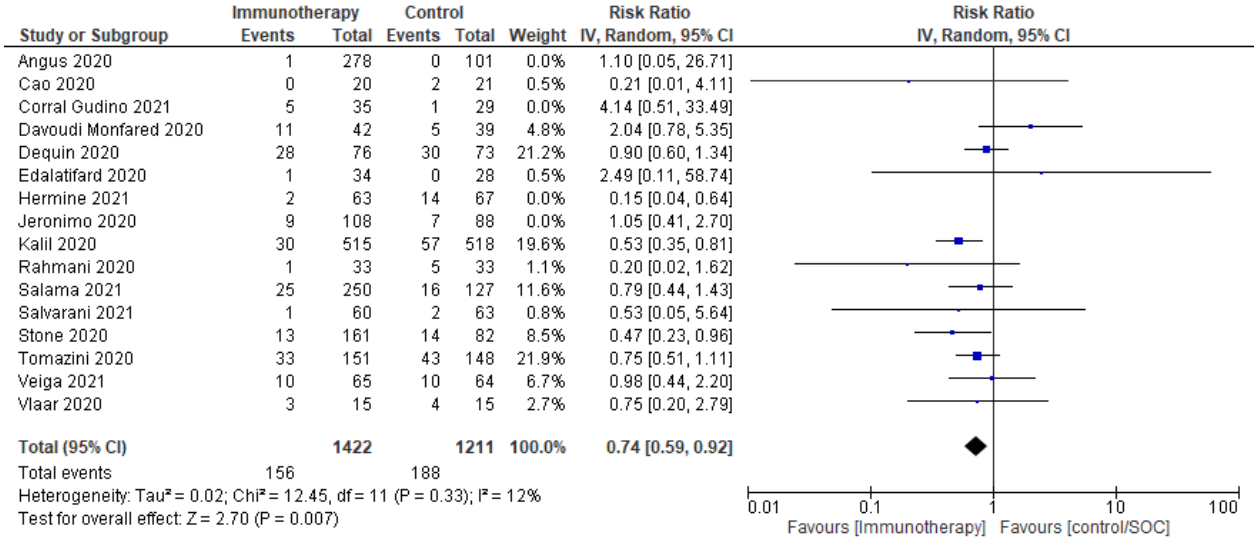
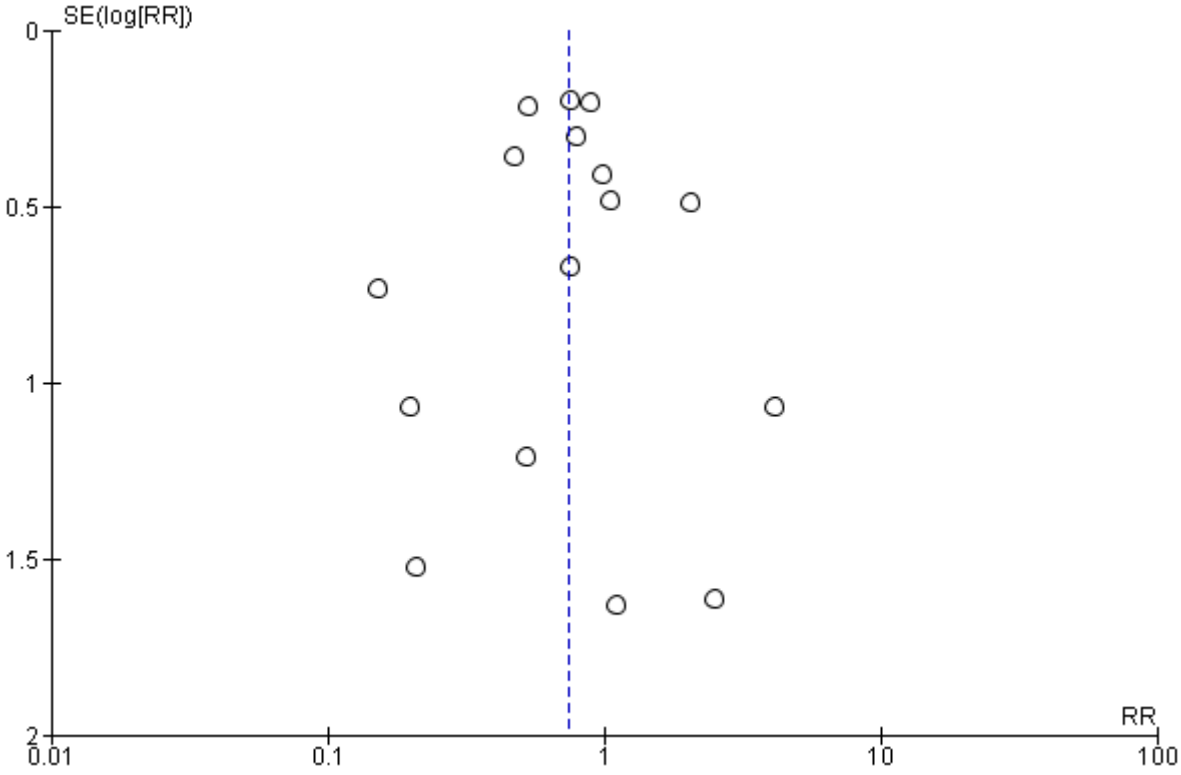


Figure 11: Funnel plot for publication bias.



Author-Year Trial name	**Design and Setting**	**Participants**	**Intervention Dose/Route and duration**	**SOC**	**Co-intervention (%)**	**Outcomes**
Salama 2021 EMPACTA	Double blind placebo control Multicenter	I: 249 C:128	Tocilizumab IV 8mg/kg 1-2 doses	Antiviral, Remdesivir:I:131(52.6) C:75 (58.6)	Steroids I:200 (80.3), C:112(87.5)	Total infection: I:25/250, C:16/127
Stone 2020 BACC Bay Tocilizumab	Double blind placebo control Multicenter	I:161 C:81	Tocilizumab IV 8mg/kg (max 800mg), 1dose	Antiviral, HCQ, Remdesivir:I: 53 (33)C: 24 (29)	Steroids: I: 18 (11%) C: 5(6%)	Total infection I: 13/161, C: 14/82
Veiga 2021	Open label Multicentre	I:65 C: 64	Tocilizumab IV 8mg/kg (max 800mg), 1 dose	HCQ, AZM, antibiotics	Steroids: I: 45 (69)C: 47 (73)	Total infection: I: 10/65, C: 10/64
Salvarani 2021	Open-label Multicenter	I:60 C: 66	Tocilizumab IV 8mg/kg (max 800mg), 2 doses	Varied as per treatment protocol of each center	Steroids: I: 7 (11.7) C: 5 (8.3)	Total Infection: I: 1/60C: 2/63
Hermine 2021 CORIMUNO-TOCI1	Open-label Multicenter	I: 63 C:67	Tocilizumab 8mg/kg (1st dose); 400mg (2nd dose) 1 or 2 doses	AZM, HCQ, LPV/r, LPV, RDV, Oseltamivir,	Steroids: I: 21 (33) C: 41 (61) Anakinra: I: 1 (2) C: 3 (4.4) Eculizimab I:0 C: 1 (1.6)	Total infection: I: 2/63 C: 14/67
Dequin 2020 CAPE-COD	Double blind placebo control Multicenter	I: 76 C:73	Hydrocortisone IV 200mg/dayx7d,100mg/day x4d, 50mg/day x3d	HCQ,AZM, LPV/r, RDV	Tocilizumab: I: 1(1.3) C: 2(2.7) Eculizumab: I: 3(3.9)C: 2(2.7)	Total infection: I: 28/76 C: 30/73
Angus 2020 REMAP-CAP	Open label Multicenter	I: 278 C:101	Hydrocortisone IV 50mg q6hrs x7days or 50 mg q6hrs until shock resolved/vasopressors discontinued for 24 hrs, max 28 days			Total infection: I: 1/278 C: 0/101
Edalatifard 2020	Single blind Multicenter	I:34 C:24	Methylprednisolone IV 250mg/day x 3d (3 doses)	HCQ, LPV, naproxen		Total infection: I: 1/34 C: 0/28
Tomazini 2020 Codex	Open-label Multicentre	I: 151 C:148	Dexamethasone IV 20mg x5d; then 10mgx5d 10 doses	AZM, antibiotics, HCQ	Steroids: C: 52 (35.1)	Total infection: I: 33/151 C: 43/148
Jeronimo 2020 Metcovid	Double blind Single center	I: 108 C:88	Methylprednisolone IV: 0.5mg/kg BID x 5d 10 doses	Antibiotics		Total infection: I: 9/108 C: 7/88
Corral-Gudino 2021 GLUCOCOVID	Open-label Multicentre	I:35 C:29	Methylprednisolone IV 40mg BID x 3d, then 20mg BID x 3d 12 doses	Antibiotics, AZM, HCQ, LPV/r		Total infection: I: 5/35 C: 1/29
Vlaar 2020 PANAMO	Open label Multicentre	I: 15 C:15	Anti-C5a Ab (IFX-1) IV 800mg Up to 7 doses	HCQ		Total infection: I: 3/15 C: 4/15
Rahmani 2020	Open-label Single center	I:33 C:33	Interferon SQ B-1b 250mcg every 2nd day for 2 weeks	LPV/r or ATV/r, HCQ	Steroids: I: 5 (15.15) C: 9 (27.27)	Total infection: I: 1/33 C: 5/33
Davoudi-Monfared 2020	Open-label Single center	I:42 C:39	Interferon B-1a 44mcg/mL SQ (12 MIU/mL) 3x/week for 2 weeks	HCQ, LPV/r, ATV/r	Steroids: I: 26 (61.9) C: 17 (43.58)	Total infection: I: 11/42 C: 5/39
Kalil 2020 ACTT-2	Double blind Placebo control Multicenter	I: 515 C:518	Barcitinib: PO 4mg/day x14d or until discharge Remdesivir IV:	Remdesivir IV: 200mg x 1d, then 100mg x 9d or until discharge	Steroids: I: 87 (16.9) C: 104 (20)	Total infection: I: 30/515, C:57/518

			200mg x 1d, then 100mgx 9d or until discharge			
Cao 2020	Single blind Placebo control Multicenter	I:20 C: 21	Ruxolitinib PO 5mg BID 56 doses	Antivirals, antibiotics Placebo: Vit C PO BID 56 doses	Steroids: I: 14 (70) C: 15 (71.4)	Total infection: I: 0/20 C: 2/21

Table 1: Characteristics of RCT ATV/r: atazanavir/ritonavir; AZM: azithromycin; BID: twice a day; C: control; HCQ: hydroxychloroquine; I: intervention; IV: intravenous; LPV/r: lopinavir/ritonavir; PO: per os; RDV: remdesivir; SOC: standard of care; SQ: subcutaneous; Vit C: vitamin C

Author year	**PCR**	**Age either mean +/- SD or median (IQR)**	**Sex M n (%)**	**Co-morbidities**	**Mechanical Ventilation**	**Outcomes**
Salama 2021	100%	I: 56.0 ±14.3 C: 55.6 ±14.9	I: 150 (60.2) C :73 (57.0)	DM:I: 105 (42.0), C: 48(37.8) Obesity: I: 54 (21.6), C: 38 (29.9) BMI: I: 32.0±7.9, C: 33.1±7.2	None	Total infection: I: 25/250, C: 16/127 Pneumonia: I: 0/250 C: 8/127 Septic shock : I: 5/250 C: 3/127
Stone 2020	PCR or Ag	I: 61.6 (46.4 - 69.7) C: 56.5 (44.7 - 67.8)	I: 96 (60) C: 45 (55)	DM I: 45 (28) C: 30 (37) Obesity I: 80 (50)C: 42 (51) BMI: I: 29.9 (26.0-34.2) C: 30.2 (25.7-33.8)	(0.4)	Total infection I: 13/161, C: 14/82
Veiga 2021	100%	I: 57.4 (15.7) C: 57.5 (13.5)	I: 44 (68) C: 44 (69)	DM I: 22 (34) C: 20 (31) Obesity: I: 15 (23), C: 16 (25)	I: 11 (17) C: 10 (16)	Total infection: I: 10/65, C: 10/64
Salvarani 2021	100%	I: 61.5 (51.5-73.5) C: 60.0 (54.0 - 69.0)	I: 40 (66.7) C: 37 (56.1)	DM: I: 10 (16.7), C: 9 (13.6) Obesity: I: 16 (28.1), C:22 (36.1)	None	Total Infection: I: 1/60, C: 2/63 Sepsis: I: 0/60, C: 2/63
Hermine 2021	I: 56 (89%) C: 61 (90%)	I: 64.0 (57.1-74.3) C: 63.3 (57.1-72.3)	I: 44 (70) C: 44 (66)	DM: I: 20 (33), C: 23 (34) BMI: I: 27.9 (23.3-30.8) C: 27.4 (24.5-31.3) - determined from n=46	None	Total infection: I: 2/63, C: 14/67 Sepsis: I: 2/63, C: 11/67 IFI: I: 0/63, C: 2/67 Bacterial: I: 2/63, C: 11/67
Dequin 2020	PCR (96.6%)	I: 63.1 (51.5-70.8) C: 66.3 (53.5-72.7)	I: 54 (71.1) C: 50 (68.5)	DM: I: 13(17.1)C: 14 (19.2) Immunosuppression: I: 6 (7.9), C: 3 (4.1)	I: 62 (81.6) C:59(80.8)	Total infection: I: 28/76, C: 30/73
Angus 2020	PCR: I-A: (109/134 (81.3) C: 79/100 (79) I-B: 87/125 (69.6)	I-A: 60.4±11.5 C: 59.9±14.5 I-B: 59.5±12.7	I-A: 98 (71.5) C: 72 (71.3) I-B: 103 (70.6)	DM: I-A: 50/129 (38.8), C: 30/98 (30.5) I-B: 39/144 (27.1) Immunosuppressive disease: I-A: 7/127 (5.5), C: 2/95 (2.1), I-B: 9/144 (6.3) Immunosuppressive therapy: I-A: 8/137 (5.8), C: 6/100 (6), I-B: 7/142 (4.9)	I-A: 87 (63.5) C: 73 (50) I-B: 53 (52.5)	Total infection: I 1/278 C: 0/101 IFI: 1/278, C: 0/101
Edalatifard 2020	100%	I: 55.8±16.35 C: 61.7±16.62	I: 24 (70.6) C: 15 (53.6)	DM: I: 8 (23.5), C: 14 (50)	None	Total infection: I: 1/34, C: 0/28
Tomazini 2020	I: 144 (95.4) C:142 (95.9)	I: 60 (44.3-75.9) C:62.7 (49.6-75.7)	I: 90 (59.6) C: 97 (65.6)	DM: I: 57 (37.8), C: 69 (46.6) Obesity: I: 46 (30.5), C: 35 (23.7)	I: 151 (100) C: 148 (100)	Total infection: I: 33/151, C: 43/148 Pneumonia: I: 19/151, C: 29/ 148 Bacteremia: I: 12/151, C: 14/148 UTI: I: 1/151, C: 0/148
Jeronimo 2020	I: 161/193 (83.4) C: 157/198 (79.5)	I: 54±15 C: 57±15	I: 126 (64.9) C: 128 (64.3)	DM: I: 54/180 (30.0), C: 52/184 (28.3) BMI: I: 29.0 (25.4–32.4), C: 28.9 (25.7–34.1)	I: 66 (34) C: 67 (33.7)	Total infection: I: 9/108, C: 7/88 Bacteremia: I: 9/108, C: 7/88 Sepsis: I: 74/194, C: 77/199
Corral-Gudino 2021	100%	I: 73 (62-84) C:66 (54-78)	I: 23 (66) C:15 (55)	DM: I: 7 (20) C: 4(14)	None	Total infection: I: 5/35, C: 1/29 Pneumonia: I: 3/35, C: 1/29 Sepsis: I: 1/35, C: 0/29

