EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 patients, should baricitinib be used for treatment?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of baricitinib in addition to corticosteroids among critical COVID-19 patients on high-flow nasal cannula oxygenation, noninvasive ventilation, or invasive mechanical ventilation.	Moderate	Strong
We suggest against the use of baricitinib among pediatric patients with COVID-19.	Very low	Weak

Consensus Issues
Generally, there were no panel issues on the use of baricitinib. The present recommendation is now based on seven clinical trials with evidence on its benefit for patients with critical COVID-19.

KEY FINDINGS

- A total of seven studies reported critical outcomes on the use of baricitinib for COVID-19.
- The overall certainty of evidence was moderate because of serious inconsistency in some of the outcomes reported.
- Baricitinib appears to have benefit in terms of decreasing 28-day mortality and need for respiratory support compared to standard of care, majority of which were given corticosteroids.
- There were no excess risk of serious adverse events, venous thrombosis, or complications of infection associated with baricitinib in the studies reviewed.
- The mortality benefit appears to be limited to unvaccinated patients and to those requiring noninvasive and invasive mechanical ventilation at baseline.
- The benefits and risks of using baricitinib in patients aged 2 to 17 is still unclear.

WHAT'S NEW IN THIS VERSION?

- Five new randomized controlled trials were included.
- Use of baricitinib among vaccinated and pediatric patients were reviewed.

PREVIOUS RECOMMENDATIONS
As of 21 October 2021

We suggest the use of baricitinib in addition to dexamethasone and remdesivir as treatment for hospitalized COVID-19 patients who require low-flow oxygen, high-flow oxygen, and non-invasive ventilation. *(Low certainty of evidence, Weak recommendation)*

There is insufficient evidence to recommend baricitinib as an alternative to tocilizumab as treatment for hospitalized COVID-19 patients. *(Very low certainty of evidence)*

Consensus Issues
The recommendation to give baricitinib in addition to dexamethasone and remdesivir was made based on 2 randomized controlled trials wherein baricitinib was given as an add-on therapy to dexamethasone and remdesivir among hospitalized patients with moderate to severe COVID-19. At present, dexamethasone, a systemic corticosteroid, is considered standard of care for patients requiring oxygen supplementation *(High certainty of evidence; Strong recommendation)*, while remdesivir may be considered as an additional therapy for patients who require oxygen supplementation but not on invasive mechanical ventilation *(Low certainty of evidence, Conditional recommendation)*. Although remdesivir is not currently considered standard care, there are studies that show possible synergistic effect in concurrently giving an antiviral to shorten viral clearance plus an immunomodulator to address impending cytokine storm. Addition of baricitinib is recommended only for non-intubated patients (i.e., on low-flow oxygen, high-flow oxygen, and non-invasive ventilation).

As of writing, the available evidence on baricitinib is not as robust as tocilizumab, and there is only 1 retrospective observational study, which directly compared baricitinib versus tocilizumab. As such, there is insufficient evidence to make recommendations on whether baricitinib may be used as an alternative to tocilizumab. Strategies for conservation of tocilizumab is beyond the scope of the consensus panel, and may be discussed by the local expert group working on COVID-19 treatment algorithms.

INTRODUCTION

Baricitinib was repurposed for COVID-19 based on its ability to downregulate cytokine signaling by blocking JAK1 and JAK2, and its capacity to reduce viral endocytosis into AT2 lung cells by inhibiting AAKI [1,2]. Its use among non-COVID patients has been associated with an increased risk for thrombosis and Herpes zoster infections [3,4]. However, on-target mechanisms are unable to explain such side effects [1].

In the second iteration of the Philippine COVID-19 living clinical practice guidelines (CPG) which was published in October 2021, baricitinib was suggested to be given as an add-on therapy to dexamethasone and remdesivir in patients with COVID-19 who require conventional oxygen therapy, high-flow nasal cannula oxygen therapy, and noninvasive ventilatory support [5]. This recommendation was based on low certainty of evidence from two randomised controlled trials [6,7]. Pooled results from both trials showed a decrease in all-cause mortality and risk for disease progression among patients given baricitinib compared to those who received standard of care or placebo. Majority of the trial participants were given dexamethasone and remdesivir which were considered standard-of-care therapies at that time. Given the rapidly evolving state of the pandemic, an updated rapid review was conducted to gather the latest evidence on the efficacy and safety of baricitinib and to guide healthcare providers on when to use the drug.

REVIEW METHODS

We conducted this rapid review following the interim guidance from the Cochrane Rapid Reviews Methods Group [8]. Screening and identification of studies was reported using the PRISMA 2020 flow diagram for updated systematic reviews [9]. Quality of included studies was assessed using the Cochrane risk of bias (RoB) tool [10]. Certainty of evidence was appraised using the GRADE approach [11]. A literature search was performed across databases and registers (Medline, CENTRAL, Scopus, ClinicalTrials.gov, and MedRxiv) on January 15, 2023 as an update to a previous search done on September 6, 2021. The full

search strategy is presented in Appendix 2. Included studies were randomized controlled trials conducted among patients with COVID-19 comparing use of baricitinib against standard of care. Outcomes of interest included all-cause mortality, need for noninvasive or invasive mechanical ventilation, serious adverse events, venous thromboembolic events, and treatment-emergent infections. Non-randomized, observational, and descriptive studies were excluded. Two reviewers were involved in literature search, study selection, data extraction, risk of bias assessment, and certainty of evidence appraisal.