						IFI: I: 1/35, C: 0/29
Vlaar 2020	100%	I: 58±9 C: 63±8	I: 11 (83) C: 11 (83)	DM: I: 4 (27), C: 4 (27) Obesity: I: 2 (13), C: 4 (27)	I: 8 (53) C: 10 (67)	Total infection: I: 3/15, C: 4/15 Pneumonia: I: 1/15, C: 3/15 Sepsis: I: 0/15, C: 1/15 UTI: I: 1/15, C: 0/15
Rahmani 2020	100%	I: 60 (47-73) C: 61 (50-71)	I: 20 (60.6) C: 19 (57.57)	DM: I: 9 (27.27), C: 12 (36.36)	I: 3 (9.09) C: 6 (18.18)	Total infection: I: 1/33, C: 5/33 Septic shock: I: 1/33, C: 4/33
Davoudi-Monfared 2020		I: 56.60 (47.25-67.25) C:61.00 (50.00-70.00)	I: 22 (52.38) C: 22 (56.4)	DM: I: 13 (30.95), C: 9 (23.07) BMI: I: 25 (23-29), C: 25 (22-29)	I: 15 (35.71) C: 17 (43.58)	Total infection: I: 11/42, C: 5/39 Septic shock: I: 10/42, C: 7/39
Kalil 2020	100 %	I: 55±15.4 C:55.8±16	I: 319 (61.9) C: 333 (64.3)	DM: I: 200 (40), C: 180 (36) Immunosuppression: I: 17 (3), C: 13 (3) Obesity: , I: 295 (58), C: 272 (53) BMI: I: 32.2±8.2, C: 32.3±8.4	I: 54 (10) C: 57 (11)	Total infection: I: 30/515, C: 57/518 Pneumonia: I: 15/507, C: 31/509 IFI I1/515,C: 2/518 Sepsis: I: 4/507, C: 12/509 Septic shock: I: 7/507, C: 10/509
Cao 2020		I: 63 (51-65) C: 64 (59-71)	I: 12 (60) C: 12 (57.1)	DM: I: 5 (25.0), C: 3 (14.3)	None	Total infection: I: 0/20, C: 2/21 Sepsis: I: 0/20, C: 1/21

Table 2: Characteristics of patients in RCTs
Abbreviations: Ag: antigen; BMIL basic metabolic index; C: control; DM: diabetes; IFI: invasive fungal infection; I: intervention; PCR: polymerase chain reaction;

Author/year	**Design and Setting Country Number of patients**	**Inclusion**	**PCR**	**Intervention Dose/Route and duration**	**SOC**	**Co-intervention**	**Age (mean or median) and sex (%)**	**Co-morbidities**	**Mechanical ventilation**	**Number of infections**
Galvin Roman 2020	-Retrospective cohort -Single center (Spain) - I 58 C 88	-PCR+ -IL-6 level -Admitted with severe, critical COVID	100 %	Toci 800 mg IV (2 doses)	HCQ AZM LP/r	Steroids I:38(67), C:47(55) IFN-B:: I 2(4), C: 5(6)	Age: I: 61, C:64 M: I:40(69),C: 57(65)	DM:I:9(16), C:16(18) Obesity: 1:4(25), C: 9(10)	16 (11%)	Total Infection: I: 3/58 C:7/88 Bacteremia :I:3/58 C7/88
Falcone 2020	-Prospective cohort - Single center (Italy) -I:51 C:264	-PCR+ - pneumonia	NA	Toci 400 mg IV (1 dose) OR Bricitinib 4mg x14 days	LPV/r or DRV/r RDV HCQ	Steroids: 141/315 (45)	M: 210/315 (67)	DM: 64/315 (20)	55/315 (18%)	Total Infections I:20/51 C:49/264 OR: 5.09 95% (2.2- 11.8) p<0.001
Mehta 2021	-Prospective cohort -Multicentre (USA) -10 inpatients	- SOT (kidney or liver) in HOPE or HOPE in Action trials of HIV+ donors - PCR+	NA	Tocil (2 patients) HID-Steroids (6 patients) Combination (1 patient)	HCQ AZM		Age: 59 M: 91%	DM:45% BMI 27.3 SOT 100%, HIV100 %	46%	Total infection: I: 2/8, C 0/2 Pneumonia: I: 1/8, C:0/2 IFI: 1/8 C:0/2
Rodriguez-Bano 2020	-Retrospective -Multicenter (Spain) - I:434 C:344	-hyperinflammatory state. temp>38C O2 supp O2sat>92%. ferritin>2000 ng/mL or increase>1000 ng/mL D dimers>1500mg/mL (or x2 in 24 h), IL6>50 pg/mL	100 %	A)Toci IV variable B)Corticosteroids IH-D <250 methylpred C) Pulse steroids >250 D) Combination	HCQ LP/r AZM	C; INF 71 (21) A)Steroids 17(19), INF 24(30) B) Toci:7, INF 25(22) C)Toci:10, INF 12 (15) D) INF 27(18)	C: Age 69, F (40%) A) Age: 66, F: (27%) B) Age: 71, F: (28%) C) Age: 71, F: (30%) D) Age: 65 F: (28%)	C: DM21% Obesity 11.4% A)DM 27% Obesity 14.3% B) DM:29%Obesity:17 % C)DM:15% Obesity 7% D)DM 17% Obesity 17%	None	Total infection : Interventions: A)11/88, B) 10/115 C)8/75, D)18/150 Control: 36/339
Campochiaro 2020	-Retrospective cohort -Single center (Italy) - I: 32 C: 33	- PCR + - CRP ≥ 100 mg/L or ferritin ≥ 900 ng/mL AND increased LDH > 220 U/L) - Pulmonary infiltrates + SaO2 ≤ 92% OR PaO2:FiO2 ≤ 300 mmHg	100 %	Toci 400 mg IV 1 or 2 doses	HCQ AZM LPV/r CRO		Age: I: 64, C: 60 M: I: 29 (91),C:27(82)	DM I: 4 (12) C: 6 (18)	None	Total infection: I: 5/32, C: 4/33 Bacteremia: 4/32, C: 4/33 IFI: I: 1/32, C: 0/33

Biran2020	-Retrospective cohort -Multicenter (USA) -I: 210, C: 420	- ≥18 years -PCR + - ICU support	100 %	Toci 400mg IV (1 dose)	HCQ , AZ M	Steroids: I: 97 (46), C: 191 (45)	Age: I: 62, C: 65 M:I:55(74),C:281 (67)	DM: I: 77 (37),C: 158 (38) Obesity I:76 (36),C: 154(37)	I: 198 (94) C: 389 (93)	Total infection:!: 36/210., C: 54/420 Bacteremia I: 18/210, C: 33/420 Pneumonia: I: 25/210, C: 30/420
Gupta 2020	-Retrospective cohort -Multicenter (USA) -I: 433, C: 3491	-≥18 years -confirmed COVID-19 - ICU from March 4 to May 10, 2020 for illness directly attributable to COVID-19	100 %	Toci	HCQ , AZ M Anti b	Steroids: I: 81 (18.7), C: 467 (13.4)	Age: I:58, C: 63 M: I:299(69.1), C:2165(62)	DM: I: 165 (38.1),C: 1464 (41.9) BMI:I: 31.6 , C: 30.4	I: 282 (65.1) C: 1784 (51)	Total infection: I:140/433, C:1085/3491 Pneumonia: I: 112/433, C: 732/3491 Bacteremia: I: 29/433C: 285/3491 UTI: I: 8/433,C: 111/3491
Hill 2020	-Retrospective cohort -Multicenter (USA) -I: 43, C: 45	-between mar 19 and apr 24 2020 -PCR+	100 %	Toci 400mg IV (1 dose)	HCQ		Age: M:I:30 (70), C:31(69)	DM:I: 22 (51),C: 16 (36) Obesity I:26 (60) C: 22 (49) IS: I:4 (9), C: 10 (22)	I: 18 (42) C: 9 (20)	Total infection: I: 13/43, C: 7/45 Pneumonia: I: 9/43, C: 5/45
Canziani 2020	-Retrospective cohort -Multicenter (Italy) -I: 64 -C: 64	-clinical worsening in 24 h O2 or ventilator support -absence active bacterial infection, -elevated CRP -higher risk for mortality at blood tests, ORs elsewhere(lymphocyte, ferritin, CK,, ALT, D-dimer)	NA	Toci 8mg/kg (max 800mg) IV (2 doses)	LPV/r, Dr Cobi HCQ	Steroids: I: 31(48), C:26 (40)	Age: I: 63, C: 64 M: I: 47 (73) C:47(73)	BMI: I: 30C: 30	I: 13 (20) C: 13 (20)	Total Infection:1: 20/64, C: 25/64
Okoh 2020	-Retrospective cohort -Single center -USA -I: 20, C: 40	-≥18 years -PCR+ -no mechanical ventilation -full clinical data	100 %	Tocil 8mg/kg (max 800mg), IV (1-2 doses)	HCQ , Anti b	Steroids: I: 1 (5),C: 8 (20)	Age: I: 54, C: 59 M I:10 (50), C:24(60)	DM: I: 9 (45), C: 20 (50) BMI:I: 30, C: 29	None	Total Infection: I: 2/20, C: 5/40 Sepsis:I: 2/20, C: 5/40
Ringer 2020	-Case-control study -Single center (USA) -I: 48, C: 42	->18 -PCR+ - diagnosis 72 hrs hospitalization -Cytokine lab 72hrs of admission -SOT on IS at COVID-19 diagnosis	100 %	Toci 8mg/kg IV (1 dose)	HCQ , AZ M RDV	Steroids	Unknown	Unknown	unknown	Total Infection: I: 8/48, C: 4/42
Roumier 2020	-Case-control study -Single center (France)	- 16-80 -severe or rapidly deteriorating COVID-19 pneumonia	I: 47 (96 %)	Toci 8mg/kg (max 800mg) IV 1-2 doses	Anti-viral, HCQ ,	Steroids: I: 8 (16.3%) C: 6 (12.8%)	I: 57.8 (11.5); C:60 (12.8) M: I:82%, C:81%	DM:I: 12 (24) C: 14 (30) Obesity I: 9 (18) C: 13 (28)	None	Total Infection: I: 11/49, C: 18/47 Pneumonia: I: 4/49 C: 12/47 Bacteremia: I: 4/49 C: 2/47

	-I: 49,C: 47	- PCR+ or typical CT chest - >/= 5 days of COVID symptoms -CRP > 40mg/L	C: 43 (91 %)		steroids, antibiotics			Immunosuppression: I: 4 (8) C: 2 (4)		
Guaraldi 2020	-Retrospective cohort -Multicenter (Italy) -I: 179C: 365	-≥18 years - PCR+ -Admitted Feb 21 and March 24, 2020, or in Modena Feb 21 -April 30, 2020 - Severe pneumonia = RR>=30 or (SaO2) <93% i(PaO2)/ (FiO2) <300 mm Hg, and lung infiltrates >50% within 24–48 h	PCR: I: 179 (100 %) C: (365 %)	Toci 8mg/kg IV or 162mg SC 2 doses	HCQ, AZM, LPV/r or Dr-cobicistat	Unknown	Age: I: 64, C: 69 M: I: 127 (71), C: 232 (64)	DM: I: 17 (12.9%) C: 7 (3%)	Unknown	Total infection: I: 24/179,C: 14/365 Pneumonia: I: 8/179,C: 6/365 Bacteremia: I: 3/179. C: 4/365 IFI::I: 7/179,C: 3/365 Viral Infection:I: 5/179, C: 0/365 UTI: I: 1/179 C: 1/365
Potere 2021	-Case-control -Single center (Italy) -I: 40, C: 40	- Pescara General Hospital, Italy between 28 March and 21 April 2020 -laboratory-confirmed COVID-19 pneumonia (involving ≥20% of lung) -CRP ≥20 mg/dL -oxygen saturation <90% requiring oxygen through nasal cannulas or mask	100 %	Toci 324mg SC (162mg x 2)	unknown	Steroids: I: 26 (65%) C: 23 (57.5%)	Age: I: 56 , C: 54.5 M I: 26 (65). C: 26 (65)	DM: I: 5 (12.5%) C: 8 (20%)	None	Total Infection: I: 1/40 C: 3/40 Pneumonia: I: 1/40, C: 3/40
Kimmig 2020	-Retrospective cohort -Single center (USA) -I: 54, C: 57	-March 1, 2020 - April 27, 2020 –admitted to Covid-19 ICU	NA	Tocil 400 mg x 1 or 2 doses		Steroids I: 13 (24.1%) C: 8 (14%)	Age I: 64.5 ,C: 61.8 M I: 37 (68.) , C: 25 (43.9)	DM: I: 24 (42.1),,C: 21 (38.) Obesity: I:30 (55.),C:39 (68) Immunesuppressed I: 1 (1.8%), C: 7 (13%)		Total Infection I: 29/54, C: 16/57 Pneumonia: I: 21/54, C: 9/57 Sepsis I: 8/54, C: 7/57 IFI:I: 2/54, C: 0/56 Bacterial infection: I: 26/54,C: 16/57 Bacterial pneumonia: I: 18/54, C: 9/57
Kewan 2020	-Retrospective cohort -Single center (USA) -I: 28, C: 23	-PCR+ - Cleveland Clinic Fairview March 13 and April 19, 2020 - >18 years - severe COVID-19= oxygen for saturation <94% on RA	100 %	Toci 400 mg IV x1 dose	HCQ, AZM	None reported	Age: I: 62, C: 70 M: I:20 (7), C: 11 (48)	None reported	I: 19 (67.9) C: 3 (13)	Total Infection: I: 5/28, C: 5/23 Pneumonia: I: 4/28 C: 2/23 Invasive fungal infection I:1/28, C: 1/23 UTI: I: 0/28 C: 1/23