RESULTS

Our updated literature search yielded 1,647 unique records. After screening for relevance and eligibility, we were able to retrieve five new records [12,13,14,15,16]. This brings the total number of included studies for this evidence summary to seven. One study which commenced in 2020 was an adaptive study with parallel treatment arms consisting of convalescent plasma, sarilumab, baricitinib, and hydroxychloroquine [12]. This study was prematurely terminated for high probability of futility of the treatment arms, but we still included it for having fulfilled our eligibility criteria. Two studies were completed and published in 2021, and these were the ones included in the October 2021 update of this evidence summary [6,7]. Four of the remaining studies were completed in 2022 and but only three were able to include vaccinated patients in their trials [14,15,16]. The RECOVERY trial enrolled 1755 (42%) patients who received at least 1 dose of COVID-19 vaccine; the PANCOVID trial enrolled 267 (91%) vaccinated patients; and the Bari-SolidAct trial enrolled 96 (35%) vaccinated patients. Only one study, the RECOVERY trial, included pediatric patients aged 2 to 17 (n=33). Overall risk of bias was low for all the studies. Those which employed a platform design were assessed to have high risk of chronological bias from nonconcurrent randomization of the baricitinib and control groups.

Efficacy

All-cause mortality at 28 days was lower among COVID-19 patients who received baricitinib compared to placebo (RR 0.73; 95% CI 0.58-0.90; I^2=44%; moderate certainty). Possible sources of heterogeneity are the differences in included participants across studies, (i.e., with varying disease severity and vaccination status), and the different interventions given for COVID-19 other than baricitinib and placebo.

Two trials reported subgroup analysis according to vaccine status. The first study showed comparable 28-day mortality among patients who received at least 1 dose of the vaccine (RR 0.90; 95% CI 0.77-1.06) and those who were unvaccinated (RR 0.91; 95% CI 0.77-1.07) [14]. The second study reported a higher risk ratio for 60-day mortality among vaccinated patients (RR 1.78; 95% CI 0.78-4.07) compared to those who were unvaccinated (RR 0.51; CI 0.21-1.19) [16]. However, further analysis from the latter trial showed that vaccinated study participants were disproportionately older and had more comorbidities such as diabetes and hypertension, potentially resulting to confounding bias.

The effect of baricitinib appears to be affected by the baseline respiratory support of study participants. Our subgroup analysis showed that the mortality benefit of baricitinib is limited to patients receiving noninvasive (RR 0.74; 95% CI 0.63-0.89) and invasive mechanical ventilation (RR 0.77; 95% CI 0.60-0.98). Patients who were on conventional oxygen (RR 0.78; 95% CI 0.51-1.19) and those without oxygen therapy (RR 0.75; 95% CI 0.40-1.40) did not appear to benefit in terms of mortality. However, use of the drug significantly reduced the need for noninvasive (RR 0.80; 95% CI 0.67-0.97) and invasive mechanical ventilation (RR 0.86; 95% CI 82-0.99).

Among the pediatric population, the use of baricitinib had inconclusive benefit in terms of mortality (RR 2.13; 95% CI 0.21-21.22; low certainty) and receipt of ventilation (RR 2.67; 95% CI 0.31-23.00; low certainty) based on limited data from one trial [14].

Safety

Use of baricitinib showed a trend towards benefit in terms of decreasing the proportion of patients who experienced serious adverse events (RR 0.85; 95% CI 0.75-0.97; I^2=0%; moderate certainty). Serious adverse events observed in the trials were: cardiac arrest, multiple organ dysfunction syndrome, septic shock, pneumonia, sepsis, renal failure, respiratory failure, pulmonary thromboembolic events, hypotension. Suspected serious adverse events, which are events believed with reasonable probability arising from use of baricitinib, was presented in only one trial [14]. This study was therefore excluded in the qualitative analysis for this outcome. Major safety concerns on the use of baricitinib were thromboembolic events, particularly deep vein thrombosis and pulmonary embolism. Data from five trials showed comparable occurrence of deep vein thrombosis (RR 1.18; 95% CI 0.69-2.01; I^2=0%; moderate certainty) and pulmonary embolism (RR 0.97; 95% CI 0.79-1.19; I^2=0%; moderate certainty) between baricitinib and placebo treatment groups. Incidence of septic shock (RR 0.53; 95% CI 0.30-0.95; I^2=0%; moderate certainty) was found to be significantly reduced with the use of baricitinib.