Rojas-Marte 2020	-Case Control - Single center (USA) - I:96, C:97	-PCR+ - Severe: O2 via face mask up to 10L/m sat of >95%, very severe NRB or high flow nc sat >95%, or critical (IMV) - Toci 8 Mar and 12 Apr 2020 -control group:O2 matched cases	100 %	Toci	HCQ, AZM RDV Antib	Steroids: I: 41 (42.7) C: 32 (33)		DM: I:29 (30.2), C:38 (39.2)	I: 61(63.5) C:60 (61.9)	Total Infection: I:16/96 C: 26/97 Bacteremia: I:12/96, C:23/97 IFI: 4/96 C:3/97
Menzella 2020	-Retrospective cohort -single center (Italy) -I: 41, C: 38	-Severe COVID-19 and worsening acute respiratory failure -PCR+ -radiological findings -Severe pneumonia, NIV, all PaO2 ratio > 100 and <=200 mmHg	100 %	Toci either 8 mg/kg q12h x 2 doses or 162 mg SC x 2-4 doses		Steroids: I: 28 (68), C:27 (71)	Age I: 63.8, C: 70.3 M I: 29 (71), C: 27 (71)	BMI: I: 30.6 C: 28.4	NIM 100% IMV: none	Total Infection: I: 2/41, C: 0/38 Pneumonia: I: 2/41, C: 0/38
Somers 2020	-Retrospective cohort -single center (USA) -I: 78, C: 76	-admitted to Michigan Medicine from 9 March–20 April 2020 for severe COVID-19 pneumonia - PCR + -IMV	100 %	Toci:8 mg/kg x1 dose	RDV I: 2(3%) C: 2(3%)	Steroids: I: 23 (29), C:15 (20)	Age: I: 55, C: 60 M: I: 53(68), C:49 (64)	DM: I: 10 (13), C: 15 (20) BMI:I: 34.7, C: 33.4	100%	Total Infection: I: 42/78, C: 20/76 Pneumonia: I: 35/78,C: 15/76 Bacteremia I: 11/78,C: 7/76 IFI:I: 3/78,C: 2/76
Tsai 2020	-Retrospective cohort -single center (USA) -I: 66, C: 66	-severe disease defined as Sp02 < 95% on RA, requiring O2, requiring IMV, NIMV	NA	Toci 800mg (n=10); 600mg (n =3); 400mg (n=53) 1 or 2 doses	SOC	Steroids I: 12 (18) C: 5 (7.6)	Age: I: 62.4, C: 61.3 M: I:46 (70), C: 50(76)	DM:I: 22 (33.3),C: 19 (27.3) BMI:I: 30.5,C: 30±6.2 Immune suppressed :I: 0 C: 1 (1.5)	I: 16/66 (24.2) C: 12/66 (18.2)	Total Infection: I: 4/66,C: 4/66 Bacteremia I: 4/66,C: 4/66
DeRossi 2020	-Retrospective cohort -single center (italy) -I: 90, C: 68	-PCR+ bilateral pulmonary interstitial opacities on imaging -respiratory failure =RR=30 (SpO2)93% RA or (PaO2/FiO2) 300 mmHg	100 %	Toci either 400 mg IV x 1 dose or 324 mg SC x 1 dose	SOC		Age: I: 62.9,C: 71 M: I: 64 (71), C:49 (72)	DM: I: 14 (15.5), C: 21 (31)	None	Total Infection: I: 6/90, C: 4/68 Pneumonia: I: 5/90,C:4/68 Viral infection: I: 1/90, C: 0/68
Pettit 2020	-Retrospective cohort -single center (USA) -I: 74, C: 74	-COVID-19 admitted between March 1 2020 to 25 May 2020 who received Toci for CRS	NA	Toci: 400 mg IV for 1+ doses	SOC RDV I: 21 (28) C:		Age: I: 66, C: 65 M: I: 43 (58), C: 33 (45)	DM: I: 24 (32), C: 28 (38) Obesity: I: 38 (51), C: 34 (46) Immune suppressed	I: 25 (34) C: 23 (31)	Total Infection: I: 18/74,C: 7/74 Pneumonia I: 7/74, C: 5/74 Bacteremia: I: 3/74, C: 0/74 SSTI: I: 2/74, C: 0/74

					34 (46)			I: 9 (12) C: 23 (31)		C diff: I: 3/74,C: 1/74 IFI: I: 2/74, C:1/74 Viral infection: I: 1/74, C: 0/74
Lewis 2020	-Retrospective cohort -Multicenter (USA) - I: 497, C: 497	-PCR+ - Toci within 72 hours of presentation to hospital	100 %	Toci 400 mg IV 1 dose	SOC		Age: I: 61, C: 61.8 M: I: 352 (71),C: 327 (66)	DM: I:124 (25), C:135(27.2) BMI: I: 30.1, C: 30.4	I: 63 (12.7) C: 47 (9.5)	Total Infection: I: 171/497, C: 53/497 Pneumonia: I:129/497, C: 29/497 Bacteremia: I: 69/497, C: 18/497 UTI: I: 40/497, C: 15/497
Ip 2020	-Retrospective cohort - Multicenter (USA) -I: 134, C: 413	-PCR+ -Hospitalized March1-May5 2020 -Non pregnant -Not in RCT -NO death day 1 hospital -NO discharge in 24 hrs	100 %	Tocili 400 (1 or 2 doses. Second dose 8m/kg	SOC	Steroids I: 45 (34), C: 150 (36)	Age: I: 62, C: 69 M: I: 99 (73.8), C: 257 (62.2)	DM: I: 47 (35), C: 157 (38) Obesity: I: 51 (38), C: 152 (36.8)	N	Total Infection: I: 30/134, C: 69/413 PneumoniaI: 12/134. C: 25/413 BacteremiaI: 18/134, C:44/413
Quartuccio 2020	Retrospective cohort , single center (Italy) -I: 42, C: 69	-PCR+	100 %	Toci: 8 mg/kg Methylprednisolone 1 mg/kg then tapered after 2 days	SOC	Steroids I: 33/42 (78.6) C: 0	Age: I: 62.4, C: 56.2 M: I:33 (8.6), C:44(63.8)	None reported	None reported	Total Infection: I: 18/42, C: 0/69
Balena 2020	-Retrospective case series -Multicenter (Italy) -I(A):16, C:148 - I (B)::42	-≥ 65 years, - March 1st- June 15th 2020 -PCR+	100 %	A)Toci 8mg/kg + Steroids B)Dexamethasone	HCQ LPV/r	Steroids : I:14(87.5)	Age I: 75 C:80, Ib:81 F: I: 5(31.2) C: 83(56), Ib: 20(48)	DM: I 5(31), C: 31(21), Ib:14(34) Immunosuppression: C3(2): Ib: 4(10)	14(9)	Total Infection: Ia:7/16, C:32/148, Ib:13/42 Pneumonia: Ia:3/16, C:3/148, Ib2/42 Bacteremia: Ia:2/16.C:11/148, Ib 4/42 IFI: Ia 2/16, C:0/148; Ib 2/42 UTI: Ia:1/16, C:15/148, Ib: 3/42 Infection OR=6.72 (1.43-31.39)
Fisher 2021	-Retrospective cohort -Single centre (USA) -I:45, C:70	-PCR+ Admitted to Stony Brook University Hospital between Mar 10 and Apr 2, 2020 -Invasive mechanical ventilation	100 %	Tocilizumab 400mg IV 1-2 doses (2 doses in 3 patients) 1-2 days	HCQ	Steroids: I: 33 (73.3) C: 55 (78.6%)	Age: I: 56.2 (14.7) C: 60.6 (13.4) Sex: I: 29 (64.4%) C: 51 (72.9%)		100%	Total infection: I: 13/45 C: 18/70 OR: 1.17 (0.51-2.71)

Salton 2020	-Prospective cohort - Multi-centre (Italy) -I: 83, C: 90	-PCR+ -18 to 80 years - PaO2/FiO2 <250 mmHg - bilateral infiltrates -CRP >100 mg/Land/or ARDS	100 %	Methylprednisolone 80mg IV, then 80mg IV daily Or 16 or 20mg PO BID IV given at least 8 days (until CRP <20, or PaO2/FiO2 > 350mmHg) Oral until CRP <20% normal range, or PaO2/FiO2 >400 or SatHbO2 >95% on RA	Antibiotic AZM HCQ Vitamins		Age: I: 64.4 , C: 67.1 Sex: I:54 (65.1),C: 66 (73.3)	DM I: 19 (22.9) C: 25 (27.8) Obesity I: 19 (33.3) C: 18 (32.7) *data missing for 35 (38.9) methylprednisolone, 26 (31.3) control group	NA	Total infection: I: 1/83, C: 1/90
He 2020	-Case-control study -Single center (China) -I: 78, C:247	-Admitted to Tongji Hospital with COVID-19 from Dec 30, 2019 to Feb 29, 2020 -Nosocomial infection	NA	Steroids	Antivirals AZM	Unknown	Age M	DM	IMV: unknown	Total infection I: 25/78, C: 40/247
Ramiro 2020	Historically controlled trial -single center (Netherlands) -I: 86, C: 86	-SpO2 at rest ≤94% on RA or RR >30/min 2/3 :CRP (>100 mg/L), ferritin (>900 µg/L at 1x occasion or 2x increase of the level at admission within 48 hours) and D-dimer >1500	I: 76 (89) C: 84 (98)	Methylprednisolone +/- tocilizumab (1) MP 250 mg x1 then 80 mg x4 +/- (2) Toci 8 mg/kg x1 5 days of MP 1 day of toci	Ceft HCQ	Toci I: 37 (43) C: 0	Age: I: 67, C: 67 M:I:68 (79), C: 68 (79)	DM I: 9 (11) C: 23 (27)	NIM: I: 20 (23) C: 7 (8) IMV: I: 1 (1) C: 13 (15)	Total infection: I: 8/86, C: 7/86
Nelson 2020	-Retrospective cohort -Multicenter: (USA) -I: 42, C: 42	-PCR+ within 48 hours after admission -MV greater than 24 hours	100 %	Methylprednisolone 1mg/kg/day (max 800mg) 5 days(median 4-6)	HCQ + AZM RDV I: 1(2), C:0	Toci I: 12 (29) C: 5 (12)	Age: I: 60, C:62 M: I: 28 (67), C: 30 (71)		100%	Total infection: I: 22/42, C: 19/42 Pneumonia: I: 17/42, C: 15/42 Bacteremia: I: 1/42, C: 2/42 UTI: I: 4/42 C: 2/42
Li 2020	-Retrospective cohort -Multicentre (China) -I: 183, C: 111	-critically ill patients (ICU who required MV or had a fraction of inspired oxygen of at least 60%) -ICU in Hubei province	NA	Corticosteroids (MP – 96%) mean of 200mg/day (100-320.9) hydrocortisone equivalent 9 (5-14) days	Unknown		Age: I: 65, C: 67 M: I: 151(68), C:73 (66)	DM: I: 53 (29), C: 27 (24) Immunosuppressed: I: 7 (3), C: 7 (10)	I: 148 (80) C: 82 (73.9)	Total infection: I: 34/183, C: 10/111

		between December 30 - February 19, 2020								
Tran 2020	-Retrospective cohort -Multicenter (France, Luxembourg) -I 203 C:688	-18-80 -PCR +	100 %	Steroids: 0.8mg/kg/d prednisone eq. or at least 0.4mg/kg/d with LPV/r	HCQ LP/r RDV		Age: I:64 C:62 M: I:145(71.4), C:447(65)	DM: I:46(23), 162(28) Immunosuppression: I 14(7), 34(5)	None	Total infection: I: 50/283, C: 128:682 Pneumonia: I: 17/283, C: 61/682 IFI: I: 3/283, C: 5/682 Viral: I: 2/283, C: 5/682 Bacterial: I :20/283, C: 51/682
Luyt 2020	-Retrospective cohort -Single centre (France) Ia: 4, C: 36, Ib: 1 Ic: 1, Id: 1	-ICU-admitted patients - PCR+pneumonia, based on a 12 March and 24 April 2020 -ARDS and ECMO	100 %	Ia: steroids (>/= 0.5mg/kg/d pred equivalent) >7 doses for >7 days Ib: tocilizumab Ic: sarilumab, Id: anakinra	HCQ , RDV Lp/r				100%	Total infection: Ia: 4/5, C: 36/42, Ib: 1/1 Ic: 1/1, Id: 1/1 Pneumonia: Ia: 4/5, C: 36/42, Ib: 1/1 Ic: 1/1, Id: 1/1
Obata 2020	-Retrospective cohort - Single center (USA) - I:57 C: 169	-PCR+	100 %	Steroids	HCQ AZ M	Toci: I:20/57 (35), C:3/169 (1.8)	Age: I:70, C:64 M: I 29/57(60), C: 100/169 (60)	DM: I: 19/57 (33.3), C:54/169 (32) BMI: I: 27.4 C: 28.3	I:56% C:4.7%	Total infection: I:21/57, C:20/169 Pneumonia: I: 9/57, C:0/169 Bacteremia: I:1/57, C:9:169 IFI: I: 7/57, C: 1/169 UTI: I:4/57, C:4/169
Dheir 2020	-Retrospective, cross-sections -single center (Turkey) -I 10 C: 10	-renal Transplant -treated for COVID-19 between March 20 and October 1, 2020	100 %	Dexa 6mg x10 days		Methylpred C: 16mg/say	Age: 48, M: 70%	DM 25% BMI:25	NA	Sepsis I:0/10, C: 2/10
Spagnuloa 2020	-Retrospective cohort: Single center (Italy) -I: 59, C: 221	-February 25th 2-May 19th 2020 -moderate- severe COVID-19 -definite outcome: (discharge/death) - complete info on therapies during hospitalization - 2 NP swabs (1st admission and≥1 thereafter)	100 %	Corticosteroids (mostly methylprednisolone) 0.38 (0.21–0.53) mg/Kg/day	ART HCQ		Age: I: 67, C: 62 M: I:46(78), C:171 (77.4)	DM: I:12(20.3), C: 37 (16.7)	NA	Total infection: I: 6/59, C: 23/221