RECOMMENDATIONS FROM OTHER GROUPS

According to the WHO COVID-19 Living Guideline (updated last September 16, 2022), the use of either baricitinib or IL-6 receptor blockers (tocilizumab or sarilumab) on top of corticosteroids in patients with severe or critical COVID-19 is strongly recommended as it reduced mortality, duration of mechanical ventilation, and duration of hospital stay while resulting in little to no increase in adverse events [17]. The NIH COVID-19 Guidelines (updated last August 8, 2022) recommended the use of either baricitinib or tocilizumab as a second immunomodulatory drug to dexamethasone who have rapidly increasing oxygen requirements and systemic inflammation with moderate recommendation; a strong recommendation was given with use of per orem baricitinib over intravenous tocilizumab in patients on HFNC or NIV [18]. The IDSA COVID-19 Guidelines (section updated last April 4, 2022) conditionally recommended the use of baricitinib with steroids in patients with severe COVID-19 on HFNC or NIV as well. For those cannot receive corticosteroids, a conditional recommendation was made on the use of baricitinib with remdesivir over remdesivir alone [19].

ONGOING STUDIES AND RESEARCH GAPS

The efficacy and safety of baricitinib among vaccinated patients with severe to critical COVID is still unknown. This, however, is expected to comprise only a small number of patients given that COVID-19 vaccines are known to reduce the probability of developing severe disease [20].

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

The use of baricitinib was associated with lower 28-day mortality and need for respiratory support compared to standard of care or placebo. There were no excess risk of serious adverse events, venous thrombosis, or complications of infection noted among placebo-controlled trials.

Subgroup analyses by disease severity and vaccination status showed that the mortality benefit is limited among patients requiring mechanical ventilation (i.e. noninvasive mechanical ventilation, high-flow nasal cannula oxygen therapy, and invasive mechanical ventilation). Vaccination status did not appear to change the interpretation of the outcome based on one study [14]. Among a small sample of pediatric patients included in the same study, the benefits of using baricitinib in patients aged 2 to 17 is still unclear.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=5/10)

FACTORS	JUDGEMENT							RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)						Yes. Given the rapidly evolving state of the pandemic, recommendations from a year ago may quickly become obsolete. Additionally, new trials on baricitinib have been completed which offers additional data on vaccinated, pediatric, and mechanically ventilated patients.
Benefits	Large (1)	Moderate (2)	Small	Trivial (1)	Varies (1)	Uncertain		All-cause mortality at 28 days was lower among COVID-19 patients who received baricitinib compared to placebo (RR 0.73; 95% CI 0.58-0.90; I^2=44%; moderate certainty). The mortality benefit of baricitinib also appears to be limited among patients receiving noninvasive (RR 0.74; 95% CI 0.63-0.89) or invasive ventilation (RR 0.77; 95% CI 0.60-0.98) at baseline based on our subgroup analysis. Despite the inconclusive effect in reducing all-cause mortality among COVID-19 patients on non-oxygen requiring COVID-19 patients and patients on conventional oxygen support, the use of baricitinib significantly reduced the need for noninvasive ventilation reduce the need for non-invasive (RR 0.80; 95% CI 0.67-0.97) and the need for invasive mechanical ventilation (RR 0.86; 95% CI 82-0.99). Among the pediatric population, the use of baricitinib had inconclusive benefit in terms of mortality (RR 2.13; 95% CI 0.21-21.22; low certainty) and receipt of ventilation (RR 2.67; 95% CI 0.31-23.00; low certainty) based on limited data from one trial.
Harm	Large	Moderate (1)	Small (3)	Trivial	Varies (1)	Uncertain		Use of baricitinib showed a trend towards benefit in terms of decreasing the number of serious adverse events (RR 0.85; 95% CI 0.75-0.97; I^2=0%; moderate certainty). Serious adverse events observed in the trials were: cardiac arrest, multiple organ dysfunction syndrome, septic shock, pneumonia, sepsis, renal failure, respiratory failure, pulmonary thromboembolic events, hypotension. Major safety concerns on the use of baricitinib were thromboembolic events, particularly deep vein thrombosis and pulmonary embolism. Data from five trials showed comparable occurrence of deep vein thrombosis (RR 1.18; 95% CI 0.69-2.01; I^2=0%; moderate certainty) and pulmonary embolism (RR 0.97; 95% CI 0.79-1.19; I^2=0%; moderate certainty) between baricitinib and placebo treatment groups. Incidence of septic shock (RR 0.53; 95% CI 0.30-0.95; I^2=0%; moderate certainty) was found to be significantly reduced with the use of baricitinib.
Certainty of Evidence	High	Moderate (5)	Low	Very low				The overall certainty of evidence was moderate for the adult population. The overall certainty of evidence was very low for the pediatric population.
Balance of effects	Favors diagnostic / treatment (3)	Probably favors diagnostic / treatment (2)	Does not favor diagnostic / treatment or no diagnostic / treatment	Probably favors no diagnostic / treatment	Favors no diagnostic / treatment	Varies	Uncertain	Based on available evidence, baricitinib favored treatment. The use of baricitinib was associated with lower 28-day mortality and need for respiratory support compared to standard of care or placebo. There were no excess risk of serious adverse events, venous thrombosis, or complications of infection noted among placebo-controlled trials. In the pediatric population, probably favors no treatment due to inconclusive effect on mortality (direct evidence) and potential harm (indirectly evidence observed in the adult population)