Jiao2020	-Retrospective cohort -Multi-center (China) - I: 667, C:1377	- Jan 27 to March 21, 2020 -≥18 years - Critical criteria a) respiratory failure and need MV b) shock c) organ failures, need ICU stay -PCR or AG +	NA	Corticosteroids Unknown agent, dose and duration	Anti b Anti viral s, IVIg					Total infection I: 20/667, C: 7/1377 Sepsis: I: 405/667, C: 306/1377 Septic shock: I: 198/667, C: 44/1377
Liu 2021	-Retrospective cohort -Single centre, (China), -I: 124, C: 124	->/= 18 years old - SARS-CoV-2 pneumonia -definite outcome (death or discharge) -admitted to Jinyintan Hospital 29 Dec 2019 and 15 Feb 2020	NA	Steroids (methylpred, dex, prednisone).Low-moderate dose (<80mg/day prednisone equivalent) 5 (3-7) days	Anti b		Age: I: 61, C: 58.5 Sex M: I: 70 (56.5) C: 69 (55.6)	DM: I: 15 (12.1), C: 26 (21.0)	NIM: I: 24 (19.4), C: 20 (16.1) IMV: I: 19 (15.3) C: 21 (16.9)	Total infection: I:7/124, C: 11/124
Delliere 2020	-Retrospective -Multicenter (France) -- I: 16, C: 81	-ICU for confirmed COVID - Consent		Steroids , Sarilumab Eculuzimab, toci	LP/r AZ M HCQ		Age : 62 M: 88(81.5)	DM: 40(37) Obesity: 35 (32.4) Immunosuppressed: 10(9.3)	105 (97)	Total infection : I-A:6/16, C: 11/81, I-B 0, I-C 2/6, I-D 2/4 IFI: I-A:6/16, C: 11/81, I-B 0, I-C 2/6, I-D 2/4
Fernandez-Ruiz 2020	-Case series -Single center (Spain) - I:6	-SOT -PCR+		Toci, Steroids IFN	LP/r HCQ		Age : 71 M:77.8%			Total infection: I 0/6, C: 2/12 Bacteremia: I: 0/6, C: 1/12 Pneumonia: : I: 0/6, C: 1/12
Narrain 2020	-Retrospective -Multicenter (USA) -I-A: 1383 -C: 3076 -I-B 454 -I-C 733 -I-D: 73 -I-E 57	-PCR+ ->18 -ferritin>700 or CRP>30 or LDH>300	100 %	I-A: steroids I-B: Steroids+ Toci I-C: steroids + Anikinra I-D- Toci I-E :	HCQ Colc hicin e AZ M Vit C					Total Infection:I-A :41/1383,C: 30/3076 I-B: 44/454, I-C: 62/733, I-D:0/73 I-E:0/57 Bacteremia: I-A 31/1383, C: 24/3076, I-B:38/454, I-C: 48/733, I-D 0/73, I-E 0/57 IFI: I-A 10/1383, C: 6/3076, I-B:6/454, I-C: 14/733, I-D 0/73, I-E 0/57
Qu 2021	-Case-control -Single-centre, (China)	-PCR+ -Mild and moderate disease;	100 %	LPV/r;+IFN+ LPV/r +Novaferon+IFN ,	LVP/ r		Age C: 45 (34-55) M:C: 5 (23.8)	DMC: 2 (9.5)	Not reported	Total infection: I: 6/76, C: 1/21

	-I: 76, C: 21	-antiviral treatment due to SARS-CoV-2 infection		LPV/r +Novaferon. LP/r+IFN +Arbitaol						
Hao 2020	-Case-control -Single-centre (China) -I: 32, C:32	-PCR+	100 %	Inhaled IFN-a2b 100,000 U QID for 7 days	Lp/r	Steroids: I: 20 (62.5), C: 20 (62.5)	Age: I: 55, C: 61.5 M: I: 22 (68.8), C: 22 (68.8)	DM I: 4 (12.5) C: 7 (21.9)	I: 8 (25), C: 12 (37.5)	Septic shock I: 1/32, C: 1/32
Stebbing 2021	-Retrospective cohort -Multicenter (2 hospitals; ,Italy, Spain) -I: 83, C: 83	-PCR and CXR + -SaO2 <94% -Italy cohort: PaO2/FiO2 < 300mg, March 7 -31 2020, and moderate-to severe disease -Spain cohort: patients ≥ 70 years, March 9 -April 20 2020, no MV and moderate-to-severe disease		Baricitinib PO Italy: 4mg/day for 14 days Spain: 2mg/day for 3-11 days	HCQ Lp/R antib	Steroids: I: 71 (85.5) C: 70 (84.3)	Age: I: 74, C: 74 Sex: I: 43 (51.8), C: 42 (50.6)	DM: I: 28 (33.7%) C: 22 (26.5%)	Not reported	Total infection: I: 9/83, C: 39/518 Pneumonia: I: 1/83, C: 5/518 Bacteremia: I: 4/83, C: 8/518 Viral infection: I: 1/83, C: 1/518 UTI: I: 1/83, C: 25/518
Annane 2020	-Proof-on-concept (non-randomized controlled) -Single center(France) -I: 35, C: 45	-PCR+ -Severe disease = ICU hospitalization. - Symptomatic bilateral pulmonary infiltrates,7 days before screening; and severe pneumonia, acute lung injury, or ARDS requiring O2 .	100 %	Eculizumab IV 900mg on days 1, 8, 15, and 22 Amendment on April 17, 2020 to:1200mg days 1, 4, 6 and 900mg on days 15 and 22 with optional doses of 900mg or 1200mg on days 12,18	HCQ RDV : I: 1 (3) C:7(16) antib iotics	Steroids: I: 5 (14) C: 4 (9)	Age: I: 64, C: 55 M: I: 22 (63), C: 34 (76)	BMI: I: 26.6, C: 26.1	: I: 21 (60) C: 31 (69)	Total Infection: I: 20/35,C: 12/45 Pneumonia: I: 18/35,C: 11/45 Bacteremia: I: 4/35,C: 1/45 UTI: I: 0/35, C: 1/45
Della Torre 2020	-Prospective cohort -Single center (Italy) -I: 28,C: 28	-PCR+ -radiologically documented bilateral pneumonia -Severe COVID: (= or < 92% O2 sat on ambient - OR- PaO2/FiO2 = or < 300mmHg on supplemental oxygen) - AND- hyper-inflamed phenotype (LDH > ULN + one of: CRP = or > 100mg/L or IL-6 = or >	I00 %	Sarilumab 400mg 1 dose	HCQ , LPV/r antib iotics ,	None reported	Age: I: 56, C: 57 M: I: 24 (85), C: 20 (71)	DM: I: 3 (11), C: 6 (21)		Total infection:: I: 6/28, C: 5/28 IFI: I: 1/28, C: 0/28

		40pg/mL or ferritin = or > 900ng/mL).								
Kooistra 2020	-Prospective cohort study -Single center (The Netherlands) -I: 21 -C: 39	-mechanically ventilated admitted to ICU between March 11 and April 27 -PCR+ and by typical chest CT-scan findings. - hyperinflammation (persistent high fever and/or a high plasma level of ferritin and/or progressive organ dysfunction with no apparent reason apart from hyperinflammation) indication for Anakinra	100 %	Anakinra 300mg then 100mg every 6 hours IV	Not explicitly listed	Steroids: I: 1 (5) C: 10 (26) Remdesivir I: 3 (14) C: 11 (28)	Age: I: 63 C: 67 (59-72) Sex: I: 14 (67) C: 33 (85)	DM: I: 7 (33) C: 7 (18) BMI: I: 27.7 (25.9–29.9) C: 26.8 (24.3–31.1)	100%	Total infection: I: 7/21, C: 9/39
Cavalli 2020	-Retrospective cohort -Single center (Italy) -I-A: 29, C: 16, I-B: 7	- ≥ 18 years of age -moderate/severe ARDS (acute-onset respiratory failure with bilateral infiltrates, hypoxaemia PaO2:FiO2 ≤200 mm Hg with a PEEP of at least 5 cm H2O) -hyperinflammation (serum CRP ≥100 mg/L, ferritin ≥900/mL, or both)	I00 %	1-A: HD -Anakinra 5mg/kg BID IV Until clinical benefit (defined as 75% reduction in CRP with sustained resp. improvement) for at least 2 days or until death, bacteremia, or side effects. If sustained benefit, H-D was transitioned to L-D for 3 days. I-B: L-D Anakinra 100mg BID s/q Until clinical benefit (defined as 75% reduction in CRP with sustained resp. improvement) for at least 2 days or until death, bacteremia, or side effects.	HCQ LP/r antibiotics	None reported	Age: I-A: 62 (55-71) C: 70 (64-78) I-B: 68 (51-73) M I-A: 24 (83) C: 14 (88) I-B: 5 (71)	DM: I-A: 6 (21) C: 3 (19) I-B: 2 (29)		Total infection: I-A: 4/29, C: 2/16 I-B: Not reported Bacteremia: I-A: 4/29, C: 2/16 I-B: Not reported
Balkair 2021	-Prospective observation with historically controlled trial -Single center (Omanl)	->18 years - severe SARS-CoV-2 = PCR+ and bilateral lung infiltrates on chest X-ray, and any of: (1) RR> 30/min and SpO2 of	100 %	Anakinra s/q 100mg BD x 3d then QD for up to 7d Adjusted for GFR <30mL/min	Antibiotic AZM	Steroids: I: 25 (56) C: 16 (67) Tocilizumab: I: 0 (0) C: 1 (4)	Age: I: 49.8, C: 51.7 M:I: 35 (78), C: 17 (71)	DM: I: 16 (36) C: 12 (50)	unclear	Total infection: I: 5/45, C: 4/24 Bacteremia: I: 5/45, C: 4/24

	-I: 45, C: 24	<90% on room air; (2) SpO2 ≤93% on oxygen ≥6 L/min; or (3) ARDS								
Bozzi 2020	-Prospective cohort study -Single center (Italy) -I: 65,C: 55	-COVID-19 -> 18 years -evidence of pneumonia -ferritin >= 1000 ng/mL and/or CRP > 10 mg/dL -respiratory failure with need of supplemental oxygen (oxygen therapy from 0.4 FiO2 Venturi mask to invasive MV)		-Anakinra SQ ,200mg q8h x 3d, 100mg q8h x 11d. Total of 42 doses over 14 days -Methylprednisolone IV 1mg/kg loading, then 0.5mg/kg BID x 5d, then 0.25mg/kg BID x 5d, then 0.25 mg/kg QD until day 14. Total of 26 doses,14 days	HCQ LPV/r RDV I: 8 (12.3) C: 11 (20)		Age: I: 60, C: 63 M: I: 52 (80), C: 44 (80)	None reported	I: 18 (27.7) C: 21 (37.5)	Total infection: I: 9/65,C: 4/55 Bacteremia: I: 9/65, C: 4/55
Giudice 2020	-Retrospective cohort -Single center (Italy) -I: 7, C: 10	-18 or older -PCR+ -diagnosis of pneumonia or SARS-CoV-2-related ARDS based on the WHO criteria	100 %	-Eculizumab IV 900mg on day 0, 7, and optional 14 (if needed) -Ruxolitinib PO 10mg BID x 14d	HCQ	Steroids: I: 5 (71) C: 3 (30)	Age: I: 61, C: 63.5 M:I: 6 (86), C: 7 (70)	DM: I: 2 (29), C: 2 (20) Immunosuppression: I: 1 (14), C: 0 (0) Obesity: I: 2 (29),C: 2 (20)	I: 0 (0) C: not reported	Total infection: I: 0/7, C: 0/10
Laterre 2020	Case series with control cohort Single center(Belgium) I: 12, C: 13	-COVID-19 -severe lymphopenia: consecutive absolute lymphocyte counts of < 700/uL		IL-7 3ug/kg initial dose, then 10ug/kg twice a week for 2 weeks, IM	Not reported	Not reported	Age: I: 62 C: 59 M: I: 11 (92), C: 9 (69)	DM: I: 2 (17), C: 2 (15) BMI: I: 25.13, C:27.33	None reported	Total infection: I: 7/12, C: 11/13
Deluca 2020	Prospective cohort study Single center (Italy) -I: 13, C: 26	-no mechanical ventilation -≥18 years of age -PCR+ and radiological findings -acute lung injury: PaO2:FiO2 ≤300 mmHg, bilateral pulmonary infiltrates, and no LAH -hyperinflammation: Increased LDH AND CRP ≥100mg/L OR ferritin ≥900ug/L	100 %	Mavrilimumab 6mg/kg IV (1 dose)	HCQ AZM LPV/r	None reported	Age: I: 57. C: 60 Sex: I: 12 (92) C: 17 (65)	Not reported	none	Total infection: I: 0/13, C: 3/26

Chen 2021	Retrospective cohort Single center (China) -I: 209, C: 162	-PCR+	100 %	Corticosteroids: Highly variable dosing regimen. .Median 7 days	Anti viral s. antib iotics ,	Interferon: I: 54 (25.8) C: 13 (8)	Age: I: 65, C: 53 Sex: I: 133 (63.6), C: 87 (52.4)	DM: I:41(19.6),C: 28 (17.3)	I: 20 (9.6) C: 8 (4.9)	Bacterial pneumonia: HR =0.449 Pneumonia :HR= 0.449 Bacteremia: HR= 6.309
Kumar 2021	- Retrospective cohort - Single center (USA) - I(A): 213 C (SOC_T): 1350 I(B): 651 C(SOC_S): 912	- age >18 - admitted with ICD-10 code of COVID-19 and/or PCR positive for SARS-CoV-2	NA	Tocil, steroids Unknown dose, duration, and route	Uncl ear	Some patients received both steroids and tocilizumab	Age: unknown Sex: unknown			Total infection: I(A): 39/213 C (SOC_T): 20/1350 I(B): 46/651 C(SOC_S): 13/912
Bartoletti 2020	- Retrospective cohort - multicenter (Italy) - I: 170 C: 343	- severe pneumonia (radiologically confirmed) - RR=30 breaths/min - O2 sat 93% on RA partial, (P/F ratio)300 mm Hg.	100 %	Corticosteroids (mainly dexamethasone or methylprednisolone) Dose: >0.5mg/kg/d prednisone equivalent Doses: 4 (4-6)	HCQ , LPV/ r, DRV /r, DRV /c, RDV	Remdesivir: I: 2(1) C: 16 (5)	Age: I: 74,C: 69 Sex: 58 (34) C: 118 (34)	DM: I: 22 (13) C: 46 (13) Obesity: I: 34 (20) C: 61(18)	I: 30 (17) C: 73 (21)	Bacterial infection: HR: 1.55 (0.95-2.55)
Papamanoli 2021	- Retrospective cohort - Single center (USA) - I: 153 C: 294	- ≥18 years - admitted March 1-15 April 2020 -PCR+ - severe COVID-19 pneumonia= fever or suspected respiratory infection, plus RR>30 , or severe respiratory distress; or O2 sat <93% on RA who required high-flow oxygen (non-rebreather mask, Venturi mask with FiO2 ≥ 50% or high-flow nc, BPAP, CPAP	100 %	Methyprednisone Dose: 160mg (120-180mg) or 1.78mg/kg/day (1.33-2.23) Duration: 10 days (5-14 days)	HCQ , AZ M	Tocilizumab: I: 38 (35.3); C: 70 (23.8) Remdesivir: I: 3 (2); C: 3 (1)	Age: I: 62 , C:61 Sex: I: 104 (68), C: 187 (64)	DM: I:52(34), C:95(32)	MV: 0	Bacteremia: Incidence ratio rate 0.58 (0.29-1.18) Pneumonia: Incidence ratio rate: 0.43 (0.23-0.82)

Table 3: Characteristics of non-randomized studies

Abbreviations: ATV/r: atazanavir/ritonavir; AZM: azithromycin; BID: twice a day; BMI: basic metabolic index; C: control; DM: diabetes; IMV: invasive mechanical ventilation; I: intervention; HCQ: hydroxychloroquine; I: intervention; IV: intravenous; LPV/r:

lopinavir/ritonavir; NIMV: non-invasive ventilation; PO: per os; M::male; PCR: polymerase chain reaction;; RDV: remdesivir; SOC: standard of care; SQ: subcutaneous; Toci: tocilizumab;

Author-year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Angus2020	Low	Low	HIGH Open label	HIGH Open label	Low	Low	Unclear 5% of the no hydrocortisone group received corticosteroids, for a short period
Cao 2020	Low	Low	HIGH physicians aware of group allocations for safety concern	Low	Low	Low	Low
Corral-Gudino 2021	Low	Low	HIGH Open label	HIGH Open label	Low	Low	Low
Davoudi-Monfared 2020	Low	Low	HIGH Open label (no placebo subcutaneous injection given to the SOC group)	HIGH Open label	HIGH 7/46 drop outs in IFN group to enter other trials	Low	HIGH 64% pcr only more steroids in 1 arm
Dequin 2020	Low	Low	Low	Low	Low	Low	Low
Edalatifard 2020	Low	Unclear Not mentioned	HIGH Patients blinded to intervention but not given placebo	HIGH NO blinding	HIGH No ITT, 6 patients from control arm not included in analysis because they received steroids	Low	Low
Hermine 2021	Low	Low	HIGH Open label	HIGH Open label	Low	Low	Unclear steroids given more in control group
Jerenimo	Low	Low	Low	Low	Low	Low	Low
Kalil 2020	Low	Low	Low	Low	Low	Low	Low
Rahmani 2020	Low	Low	HIGH Open label	HIGH Open label	HIGH Did not use ITT analysis. patients excluded from analysis	Low	Unclear More steroids and more mechanical ventilations in control
Salama 2021	Low	Low	Low	Low	Low	Low	Low
Salvarani 2021	Low	Low	HIGH Open label	HIGH Open label	Low	Low	Low
Stone 2020	Low	Low	Low	Low	Low	Low	Low

Tomazini 2020	Low	Low	HIGH Open label	HIGH Open label	Low	Low	Low
Veiga 2021	Low	Low	HIGH Open label	HIGH Open label	Low	Low	Low
Vlaar 2020	Low	Low	HIGH Open label	HIGH Open label	Low	High In clinicaltrials.gov, primary outcome was mortality, not change in PaO2/FiO2.,the new primary outcome changed during trial as positional monitoring was not possible.	Low

Table 4: Risk of bias in randomized clinical trials.

Study Name	**Developing and applying appropriate eligibility criteria**	**Measurement of exposure**	**Measurement of outcome**	**Controlling for confounding**	**Completeness of data**
Galvin Roman 2020	Low	Low	Unclear no secondary infections but there were 10 positive blood cultures	High -Toci worse baseline respiratory status -No adjustment for confounders	Low
Falcone 2020	Low	Unclear Did not separate by drug used, and unclear about steroids co-intervention	Low	Unclear Did not adjust by steroid	Low
Mehta 2021	Low	HIGH NO dosing available	HIGH NO definition for infection	HIGH No adjustment	Unclear Unclear duration of follow up
Rodriguez-Bano 2020	Low	Low	HIGH NO definition for infection	HIGH NO adjustment for confounders for infection outcome	Low

Campochiaro2020	Low	Low	LOW Infections were bacteremia, candidemia, and invasive fungal infection	HIGH No adjustment for confounding variables	LOW No missing data
Biran2020	Low	Low	UNCLEAR Bacteremia and pneumonia defined as positive cultures from blood and sputum but no comment on whether colonization and true infection were differentiated and how	HIGH No adjustment for confounders	LOW No missing data
Gupta 2020	Low	HIGH Immunotherapy dose	HIGH No clear definition given – used suspected or confirmed infection based on chart review	HIGH No adjustment for confounding variables	LOW
Hill 2020	Low	LOW	LOW One dose of tocilizumab 400mg IV administered	High No adjustment for cofounding variables	LOW No missing data
Canziani 2020	Low	Low	HIGH Infection definition based on high procalcitonin levels	HIGH Unadjusted baseline variable difference between groups	LOW No missing data
Okoh 2020	LOW	LOW	LOW	LOW Propensity score performed	LOW
Ringer 2020	Low	LOW	LOW	High Confounding variables not controlled	LOW No missing data
Roumier 2020	LOW Used a propensity score analysis	LOW Use common terminology criteria for adverse events (CTCAE) definition	LOW Patients given one or two doses depending on clinical improvement	HIGH Control group identified retrospectively	LOW No missing data

Guaraldi 2020	HIGH Not controlled for confounding variables	UNCLEAR Infection not defined explicitly, although outcomes included UTI, pneumonia, bacteremia, PJP	LOW Given subcutaneous or IV tocilizumab based on availability	LOW Inclusion/ exclusion criteria given	LOW No missing data
Potere 2021	UNCLEAR Matched cases to control, but unclear if done for all variables; controls from a different time period in the pandemic	HIGH Infections not explicitly defined; organisms not identified	LOW All patients given two doses of subcutaneous tocilizumab	LOW Inclusion/ exclusion criteria stated	LOW No missing data
Kimmig 2020	Low	Low	High Included both suspected and confirmed infection	High No adjustment of confounders	Low All patients followed up for sufficient time course
Kewan 2020	Low	Low	Low Hospital acquired infections not defined, but the causative organism for each was given and infections are well described	High Toci more sick at baseline and more corticosteroids No adjustment of confounders	Low
Rojas-Marte 2020	Low	High No dosing provided	Unclear Bacteremia, fungemia (no definition provided)	High No adjustment of confounders	Low
Menzella 2020	Low	Low	High No standardized definition for infection outcomes	High No adjustment of confounders	Low
Somers 202	Low	Low	Low	High No adjustment of confounders	Low
Tsai 2020	Low	High Various tocilizumab dosing strategies	Low Bacteremia used as definition	Low Propensity score matching used	Low
DeRossi 2020	Low	Unclear Variable dosing and routes used	Unclear No mention of how definitions were used aside from use of procalcitonin	High No adjustment of confounders	Low

Pettit 2020	Low	Low	Low	High Limited matching of key variables between groups	Low
Lewis 2020	Low Cohorts matched for variables of interest	Unclear Specific dosing of tocilizumab not clear	High Culture data without clear clinical correlation guided diagnoses	Low Cohorts well matched and propensity scoring used	Low All patients followed up for sufficient time course
IP 2020	Low Similar location and illness severity between groups	Low The majority of patients received similar tocilizumab dosing	Unclear Not clear what definitions for pneumonia were used	High Did not control for confounding	Low All patients followed up for sufficient time course
Quartuccio 2020	High Intervention and control populations on different units frequently	Low Dosing clearing outline and consistent	High No clear definition of bacterial infection	High No control for confounding factors in analysis	Low All patients followed up for sufficient time course
Balena 2020	Low	Unclear Unclear steroids dosing	Low	High No adjustment for confounders	Low
Fisher 2021	Low	Low	Low	High univariate analysis only	Low
Salton 2020	Low	Low	High Determination of bacterial superinfection was not described and is not clear how this was identified	High Confounding variables were not considered nor adjusted with regards to infection outcome	Low
He 2020	Low	High no dose/ duration specified	High No definition given for nosocomial infection	Low	Low
Ramiro 2020	Low	Low	High no definition for infection, only bacterial infection also not all pcr positive	High Not adjusted confounders for outcome infection	Low

Nelson 2020	Low	Low	Unclear Positive clinical cx, no differentiate infection/colonization	Low Infection rates adjusted with propensity scoring	Low
Li 2020	Low	High variable steroid doses and no fixed duration. mostly methylpred but some other steroids used although different outcomes analyzed according to dosing of steroidsm infection outcome not analuzed according to steroid dose	High No definition for secondary infections given	High Steroid group sicker with more ventilation and more IS pre. infection outcome no adjustement for other covariates	Low
Tran 2020	Low	Low	Unclear definition or criteria to determine infection diagnosis, but presented bacterial, fungal , viral separate and undocumented infections separate	High infection presented without assessing confounder and without propensity scoring	Low
LuYt 2020	Low	High Dosing of different immunotherapy not presented	Low	High No adjustment of confounders	Low
Obata 2020	Low	High Significantly variability in steroid type, dose, duration and concomitant immunomodulatory treatments	Unclear Infection outcome listed at pathogen level but no definition used	High No adjustment of confounders, 2 arms very different	Low
Dheir 2020	Low	Unclear Unclear indication for Dexa	High Only mentions but without definition	High No adjustment for confounders	High Missing infection outcome
Spagnuolo 2020	Low Criteria given for moderate-severe COVID, excluded those on chronic steroids	High No information on steroid doses	High Only mentions secondary infection. Infections not defined	High no adjustment for secondary infection just for viral clearance. Steroid group had worse respiratory status on admission	Unclear Just gives information on "subsequent infections" with no time course given. Both infection rates stated to be 10.4% but that

					gives 6.14 for the n of 59 in steroid group.
Jiao 2020	Low	High No information provided with regards to glucocorticoids used, dose, route of administration, duration, etc.	Unclear not clear if differentiated colonization vs infection	High No consideration or adjustment of confounders to the infection outcomes. adjusted only according to critically ill vs not	Low all infection outcome data was present with no missing patients.
Liu 2021	Low	Unclear different doses and starting times for steroids	Low	Low *A propensity score*	Low
Delliere 2020	Low	High No dosing provided for different immune-targeted therapy	Low	High Univariate analysis only	Low
Fernandez-Ruiz 2020	Low	High No dosing of steroids	High No definition of outcome	High no adjustment for confounders	Low
Narrain 2020	Low	High No dosing available	Unclear Bacteremia, fungemia (but not clear if clinically significant contaminant)	High Baseline characteristic differ and not adjusted for	High Censoring on April for those that were still in hopsital
Qu 2021	Low All patients appear to be from the same group of hospitalized patients.	Low outcome for each combination and dosing provided	High No description of how secondary infection outcomes were determined.	High Confounding factors do not seem to have been considered nor adjusted for in analyses (eg. antibiotic use, corticosteroids, etc.) No adjustment made for outcomes other then viral clearance	Low
Hao 2020	Low	Low	High Table only says shock, unclear if due to infection. No definition for infections given.	Low	Low No patients lost to follow-up

Stebbing 2021	Low	Low	Unclear	High Although propensity scores were used, the infection outcomes were matched only in one of the two cohort.	Low
Annane 2020	Low	High Different dose regiment was used after protocol amendment during study duration	Low	High No adjustment for confounding in infection outcomes	Low All patients followed for 28 days
Della Torre 2020	Low	Low Description of dosing	Unclear No definition provided, only adverse events. Organism in bacteremia is named, but unclear if this is the only bacteremia	High No controlling for confounders	Low No missing data and all patients were followed at least 28 days hours
Kooistra 2020	Low	Low Description of dosing and route provided	Low	High No control of confounding for infection nor the higher baseline ferritin, CRP, and temp present in intervention group	Low
Cavalli 2020	Low All patients were from the same group of hospitalized patients.	Low	Low Definition of infection outcome (bacteremia) was well described and outlined in supplementary materials.	High Confounding factors were not adjusted for nor considered with regards to infection outcomes	High Low-dose anakinra patients were all dropped around 7 days without sufficient time for follow up for infection outcomes. Other patients followed at least 21 days
Balkair 2021	High two populations are from different groups of patients in a temporal aspect. The intervention group was prospectively recruited whereas the control group is historical.	Low Description of dosing and route provided.	Low	High Confounding factors were not considered nor adjusted for with regards to infection outcomes	Low Both groups had follow up of 14 days as described in their protocols
Bozzi 2020	Low	Low Treatment protocol were well defined	Low Only bloodstream infections, presumably with positive cultures, were included	High No controlling for confounding variables	Low

Giudice 2020	Low 17 consecutive patients were enrolled	Low Treatment protocol were well defined	High No definition for infection outcomes provided	High No adjustment for confounding factors (eg. higher FiO2, lower median PaO2/FiO2 in intervention)	Low
Laterre 2020	Low Criteria were made and applied	Low All intervention patients received the same dosing regimen	High No description of how secondary infection were determined	Low Use of matched controls	Low No data missing, all patients followed sufficiently
Deluca 2020	Low Patients from same group	Low All patients with the intervention received the same dose, number of doses, by the same route	High No definition for infection provided	High No controlling of confounding for infection outcomes	Low All patients were followed and data is complete
Chen 2021	Low Patients are all hospitalized with moderate to severe COVID	High Highly varied therapy use including different agents, doses, regimens, duration, etc.	High No definition of infection and if culture proven or just suspected	High propensity score matching confounding factors are not all accounted for including an interferon use, etc. It is also unclear how many patients were actually in the matched cohorts as the numbers are identical to the unmatched cohorts.	Low
Kumar 2021	Low	Low	High Unknown number of patients received combination of immunomodulators Unknown dose of tocilizumab and steroids	Low	Low
Bartoletti 2020	Low	Low	High No clear route, dosing, or duration	Low	Low
Papamanoli 2021	Low	Low	Unclear Dose not standardized, wide range of duration (5-14)	Low	Low

Table 5: Risk of bias in non-randomized studies

Table 6: GRADE
Author(s):
Question: Does immune-based therapy in COVID-19 increase the risk of secondary infection?
Setting: Hospitalized
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunotherapy	Control	Relative (95% CI)	Absolute (95% CI)		
New outcome (assessed with: n)												
16	randomised trials	serious [a]	not serious	not serious [b]	not serious [c]	none	173/1906 (9.1%)	210/1496 (14.0%)	**RR 0.74** (0.58 to 0.96)	**36 fewer per 1,000** (from 59 fewer to 6 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