Values	Important uncertainty or variability		Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability		
Resources Required	Uncertain		Large cost	Moderate cost (3)	Negligible costs or savings	Moderate savings (2)	Large savings	Estimated Costs: • ₱19,380.48 per 14-day treatment course if eGFR >60 mL/min/1.73 m^2 (₱1,384.32 per 4mg tablet) • ₱19,380.48 per 14-day treatment course if eGFR <60 mL/min/1.73 m^2 (₱1,384.32 per 2mg tablet) (Reference: DOH memorandum entitled OSEC-HTAC Recommendations on COVID-19 Investigational Drugs; 2021 Procurement Cost Survey)
Certainty of evidence of required resources	No included studies (3)		Very low	Low	Moderate (2)	High		
Cost effectiveness	No included studies	Varies	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention (3)	Favors the intervention (2)	In an economic model study which simulated the use of baricitinib and its effect on inpatients' stay, discharge to post-acute care, and recovery using the base-case payor perspective model, the use of baricitinib was reported to be cost effective. From a payor perspective model, base-case incremental cost-effectiveness ratios were 25,774 USD/QALY gained and 20,638 USD/LY gained. From a hospital perspective, treatment with baricitinib was less costly with an incremental cost of 38,964 USD per death avoided in the mortality-only scenario. With the addition of baricitinib, survival was increased by 5.1% and the use of mechanical ventilation was reduced by 1.6%. (Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8487786/pdf/main.pdf)
Equity	Uncertain	Varies (2)	Reduced	Probably reduced (1)	Probably no impact (1)	Probably increased (1)	Increased (1)	
Acceptability	Uncertain		Varies	No	Probably no	Probably yes (3)	Yes (2)	
Feasibility	Uncertain		Varies	No	Probably no	Probably yes (3)	Yes (2)	
Recommendation	For treatment / intervention				Against treatment / intervention			
Strength of recommendation	Weak				Strong			

Appendix 2: Search Yield and Results

Database or Register	Search String	Records
Medline	Baricitinib AND COVID-19	377
CENTRAL	Baricitinib AND COVID-19 in All Text	63
Scopus	Baricitinib AND COVID-19 AND (LIMIT-TO (DOCTYPE, “ar”))	1399
ClinicalTrials.gov	Baricitinib | COVID-19	29