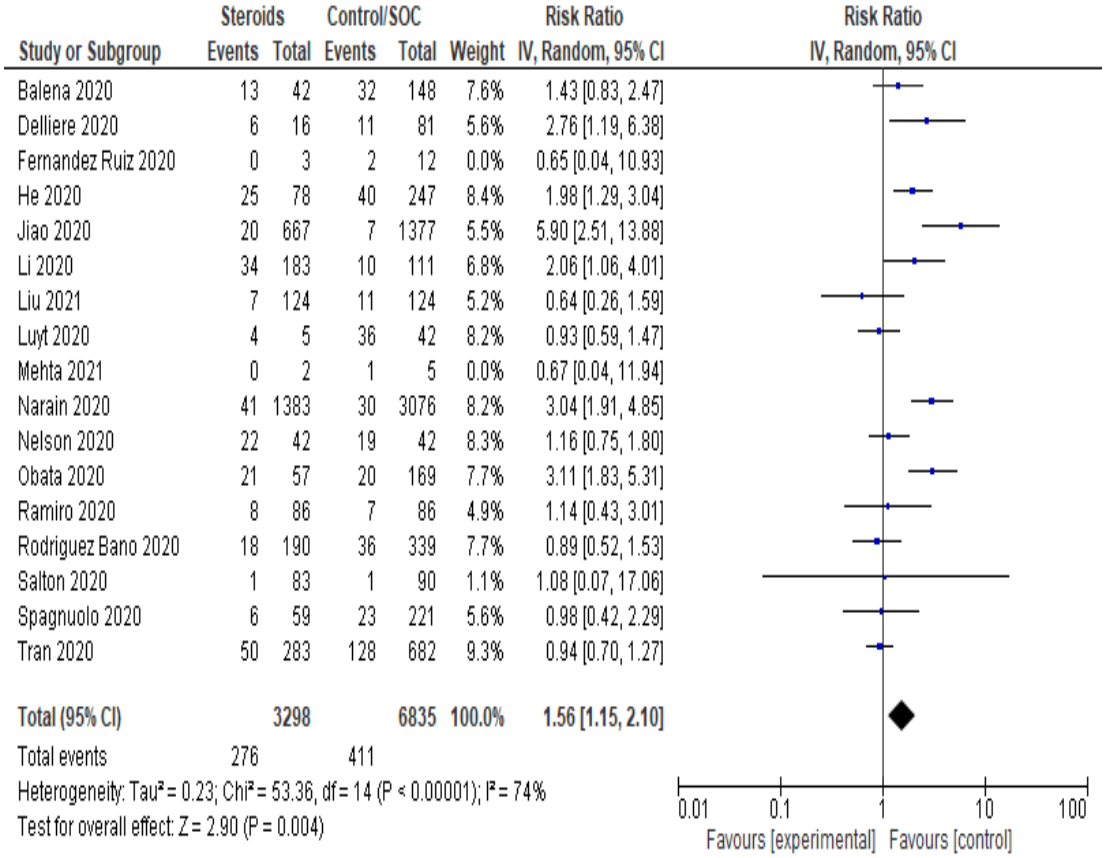
a. few studies have high risk of bias (those studies did not have a high weight in the meta-analysis)
b. Although different immunotherapeutic agents are included as intervention, they all act on the aberrant immune system caused by COVID-19
c. Although several studies have a wide CI due to low number of events, the pooled estimated have a narrow CI and this is also clinically significant

CHAPTER V

APPENDIX

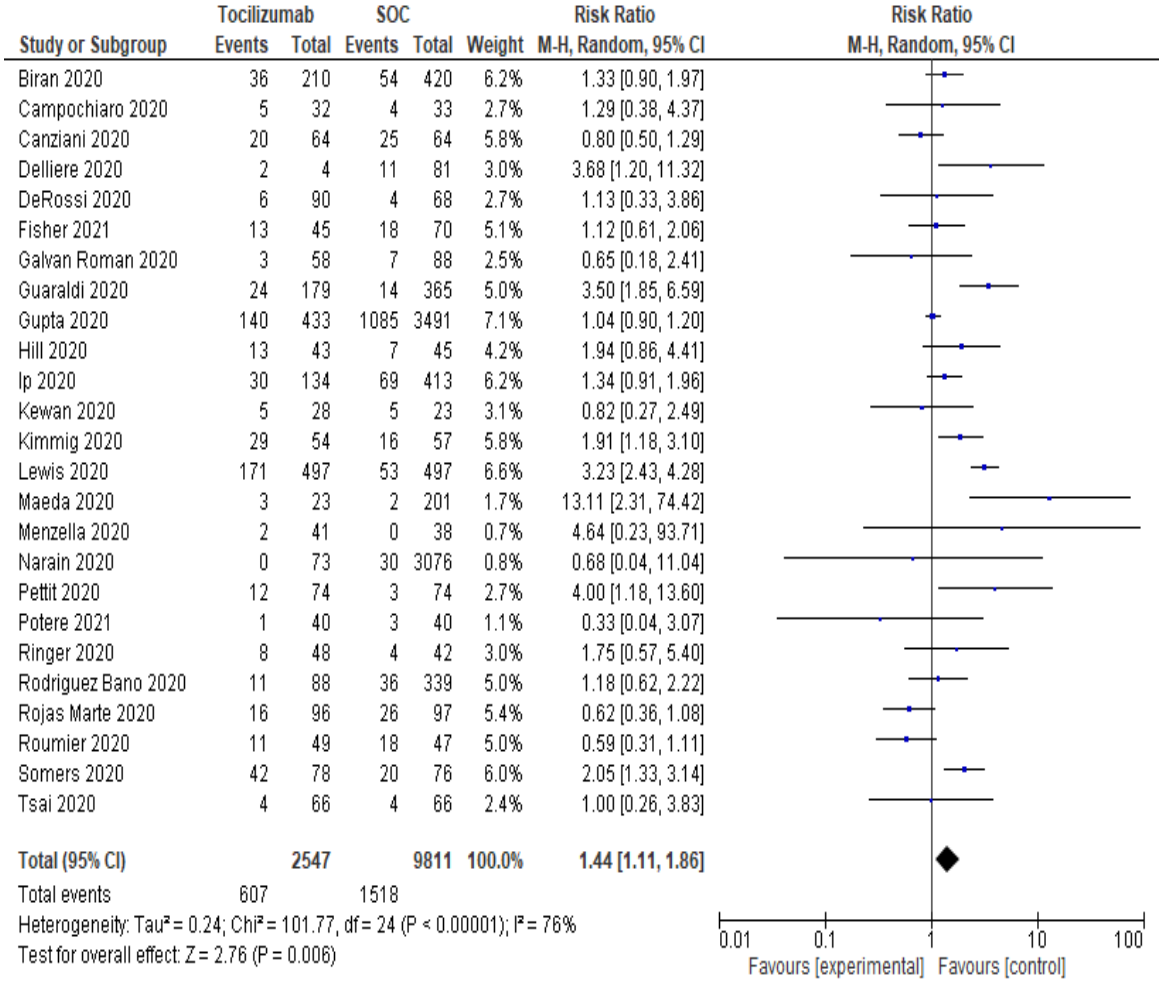
Supplementary A

Figure A: Risk of infection with Steroids in non-randomized studies



Supplementary A

Figure B: Risk of infection with Tocilizumab in non-randomized studies



Supplementary B:

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	I
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	9
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	18
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	20
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	23
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	23
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	24
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	24
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	24
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	24
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details	25

Section and Topic	Item #	Checklist item	Location where item is reported
		of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	25
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	25
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	25
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	26
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	26
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	25, 27
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	27
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	28 and figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary C
Study characteristics	17	Cite each included study and present its characteristics.	Table 1, 2 , 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 4, 5

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1 and 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	30 and Figures
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	29-32 and Figures
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	29-32and Figure
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	29-32 and Figure
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	ND
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	32
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	33
	23b	Discuss any limitations of the evidence included in the review.	36
	23c	Discuss any limitations of the review processes used.	36
	23d	Discuss implications of the results for practice, policy, and future research.	34
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	Methods
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	Methods
Study registries	3	List any study registries searched.	Methods
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	N/A
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	N/A
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	Methods
Other methods	7	Describe any additional information sources or search methods used.	N/A
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Supplement B
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	Methods

Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	Methods
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	N/A
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	Methods
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	Methods
PEER REVIEW			
Peer review	14	Describe any search peer review process.	N/A
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	Methods
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	Methods

PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews

Supplementary C

Ovid MEDLINE(R) ALL <1946 to February 03, 2021>

#	Search Statement	Results
1	((((exp Coronavirus/ or exp Coronavirus Infections/ or (D614G or coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.) and ((20191* or 202*).dp. or 20190101:20301231.(ep).)) not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.) or ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox. or "severe acute respiratory syndrome coronavirus 2".os.)) and 20191201:20301231.(dt).	103443
2	("Immun* therap*" or immunotherap* or steroids or steroid or glucocorticoid* or "adalimumab anti TFN" or "anti-tumor necrosis factor" or "anti-tumour necrosis factor" or "anti CD147" or betamethasone or colchicine or corticosterone or cortisone or dexamethasone or fedratinib or fludrocortisone or fluprednisolone or "glycrrhetinic acid" or "glycyrrhizic acid" or methylprednisolone or paramethasone or prednisone or prednisolone or methylpred or interferon or "IFN alpha-2a" or "IFN alpha-2b" or "anti-IL6" or "IL6-R" or Tociluzumab or (tobramycin adj2 dexamethasone) or Actemera or Roactemera or Sarilumab or Kevzara or anikara or (interleukin adj inhibitor*) or "monoclonal antibod*" or "Jak inhibitor*" or (janus adj3 inhibit*) or baricitinib or ruxolitinib or "BTK inhibitor acalabrutinib").ti,ab,kw.	849997
3	exp *Anti-Inflammatory Agents/ or exp *Immunotherapy/	417997
4	2 or 3	1142115
5	1 and 4	3759
6	(mortality or death or survival or "treatment outcome*" or "fatal outcome*" or "polymicrobial infection*" or "viral bacterial infection*" or "nosocomial infection*" or ((ventilat* or hospital* or ICU or "intensive care unit*") adj3 (day* or days or "length of stay*" or los or duration))).ti,ab,kw.	2270558

7	incidence.sh. or exp mortality/ or follow-up studies.sh. or prognos:.tw. or predict:.tw. or course:.tw.	3629180
8	Intensive Care Unit/ and ("length of stay" or los or day or days or duration).ti,ab,kw.	16644
9	exp Treatment Outcome/ or Length of Stay/	1155850
10	exp Death/ or exp Survival/	155710
11	6 or 7 or 8 or 9 or 10	5730062
12	("Immun* therap*" or immunotherap* or steroids or steroid or glucocorticoid* or "adalimumab anti TFN" or "anti-tumor necrosis factor" or "anti-tumour necrosis factor" or "anti CD147" or betamethasone or colchicine or corticosterone or cortisone or dexamethasone or fedratinib or fludrocortisone or fluprednisolone or "glycrrhetinic acid" or "glycyrrhizic acid" or methylprednisolone or paramethasone or prednisone or prednisolone or methylpred or interferon or "IFN alpha-2a" or "IFN alpha-2b" or "anti-IL6" or "IL6-R" or Tociluzumab or (tobramycin adj2 dexamethasone) or Actemera or Roactemera or Sarilumab or Kevzara or anikara or (interleukin adj inhibitor*) or "monoclonal antibod*" or "Jak inhibitor*" or (janus adj3 inhibit*) or baricitinib or ruxolitinib or "BTK inhibitor acalabrutinib").ti,ab,kw.	849997
13	((secondary adj3 infection*) or (infect* adj3 complication*) or "ventilator acquired" or "hospital acquired infection*" or "hospital associated infection*" or "polymicrobial infection*" or "viral bacterial infection*" or "nosocomial infection*" or coinfection or "cross infection*").mp. or Coinfection/ or Cross-Infection/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	171273
14	mycoses/ or exp aspergillosis/ or exp candidiasis/ or exp cryptococcosis/ or exp invasive fungal infections/ or exp lung diseases, fungal/ or exp microsporidiosis/ or paracoccidioidomycosis/ or phaeohyphomycosis/ or exp pneumocystis infections/ or exp zygomycosis/	98943
15	(mycobacter* or fungus or fungal or mycosis or mycoses or aspergill* or candid* or yeast or mold or molds or mould or moulds or cryptococcosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	950471
16	14 or 15	964075
17	bacterial infections/ or exp bacteremia/ or exp gram-negative bacteria/ or exp Gram-Positive Bacteria/ or exp gram-negative bacterial infections/ or gram-positive bacterial infections/ or pneumonia, bacterial/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/	1452792

	or pneumonia, staphylococcal/	
18	("bacteri* infect*" or bacteriosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	129167
19	superbacteria*.mp. or exp Sepsis/ or sepsis.mp.	186930
20	exp Enterobacteriaceae/	404571
21	exp Staphylococcus aureus/	76792
22	exp Klebsiella Infections/ or exp Klebsiella pneumoniae/	17944
23	exp Methicillin-Resistant Staphylococcus aureus/	15161
24	"multi drug resistan*".mp.	10194
25	(Enterobacteriaceae or legionella or tubuculosis or "staphylococcus aureus" or Klebsiellia or MSRA or "bacterial pneumonia").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	174265
26	exp bronchitis/ or common cold/ or influenza, human/ or laryngitis/ or pharyngitis/ or rhinitis/ or sinusitis/ or exp supraglottitis/ or tracheitis/	118782
27	herpesviridae/ or cytomegalovirus/	28395
28	exp Chickenpox/	7500
29	herpesviridae/ or herpesvirus 3, human/	14664
30	varicella-zoster.mp.	9883
31	herpesviridae infections/ or exp varicella zoster virus infection/ or herpes zoster/	32682
32	exp Metapneumovirus/	1328
33	(metapneumovirus* or hmpv or influenza or rsv).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	127377
34	exp enterovirus/ or rhinovirus/	26597
35	(rhinovirus* or enterovirus*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	25223
36	exp Respiratory Syncytial Viruses/ or exp Respiratory Syncytial Virus, Human/	9066
37	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	2781044

38	11 or 37	7963644
39	1 and 2 and 38	1663
40	remove duplicates from 39	1588
41	("20201028" or 202011* or 202012* or 2021*).dt,ez,da.	620516
42	40 and 41	718

Embase 1974 to 2021 February 04

#	Search Statement	Results
1	(((exp Coronavirus/ or exp Coronavirus Infections/ or (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.) not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.) or (((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or ("coronavirus disease 2019" or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or "covid 2019" or d614G or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or ("coronavirus disease 2019" or severe acute respiratory syndrome coronavirus 2).sh,dj.) and 20191201:20301231.(dc).	100336
2	("Immun* therap*" or immunotherap* or steroids or steroid or glucocorticoid* or adalimumab or "anti TFN" or "anti-tumor necrosis factor" or "anti-tumour necrosis factor" or "anti CD147" or betamethasone or colchicine or corticosterone or cortisone or dexamethasone or fedratinib or fludrocortisone or fluprednisolone or "glycrrhetinic acid" or "glycyrrhizic acid" or methylprednisolone or paramethasone or prednisone or prednisolone or methylpred or interferon or "IFN alpha-2a" or "IFN alpha-2b" or "anti-IL6" or "IL6-R" or Tociluzumab or (tobramycin adj2 dexamethasone) or Actemera or Roactemera or Sarilumab or Kevzara or anikara or (interleukin adj inhibitor*) or "monoclonal antibod*" or "Jak inhibitor*" or (janus adj3 inhibit*) or baricitinib or ruxolitinib or "BTK inhibitor acalabrutinib").ti,ab,kw.	1161235
3	exp *antiinflammatory agent/	701748
4	2 or 3	1715924
5	(mortality or death or survival or (secondary adj3 infection*) or (infect* adj3 complication*) or "treatment outcome*" or "fatal outcome*" or	3343448

	coinfection* or "cross infection*" or "hospital acquired infection*" or "hospital associated infection*" or "polymicrobial infection*" or "viral bacterial infection*" or "nosocomial infection*" or ((ventilat* or hospital* or ICU or "intensive care unit*") adj3 (day* or days or "length of stay*" or los or duration))).ti,ab,kw.	
6	exp death/ or mortality/	1393722
7	exp treatment outcome/	1749837
8	exp survival prediction/ or exp survival/ or exp survival rate/ or exp post treatment survival/	1171461
9	follow-up.mp. or prognos:.tw. or ep.fs.	3763656
10	exp artificial ventilation/ or exp intensive care unit/	383016
11	exp "length of stay"/ or (day* or days or "length of stay*" or los or duration).ti,ab.	3847743
12	10 and 11	127344
13	5 or 6 or 7 or 8 or 9 or 12	7458506
14	((infect* adj3 complication*) or ((hospital or health care or ventilator) adj3 (acquired or associated) adj3 infect*) or "polymicrobial infection*" or "viral bacterial infection*" or "nosocomial infection*" or coinfection or "cross infection*").mp.	127110
15	(mycobacter* or fungus or fungal or mycosis or mycoses or aspergill* or candid* or yeast or mold or molds or mould or moulds or cryptococcosis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1206220
16	("bacteri* infect*" or bacteriosis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	158028
17	superbacteria*.mp. or exp Sepsis/ or sepsis.mp.	313721
18	"multi drug resistan*".mp.	15605
19	(Enterobacteriaceae or legionella or tubuculosis or "staphylococcus aureus" or Klebsiellia or MSRA or "bacterial pneumonia").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	263070
20	varicella-zoster.mp.	20825
21	(metapneumovirus* or hmpv or influenza or rsv).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	167698
22	(rhinovirus* or enterovirus*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	26689
23	exp mycosis/	190798
24	bacterial infection/ or exp bacterial pneumonia/ or bacterial	303287

	superinfection/ or exp enterobacteriaceae infection/ or exp gram negative infection/ or exp gram positive infection/ or exp staphylococcus infection/ or exp streptococcus infection/	
25	exp sepsis/	275403
26	respiratory tract inflammation/ or exp "inflammation of the lungs, bronchi and pleura"/ or exp laryngitis/ or exp pharyngitis/ or exp rhinitis/ or exp sinusitis/ or exp supraglottitis/ or exp tonsillitis/ or tracheitis/	547686
27	exp influenza/	90034
28	exp common cold/	8513
29	exp cytomegalovirus infection/ or exp Herpesviridae/ or exp Varicella zoster virus/	158681
30	exp chickenpox/	11650
31	exp Enterovirus/	20400
32	exp Rhinovirus/	8808
33	exp Metapneumovirus/	3640
34	exp pneumovirus/	5635
35	exp mixed infection/ or exp secondary infection/ or exp cross-infection/	62289
36	exp hospital infection/	47938
37	exp ventilator associated pneumonia/ or exp health care associated pneumonia/ or exp infectious complication/	185376
38	or/14-37	2850855
39	13 or 38	9391926
40	1 and 4 and 39	3109
41	remove duplicates from 40	3023
42	limit 41 to dc=20201028-20210205	1409

SCOPUS Searched Feb 05, 2020 Result =2418

((TITLE-ABS-KEY (("Immun* therap*" OR immunotherap* OR steroids OR steroid OR glucocorticoid* OR "anti TFN" OR "anti-tumor necrosis factor*" OR "anti-tumour necrosis factor" OR anti-cd147 OR colchicine OR adalimumab OR betamethasone OR corticosterone OR cortisone OR dexamethasone OR fedratinib OR fludrocortisone OR fluprednisolone OR "glycrrhetinic acid" OR "glycyrrhizic acid" OR methylprednisolone OR paramethasone OR prednisone OR prednisolone OR methylpred OR interferon OR "IFN alpha-2a" OR "IFN alpha-2b" OR anti-il6 OR il6-r OR tociluzumab OR (tobramycin AND dexamethasone) OR actemera OR roactemera OR sarilumab OR kevzara OR anikara OR "interleukin inhibitor*" OR "monoclonal antibod*" OR "Jak inhibitor*" OR "janus inhibit*" OR baricitinib OR ruxolitinib OR "BTK inhibitor acalabrutinib")))) AND ((((TITLE-ABS-KEY ((coronavirus* OR "corona virus*" OR oc43 OR nl63 OR 229e OR hku1 OR hcov* OR ncov* OR covid* OR "sars-cov*" OR sarscov* OR "Sars-coronavirus*" OR "Severe Acute Respiratory Syndrome Coronavirus*" OR d614g))) AND NOT ((TITLE-ABS-KEY ((sars OR

sars-cov OR mers OR mers-cov OR "Middle East respiratory syndrome or camel*" OR dromedar* OR equine OR coronary OR coronal OR covidence* OR covidien OR influenza AND virus OR hiv OR bovine OR calves OR tgev OR feline OR porcine OR bcov))) OR (TITLE-ABS-KEY ((ped OR pedv OR pdcov OR fipv OR fcov OR sads-cov OR canine OR ccov OR zoonotic OR "avian influenza" OR h1n1 OR h5n1 OR h5n6 OR ibv OR murine AND corona*))))) OR (TITLE-ABS-KEY ((pneumonia OR covid* OR coronavirus* OR corona AND virus* OR ncov* OR 2019-ncov OR sars*) AND wuhan) OR ((2019-ncov OR ncov19 OR ncov-19 OR 2019-novel AND cov OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR coronavirus-19 OR covid19 OR covid-19 OR "covid 2019" OR ((covid OR covid19 OR covid-19) AND pandemic*2) OR (coronavirus* AND pneumonia)))) OR (TITLE ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR corona AND virus OR pandemi*))) OR (ABS ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR corona AND virus OR pandemi*))) OR (KEY ((novel OR new OR nouveau) AND (cov OR ncov OR covid OR coronavirus* OR corona AND virus OR pandemi*))))) AND ((TITLE-ABS (death OR mortality OR survival OR "treatment outcome*" OR "fatal outcome*" OR (secondary W/3 infection*) OR (infection W/3 complication*) OR "hospital associated infection*" OR "hospital acquired infection*" OR "cross infection*" OR "mixed infection*" OR "polymicrobial infection*" OR "viral bacterial infection*" OR prognosis OR coinfection OR "nosocomial infection*" OR "ventilator aquired infect*" OR "ventilator associated infect*" OR bacteriosis OR "bacteri* infect*" OR superbacteria* OR sepsis OR "multi drug resistan*" OR "multidrug resistan*" OR enterobacteriaceae OR legionella OR tubuculosis OR "staphylococcus aureus" OR klebsiellia OR msra OR "bacterial pneumonia" OR metapneumovirus* OR hmpv OR influenza OR rsv OR rhinovirus* OR enterovirus* OR mycobacter* OR fungus OR fungal OR mycosis OR mycoses OR aspergill* OR candid* OR yeast OR mold OR molds OR mould OR moulds OR cryptococcosis OR mycosis OR mycoses OR chickenpox OR "varicella-zoster" OR "gram positive" OR "gram negative" OR "common cold" OR "lung infection*" OR "pulmonary infection*" OR ((ventilat* OR hospital* OR icu OR "intensive care unit*") W/3 (day* OR days OR "length of stay*" OR duration))))) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))

PROSPERO Searched February 05, 2020

Search for	Hits

#1	(((coronavirus or corona-virus) AND (wuhan or beijing or shanghai or Italy or South-Korea or korea or China or Chinese or 2019-nCoV or nCoV or COVID-19 or Covid19 or SARS-CoV* or SARSCov2 or ncov)) OR (pneumonia AND Wuhan) or "COVID-19" or "2019-nCoV" or "SARS-CoV" or SARSCOV2 or 2019-nCov or "2019 coronavirus" or "2019 corona virus" or covid19 or ncov OR "novel corona virus" or "new corona virus" or "nouveau corona virus" or "2019 corona virus" OR "novel coronavirus" or "new coronavirus" or "nouveau coronavirus" or "2019 coronavirus") NOT Animal:DB	3165
#2	"immun* therap*" NOT Animal:DB	256
#3	immunotherap* or anti-inflammator* or antiinflammator* NOT Animal:DB	1964
#4	anti-TFN or "anti-tumor necrosis fractor" NOT Animal:DB	0
#5	"anti-tumour necrosis factor" or anti-CD147 or steroids or steroid or glucocorticoid* or adalimumab or betamethasone or colchicine or corticosterone or cortisone or dexamethasone or fedratinib or fludrocortisone or fluprednisolone NOT Animal:DB	2229
#6	"glycrrhetinic acid" or "glycyrrhizic acid" or methylprednisolone or paramethasone or prednisone or prednisolone or methylpred or interferon NOT Animal:DB	753
#7	"IFN alpha-2a" OR "IFN alpha-2b" or anti-IL6 or IL6-R or Tociluzumab or tobramycin-dexamethasone or Actemera or roactemera or Kevzara or anikara NOT Animal:DB	12
#8	"interleukin inhibitor*" or "monoclonal antibod*" or "Jak inhibitor*" or "janus inhibit*" or baricitinib or ruxolitinib or "BTK inhibitor acalabrutinib" NOT Animal:DB	502
#9	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	4771
#10	mortality or death or survial or "treatment outcome*" or "fatal outcome*" or "secondary infection*" or coinfection* or "cross-infection*" or "fungal infection*" or "infection complication*" OR "hospital associated infection*" OR "hospital acquired infection*" "mixed infection*" OR "polymicrobial infection*" OR "viral bacterial infection*" OR prognosis OR "nosocomial infection*" or "length of stay" OR ((ventilat* OR hospital* OR icu OR "intensive care unit*") and (day OR days OR duration))	39576
#11	"ventilator aquired infect*" OR "ventilator associated infect*" OR bacteriosis OR "bacteri* infect*" OR superbacteria* OR sepsis OR "multi drug resistan*" OR "multidrug resistan*" OR enterobacteriaceae OR legionella OR tubuculosis OR "staphylococcus aureus" OR klebsiellia OR msra OR "bacterial pneumonia" OR metapneumovirus* OR hmpv OR influenza OR rsv OR rhinovirus* OR enterovirus* OR mycobacter* OR fungus OR fungal OR mycosis OR mycoses OR aspergill* OR candid* OR yeast OR mold OR molds OR mould OR moulds OR cryptococcosis OR mycosis OR mycoses OR chickenpox OR	5682

"varicella-zoster" OR "gram positive" OR "gram negative" OR "common cold" OR "lung infection*" OR "pulmonary infection*"

#12 #10 OR #11 41763

#13 #1 AND #9 AND #12 230

Cochrane Library Searched February 05, 2020

ID Search Hits
#1 MeSH descriptor: [Anti-Inflammatory Agents] explode all trees 13396
#2 Immun* next therap* or immunotherap* or steroids or steroid or glucocorticoid* or adalimumab or betamethasone or corticosterone or cortisone or dexamethasone or fludrocortisone or fluprednisolone 61165
#3 glycrrhetinic next acid or glycyrrhizic next acid or methylprednisolone or paramethasone or prednisone or prednisolone or methylpred 20400
#4 "anti IL6 " or "IL6 R" or Tociluzumab or "tobramycin dexamethasone" or Actemera 120
#5 (Sarilumab or Kevzara or anikara or interleukin next inhibitor* or monoclonal next antibod* or Jak next inhibitor* or janus next inhibit* or baricitinib or ruxolitinib or BTK next inhibitor next acalabrutinib):ti,ab,kw 10717
#6 #1 or #2 or #3 or #4 or #5 91213
#7 mortality or survival or death or "health outcome" 206640
#8 MeSH descriptor: [Mortality] explode all trees 13304
#9 MeSH descriptor: [Survival] explode all trees 127
#10 MeSH descriptor: [Death] explode all trees 2196
#11 #7 or #8 or #9 or #10 207118
#12 (pandemic* or epidemic* or quarantin* or ebola* or Covid19 or "covid 19"):ti,ab,kw 7960
#13 MeSH descriptor: [Coronavirus] 1 tree(s) exploded 4
#14 MeSH descriptor: [Coronavirus Infections] explode all trees 630
#15 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*) 5064
#16 #13 or #14 or #15 5084
#17 (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or

coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*)
102473

#18 #16 not #17 2353

#19 (pneumonia or covid* or coronavirus* or corona virus* or ncov* or "2019-ncov" or sars*) and Wuhan 216

#20 #12 or #18 or #19 8135

#21 ("ventilator aquired infect*" OR "ventilator associated infect*" OR bacteriosis OR "bacteri* infect*" OR superbacteria* OR sepsis OR "multi drug resistan*" OR "multidrug resistan*" OR enterobacteriaceae OR legionella OR tubuculosis OR "staphylococcus aureus" OR klebsiellia OR msra OR "bacterial pneumonia" OR metapneumovirus* OR hmpv OR influenza OR rsv OR rhinovirus* OR enterovirus* OR mycobacter* OR fungus OR fungal OR mycosis OR mycoses OR aspergill* OR candid* OR yeast OR mold OR molds OR mould OR moulds OR cryptococcosis OR mycosis OR mycoses OR chickenpox OR "varicella-zoster" OR "gram positive" OR "gram negative" OR "common cold" OR "lung infection*" OR "pulmonary infection*"):ti,ab,kw
54100