Appendix 3: PRISMA Flow Diagram

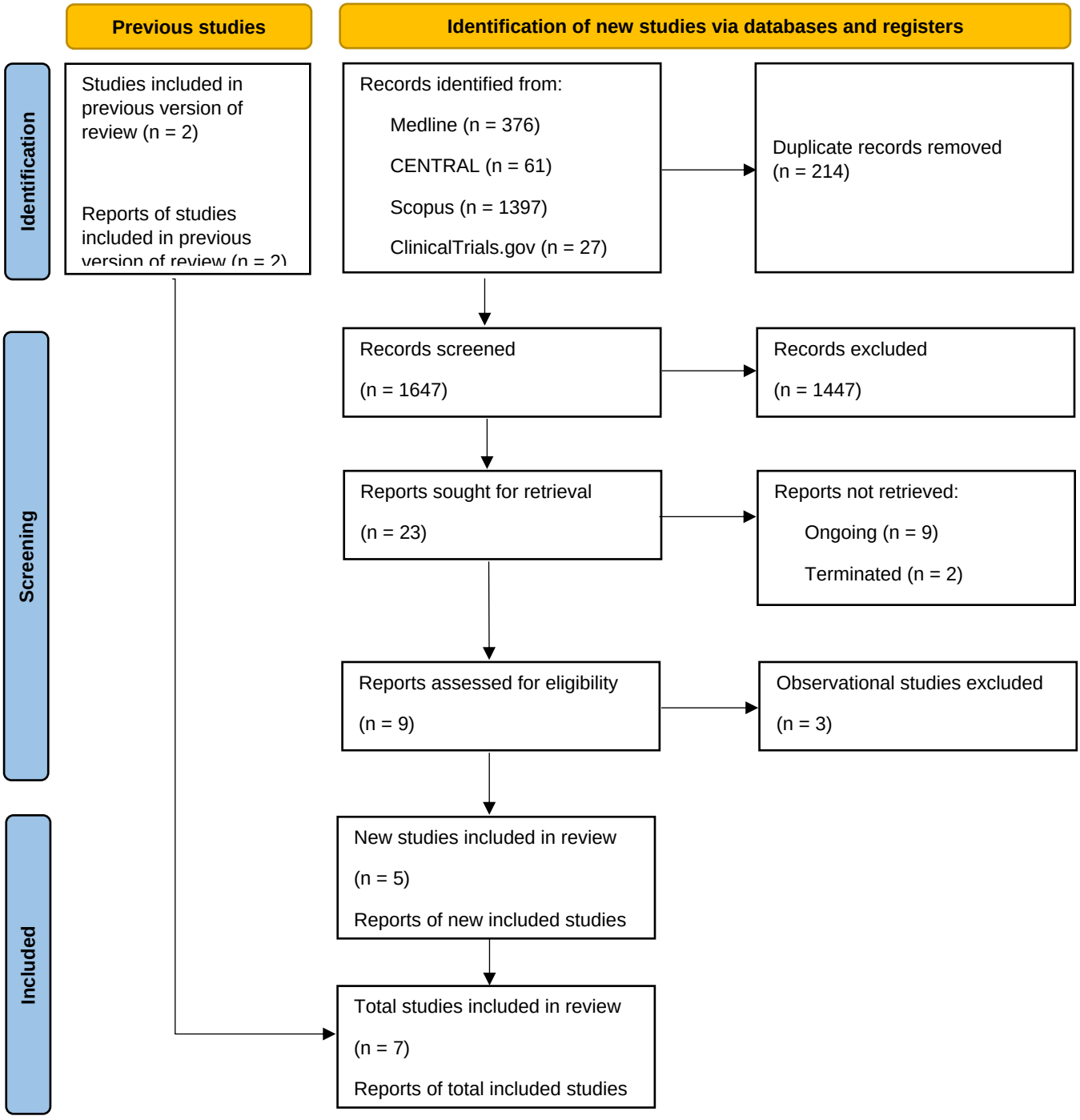

Figure 1. PRISMA 2020 flow diagram for updated systematic reviews.

Appendix 4: Characteristics of Included Studies

Study ID	Population	Intervention and Comparator	Outcome	Study Design
1. EudraCT 2020-001367-88 (CCAP-RCT) July 17, 2020 (Pre-maturely terminated)	Inclusion: adults (≥18 years) lab-confirmed COVID-19 With hypoxemia or radiographic signs of pneumonia Exclusion: eGFR <30, severe liver dysfunction, history of TB, ANC <1000, ALT >5x ULN, Plt <50, immunosuppression Trial site: Denmark	Interventions: Baricitinib 4 mg daily for 7 days Hydroxychloroquine Sarilumab Control: Placebo (dexamethasone use not specified)	Primary outcome: all-cause mortality in 28 days Secondary outcome: SAE, ventilator free days, length of hospital stay	Double-blind RCT
2. Kalil 2021 (ACTT-2) March 4, 2021	Inclusion: hospitalized adults Exclusion: use of other experimental drugs (including dexamethasone) Characteristics: Moderate (68.3) and severe (31.7) COVID-19, Unvaccinated Enrollment: May 8, 2020 to July 1, 2020 Trial sites: USA, Singapore, South Korea, Mexico, Japan, Spain, UK, Denmark	Intervention: remdesivir and baricitinib Comparator: remdesivir and placebo (dexamethasone use not specified) Remdesivir 200 mg IV on D1, then 100 mg D2-10 Baricitinib 4 mg OD (2 mg if eGFR <60) for 14 days or until hospital discharge	Primary outcome: time to recovery (first day attaining category 1, 2, 3 on an 8-point scale) Secondary outcome: Clinical status at day 15 (8-point scale) Time to discharge Time to NEWS ≤2 Number of days on O2, NIV, MV, HFNC, ECMO Use of O2, NIV, HFNC, MV, ECMO Mortality at 14 and 28 days after enrollment Safety outcomes: Grade 3 and 4 AE SAE	Double-blind RCT
3. Marconi 2021 (COV-BARRIER)	Inclusion: Hospitalized adults (≥18 years)	Intervention: baricitinib (92%	Primary composite outcome:	Double-blind RCT