#22 MeSH descriptor: [Cross Infection] explode all trees 1456

#23 MeSH descriptor: [Coinfection] explode all trees 171

#24 MeSH descriptor: [Mycoses] explode all trees 2446

#25 MeSH descriptor: [Bacterial Infections] explode all trees
15710

#26 MeSH descriptor: [Sepsis] explode all trees 4572

#27 MeSH descriptor: [Enterobacteriaceae] explode all trees 1227

#28 MeSH descriptor: [Staphylococcus aureus] explode all trees 810

#29 MeSH descriptor: [Pneumonia, Staphylococcal] explode all trees 33

#30 MeSH descriptor: [Lung Diseases, Fungal] explode all trees 335

#31 MeSH descriptor: [Respiratory Tract Infections] explode all trees
15271

#32 MeSH descriptor: [Klebsiella Infections] explode all trees 78

#33 MeSH descriptor: [Methicillin-Resistant Staphylococcus aureus] explode all trees 214

#34 MeSH descriptor: [Enterovirus] 1 tree(s) exploded 8

#35 MeSH descriptor: [Rhinovirus] 1 tree(s) exploded 3

#36 MeSH descriptor: [Metapneumovirus] 1 tree(s) exploded 0

#37 MeSH descriptor: [Herpesvirus 3, Human] explode all trees 140

#38 MeSH descriptor: [Respiratory Syncytial Viruses] 1 tree(s) exploded 12

#39 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
76391

#40	#10 or #39	78511	
#41	#6 and #20 and #40		238

Supplementary C: Table of excluded studies and reason for exclusion

Study	Exclusion Criteria
Mikulska 2020	No comparator group
Maeda 2020	Duplicate : Same patients/cohort as Obata 2020
Kumar 2020	Duplicate
Tran 2020	Duplicate
Obata 2020	Abstract only
Galvez-Romero 2020	No comparator group
Nebreda-Mayoral 2021	Others: No data on lack on infection in intervention arm
Nasa 2020	No outcome of interest in control group
Hu 2020	No outcome of interest
Delliere 2021	Duplicate
Chaudhary 2021	No outcome of interest
Jungmayr 2020	Letter to editor
Jamous 2020	No outcome of interest
Pereda 2020	No outcome of interest
Guo 2020	Outcomes not assessed according to immunotherapy given
Gutierrez-Abejon 2020	Outcomes not assessed according to immunotherapy given
delaFlorMerino 2020	Outcomes not assessed according to immunotherapy given
Ringer 2021	Duplicate
Potere 2020	Duplicate
Papamanoli 2020	Duplicate
Okoh 2021	Duplicate
Rahmani 2020	Duplicate
Davoudi-Monfared 2020	Duplicate
Bartoletti 2020	Duplicate
Schroeder 2020	Outcomes not assessed according to immunotherapy given
Ramirez 2021	Outcomes not assessed according to immunotherapy given
Ooi 2020	No outcome of interest
Guirao 2020	No outcome of interest
Kumar 2020	Duplicate
Yuan 2020	Outcomes not assessed according to immunotherapy given
Mady 2020	No Comparator group
Castelnovo 2021	No outcome of interest in control group
Rodriguez-Tajes 2021	No Comparator group
Patel 2020	No Comparator group
Albertini 2021	No outcome of interest in control group
Mareev 2020	No outcome of interest
Tian 2020	No outcome of interest
Perrone 2020	No outcome of interest
Eastin 2020	Outcomes not assessed according to immunotherapy given
ToqueroDiez 2020	abstract only

Loinaz 2020	Outcomes not assessed according to immunotherapy given
Zhu 2020	No outcome of interest
Li 2020	Outcomes not assessed according to immunotherapy given
Bartoletti 2021	Duplicate
Huet 2020	No outcome of interest in control group
Wilson 2020	abstract only
DeGreef 2020	abstract only
Urendes 2020	abstract only
Anudeep 2020	Outcomes not assessed according to immunotherapy given
Rosas 2020	No outcome of interest
LopezZuniga 2021	No outcome of interest
CruzaLeganes 2020	abstract only
Pasulo 2020	abstract only
Khamis 2021	No outcome of interest
Anonymous 2020	Editorial
Stefan 2021	Outcomes not assessed according to immunotherapy given
Rogiers 2020	abstract only
Rodriguez-Gonzalez 2021	No outcome of interest
Ashimov 2020	No Comparator group
Liu 2020	No outcome of interest
Li 2021	No outcome of interest
Giacobbe 2020	Others: We don't know the denominator
Pisano 2020	abstract only
Wu 2020	Outcomes not assessed according to immunotherapy given
Rubio-Rivas 2020	No Comparator group
Monreal 2020	No Comparator group
Ramirez 2020	Outcomes not assessed according to immunotherapy given
Yang 2020	No outcome of interest
Calles 2020	No outcome of interest
Wang 2020	No outcome of interest
Fu 2020	No outcome of interest
Rossotti 2020	Outcomes not assessed according to immunotherapy given
Xie 2020	No outcome of interest
Berenguer 2020	No outcome of interest
Wan 2020	Outcomes not assessed according to immunotherapy given
Martinez-Sanz 2020	No outcome of interest
Vahedi 2020	No outcome of interest
Santos 2020	Outcomes not assessed according to immunotherapy given
Yan 2020	Outcomes not assessed according to immunotherapy given
Razanamahery 2020	No outcome of interest
Gusev 2020	No outcome of interest
Bersanelli 2020	No outcome of interest
Saggi 2020	No outcome of interest

Lee 2020	No outcome of interest
Mei 2021	No outcome of interest
WHOSolidarityTrialConsortium 2020	No outcome of interest
SzenteFonseca 2020	No outcome of interest
Boari 2020	No outcome of interest
Lence 2020	abstract only
Omer 2020	abstract only
Hasan 2021	No Comparator group
Saggi 2020	abstract only
OnievaCalero 2020	abstract only
Pinato 2020	No outcome of interest
Chen 2020	No outcome of interest
Johnson 2020	Editorial
Lumlertgul 2020	abstract only
Bronte 2020	No outcome of interest in control group
Maritati 2020	No Comparator group
Baghaei 2021	No outcome of interest
Bozzi 2021	Duplicate
Baghaei 2020	Duplicate
Antony 2020	No Comparator group
Li 2020	No outcome of interest
Sinha 2020	No Comparator group
GarciaOlivares 2020	abstract only
Mahale 2020	Outcomes not assessed according to immunotherapy given
Xia 2021	No outcome of interest
SanzHerrero 2021	No outcome of interest
delaFlorMerino 2021	Outcomes not assessed according to immunotherapy given
Chen 2020	Outcomes not assessed according to immunotherapy given
Dastan 2020	No outcome of interest
Wang 2020	No outcome of interest in control group
Iacovoni 2020	Outcomes not assessed according to immunotherapy given
Lara 2020	Outcomes not assessed according to immunotherapy given
Hong 2020	Outcomes not assessed according to immunotherapy given
Xin 2020	No outcome of interest
Wu 2020	Outcomes not assessed according to immunotherapy given
	Prospero
Valette 2020	Letter to editor
Moon 2020	Letter to editor
Paterson 2020	Wrong study design: cases with neurological sequale collected and no immunotherapy given
NCT04519385 2020	Protocol
LoCaputo 2020	Letter to editor

Castellano 2020	Wrong study design: case report
Du 2020	Outcomes not assessed according to immunotherapy given
	Prospero
Maoujoud 2020	Letter to editor
Bhadade 2020	Outcomes not assessed according to immunotherapy given
Chilimuri 2020	No outcome of interest
Marta 2020	No outcome of interest
Aouba 2020	No outcome of interest
Sanchez-Alvarez 2020	Wrong study design : registry
Eastin 2020	No outcome of interest
Lenka 2020	No outcome of interest
Al-Darzi 2020	Outcomes not assessed according to immunotherapy given
Campins 2020	No outcome of interest
Bossini 2020	Outcomes not assessed according to immunotherapy given
Huang 2020	Outcomes not assessed according to immunotherapy given
Yang 2020	Outcomes not assessed according to immunotherapy given
Khamis 2020	No outcome of interest
Sanchez-Piedra 2020	Wrong study design : Immunotherapy before COVID outcome according to treatment precOVID
Zhang 2020	Outcomes not assessed according to immunotherapy given
Banerjee 2020	No outcome of interest
Bhatraju 2020	No outcome of interest
PiÃ±ana 2020	No outcome of interest
Guo 2020	abstract only
Mahase 2020	Letter to editor
Yang 2020	No outcome of interest
Ucciferri 2020	No Comparator group
Li 2020	No outcome of interest
Aversa 2020	Outcomes not assessed according to immunotherapy given
Gandolfini 2020	No outcome of interest
Chen 2020	Outcomes not assessed according to immunotherapy given
Khan 2020	No outcome of interest
Ding 2020	No outcome of interest
Baghaei 2021	No outcome of interest
Cauchois 2020	No outcome of interest in control group
Rodriguez-Molinero 2021	No outcome of interest
Li 2020	Outcomes not assessed according to immunotherapy given
Tortajada 2021	No outcome of interest
Zhao 2021	No outcome of interest
Woodhead 2020	abstract only
FalconMarchena 2020	abstract only
Ruiz 2020	abstract only
Kooistra 2020	abstract only

Li 2021	No outcome of interest
Russo 2020	abstract only
Nasir 2020	No Comparator group
Valenzuela 2020	No Comparator group
Generali 2020	No outcome of interest
Akhtar 2021	No outcome of interest
Huang 2020	No outcome of interest
Roomi 2020	No outcome of interest
Capra 2020	No outcome of interest in control group
Sandhu 2020	No outcome of interest
Zuccon 2020	No outcome of interest
Ji 2020	No outcome of interest
SanzGarcia 2020	abstract only
Lambermont 2020	No outcome of interest
Tan 2021	No outcome of interest
Hu 2020	No outcome of interest
Zha 2020	No outcome of interest
Potere 2020	No outcome of interest in control group
Klopfenstein 2020	No outcome of interest
Martinez-Sanz 2020	No outcome of interest
Klopfenstein 2020	No outcome of interest
Nakamura 2020	No Comparator group
Dupuis 2020	abstract only
Salvati 2020	No outcome of interest
Serino 2020	abstract only
Lian 2020	No outcome of interest
Greco 2020	No Comparator group
Yan 2020	No outcome of interest
Du 2020	Outcomes not assessed according to immunotherapy given
SisÃ³-Almirall 2020	No outcome of interest
Tortajada 2020	No outcome of interest
Hu 2020	No outcome of interest
Huang 2020	No outcome of interest
Yip 2020	No outcome of interest
Liu 2020	No outcome of interest
Holt 2020	No outcome of interest
Brunetti 2020	No outcome of interest
Pereira 2020	No outcome of interest
Stallmach 2020	No outcome of interest
Wadud 2020	abstract only
Fernandez-Cruz 2020	No outcome of interest
Benucci 2020	No Comparator group
Zhao 2020	No outcome of interest

Huang 2020	No outcome of interest
Sanchez-Alvarez 2020	No outcome of interest
Cantini 2020	No outcome of interest in control group
Li 2020	No outcome of interest
SanzHerrero 2020	No outcome of interest
Gokhale 2020	No outcome of interest
Comel 2020	Wrong study design: case report
Majmundar 2020	No outcome of interest
RECOVERYCollaborativeGroup 2020	No outcome of interest
Wang 2020	No outcome of interest
Li 2020	Outcomes not assessed according to immunotherapy given
Ruiz-Irastorza 2020	No outcome of interest
Xu 2020	No outcome of interest
Chen 2020	Wrong study design: case report
Liu 2020	No outcome of interest
Crespo 2020	No outcome of interest
Jin 2020	No outcome of interest
Sciascia 2020	No Comparator group
Keller 2020	No outcome of interest
Liu 2020	No outcome of interest
Fox 2020	Outcomes not assessed according to immunotherapy given
Wang 2020	No outcome of interest
Yao 2020	No outcome of interest
McCarthy 2020	No Comparator group
Guisado-Vasco 2020	No outcome of interest
Rossi 2020	No outcome of interest
Strohbehn 2020	preprint
Deftereos 2020	No outcome of interest
Fried 2020	No outcome of interest
Crespo 2020	No outcome of interest
Hu 2020	No outcome of interest
DiGiambenedetto 2020	Letter to editor
Petrak 2020	No Comparator group
Hong 2020	abstract only
Price 2020	No outcome of interest in control group
Zhou 2020	No outcome of interest
Conrozier 2020	No Comparator group
Dubernet 2020	No outcome of interest
Cravedi 2020	No outcome of interest
Peinado 2020	abstract only
Wang 2020	No outcome of interest
Xu 2020	No outcome of interest

Palmieri 2020	Outcomes not assessed according to immunotherapy given
Li 2020	No outcome of interest
Zhang 2020	No outcome of interest
Roman 2020	abstract only
MateosGonzalez 2021	Outcomes not assessed according to immunotherapy given
Segrelles-Calvo 2021	No Comparator group
Borie 2020	No outcome of interest in control group
AvilesParra 2020	abstract only
Potalivo 2020	No outcome of interest
Han 2020	No outcome of interest
Mastroianni 2020	abstract only
Wu 2020	No outcome of interest
PascualPareja 2020	No outcome of interest
Rodriguez-Gonzalez 2020	No outcome of interest
Merugu 2020	No outcome of interest
Widysanto 2021	No outcome of interest
Wadud 2020	abstract only
Temesgen 2020	No outcome of interest
Drapkina 2020	No outcome of interest
DeLuca 2020	abstract only
Mongardon 2021	No outcome of interest
Tekin 2021	Wrong study design (Case report : 2 cases)
Gupta 2021	Duplicate
Ruiz-Antoran 2020	No outcome of interest in control group
Tamburello 2020	abstract only
Xu 2020	No outcome of interest in control group
Monk 2020	No outcome of interest
Jimenez-Britez 2020	No comparator group
You 2020	No outcome of interest
Rodriguez-Molinero 2021	No outcome of interest
Nebreda-Mayoral 2020	Duplicate
Falcone 2020	No outcome of interest
Sakoulas 2020	No immunotherapy given (IVIG)
Coll 2020	Outcomes not assessed according to immunotherapy given
Corominas 2021	No Comparator group
Sungurtekin 2020	Outcomes not assessed according to immunotherapy given
Yousaf 2020	No outcome of interest
Mourad 2020	Letter to editor
Riche 2020	No Comparator group
Zheng 2020	No outcome of interest
Piano 2020	Letter to editor
Fadel 2020	No Comparator group
Navarro-Millan 2020	No outcome of interest in control group

Kaminski 2020	No Comparator group
BorkuUysal 2020	No Comparator group
Lanthier 2020	Letter to editor
TrellesGarcia 2020	abstract only
Raziq 2020	abstract only
Alattar 2020	No Comparator group
Lipworth 2020	Letter to editor
Yarza 2020	Outcomes not assessed according to immunotherapy given
Fredi 2020	Wrong study: Compare patients with confirmed COVID-19 vs not
Trujillo 2020	No Comparator group

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