December 1, 2021	With evidence of pneumonia or symptomatic COVID At least 1 elevated inflammatory marker (CRP, D-dimer, LDH, ferritin) -Amended to include only patients who required O2 support Exclusion: use of invasive MV, receiving immunosuppressants (including high dose steroids), use of CCP or IVIg, neutropenia, lymphopenia, ALT/AST 5x ULN, eGFR <30 Unvaccinated Trial sites: Puerto Rico, Argentina, USA, Japan, UK, India, Russia, Spain, South Korea, Brazil, Mexico, Italy, Germany	given dexamethasone) Comparator: placebo (90% given dexamethasone) Baricitinib 4 mg OD (2 mg if eGFR <60) for 14 days or until hospital discharge	proportion who progressed to HFNCC, NIV, MV, ECMO, or death by day 28 Secondary outcomes: All-cause mortality by day 28 and 60 Improvement in NIAID-OS Ventilator-free days Time to recovery Duration of hospitalization Increase in SpO2 ≥94% Adverse events on days 1-28	
4. Ely 2022 (COV-BARRIER) April 1, 2022	Critically ill adult patients on MV or ECMO With evidence of pneumonia or symptomatic COVID At least 1 elevated inflammatory marker (CRP, D-dimer, LDH, ferritin) Dexamethasone 6 mg IV OD permitted Exclusion: use of invasive MV, receiving immunosuppressants (including >20 mg per day prednisone equivalent for ≥14 days), use of CCP or IVIg, neutropenia, lymphopenia, ALT/AST 5x ULN, eGFR <30	Intervention: baricitinib (88% given corticosteroids) Comparator: placebo (84% given corticosteroids) Baricitinib 4 mg OD (2 mg if eGFR <60) for 14 days or until hospital discharge	Endpoints: All-cause mortality at day 28 and 60 Number of ventilator-free days Overall improvement (NIAID-OS) Duration of hospitalization Time to recovery	Double-blind RCT

	Unvaccinated Trial sites: Argentina, Brazil, Mexico, USA			
5. Abani 2022 (RECOVERY) July 30, 2022	Pediatric and adult patients (≥2 years) With COVID-19 Exclusion: age <2, eGFR <15, ANC <500, active TB, pregnant, breastfeeding Vaccinated (42%) and unvaccinated (58%) Trial site: UK	Intervention: baricitinib (96% given corticosteroids) Comparator: standard of care (95% given corticosteroids) Baricitinib 4 mg OD (2 mg if eGFR <60 and for children <9 years) for 14 days or until hospital discharge	Primary outcome: all-cause mortality at 28 days Secondary outcomes: Time to hospital discharge Need for MV and death (composite) Subsidiary outcomes: Use of NIV and MV Time to cessation of MV Use of dialysis Safety outcomes: Suspected SAE	Open-label RCT (platform trial)
6. Montejano 2022 (PANCOVID) July 30, 2022	Inclusion: vaccinated (91%) and unvaccinated, hospitalized and ambulatory patients age ≥60 or with at least 2 comorbidities (hypertension, obesity, diabetes, cirrhosis, chronic neurologic disease, active cancer, heart failure, CAD, COPD) Symptomatic lab-confirmed COVID-19 SpO2 <95 and at least 1 increased inflammatory marker (IL-6, CRP, D-dimer, ferritin) (2nd randomization) Exclusion: eGFR <60, receiving steroids ≥15 mg/d in the past 7 days, HIV, severe respiratory	Interventions: 1st randomization - TDF/FTC 200/245 mg 2 tabs on D1, then 1 tab on D2-14 2nd randomization – Baricitinib (4 mg OD for 14 days, reduced to 2 mg OD for age >75) plus dexamethasone (6 mg OD for 7-10 days) Control: dexamethasone alone	Primary outcome: 28-day mortality Secondary outcomes: Time to death, ICU admission, hospital discharge, disease progression Safety outcomes: SAE	Open-label RCT (platform trial)

	failure (reservoir bag, MV, ARF) (1st randomization) Trial site: Spain			
7. Trøseid 2023 (Bari-SolidAct) January 10, 2023	Inclusion: adults (≥18 years) admitted with lab-confirmed COVID-19, classified as severe/critical COVID-19, defined as 1) SpO2 <90% on room air, 2) SpO2 90-94% with a downwards trend or signs of respiratory distress, 3) need of oxygen by NIV/CPAP/HFNC/ MV/ECMO Exclusion: suspected serious infection besides COVID-19, recent or recurrent thromboembolism, receiving immunosuppressive therapy Characteristics: 35.2% partially/fully vaccinated in intervention group; 34.6% in control group Trial sites: Austria, Belgium, France, Germany, Ireland, Italy, Luxembourg, Norway, Portugal, Spain	Intervention: baricitinib (96% given corticosteroids) Comparator: standard of care (94% given corticosteroids; tocilizumab only allowed as rescue therapy) Baricitinib 4 mg OD or until hospital discharge	Primary outcome: death within 28 and 60 days Secondary outcomes: Disease progression within 28 days, time to recovery, time to hospital discharge, occurrence of SAE	Double-blind RCT

Appendix 5: Risk of Bias Assessment

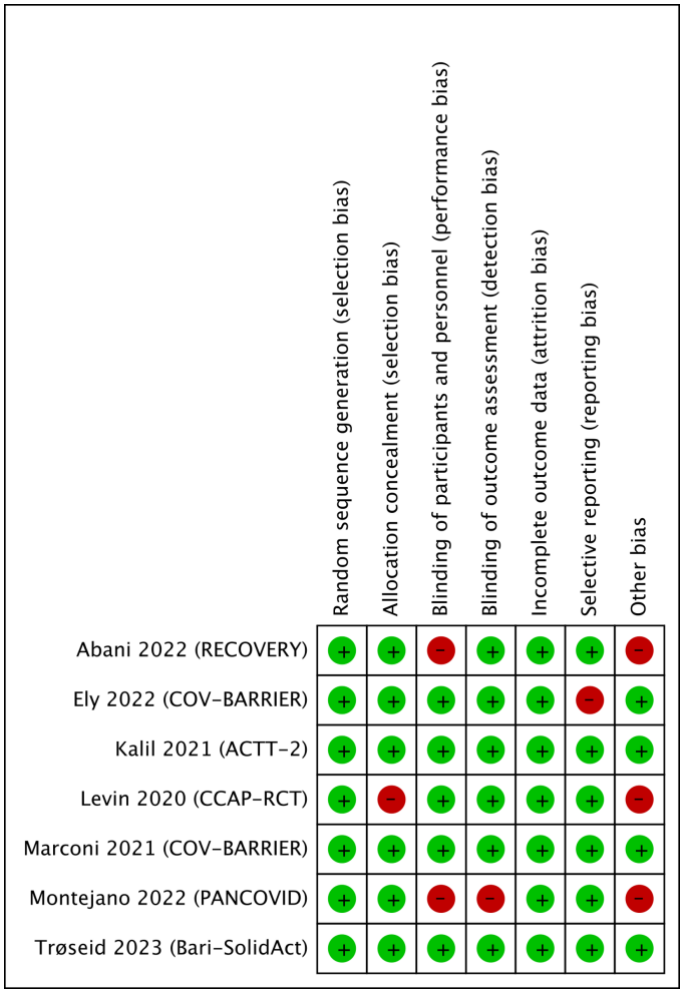

Figure 2. Risk of bias summary.

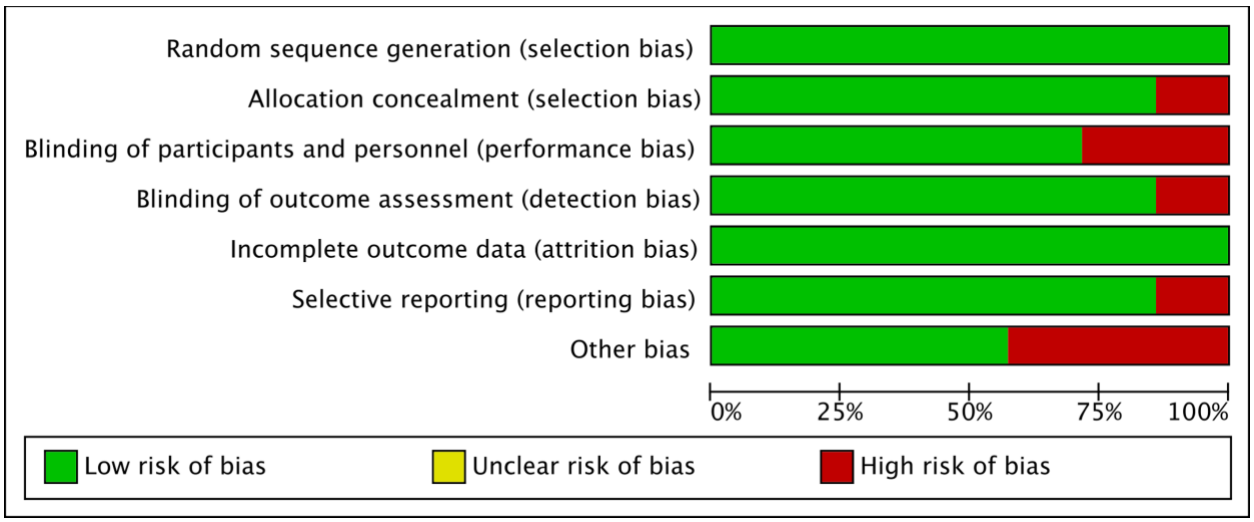

Figure 3. Risk of bias graph.

Appendix 6: Pooled Efficacy and Safety Outcomes

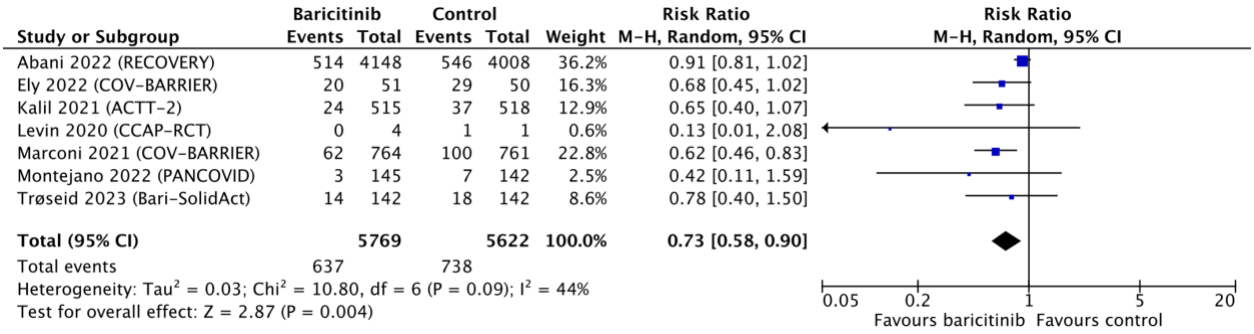

Figure 4. Effect of baricitinib on overall mortality at 28 days.

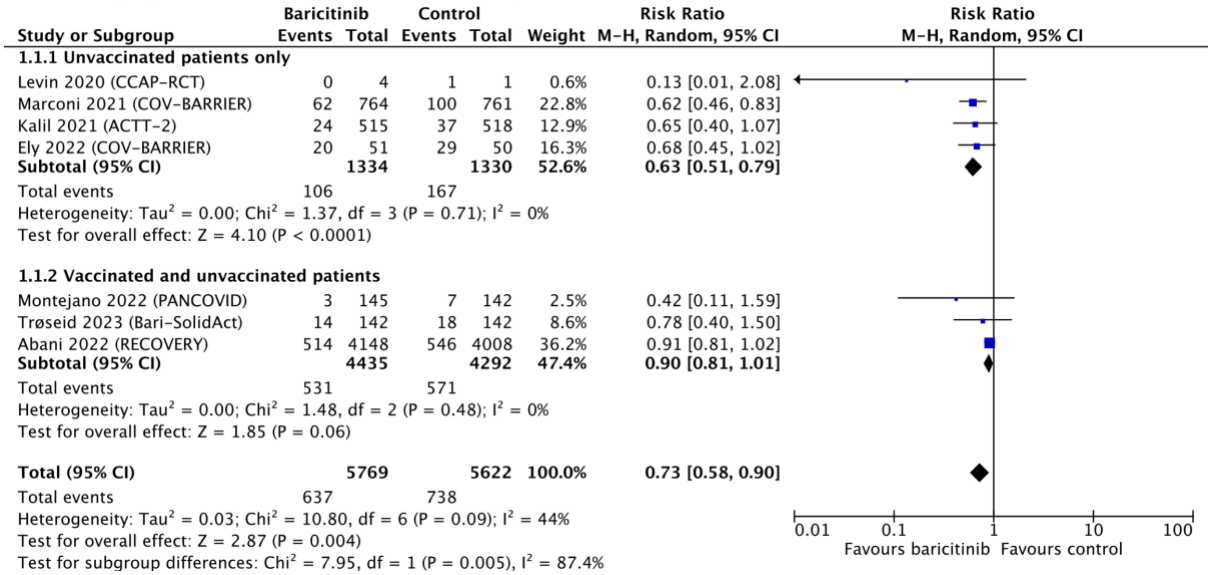

Figure 5. Effect of baricitinib on 28-day mortality by vaccination subgroups.

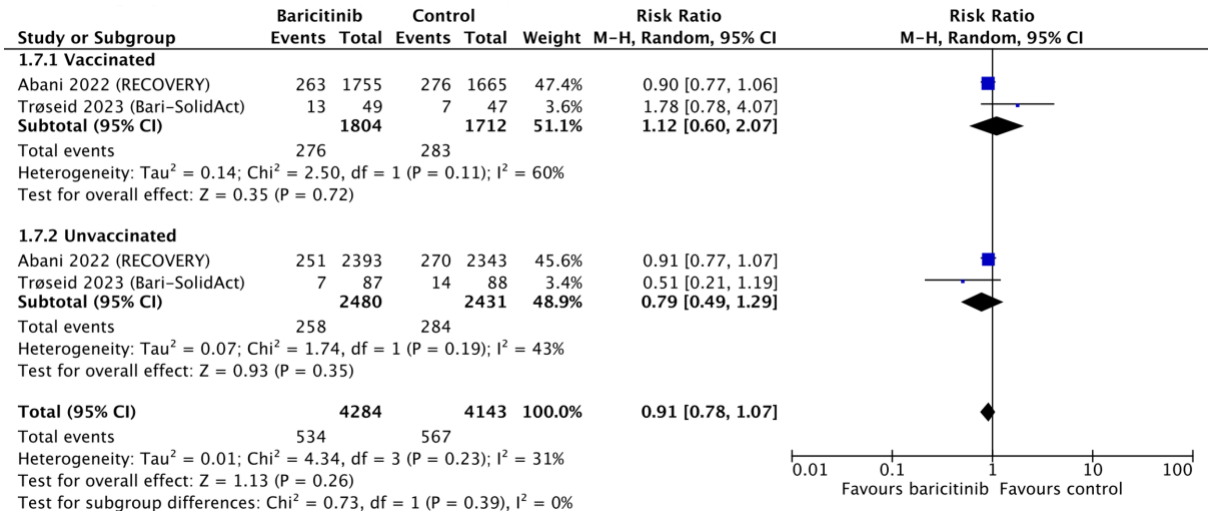

Figure 6. Effect of baricitinib on mortality by vaccination status.

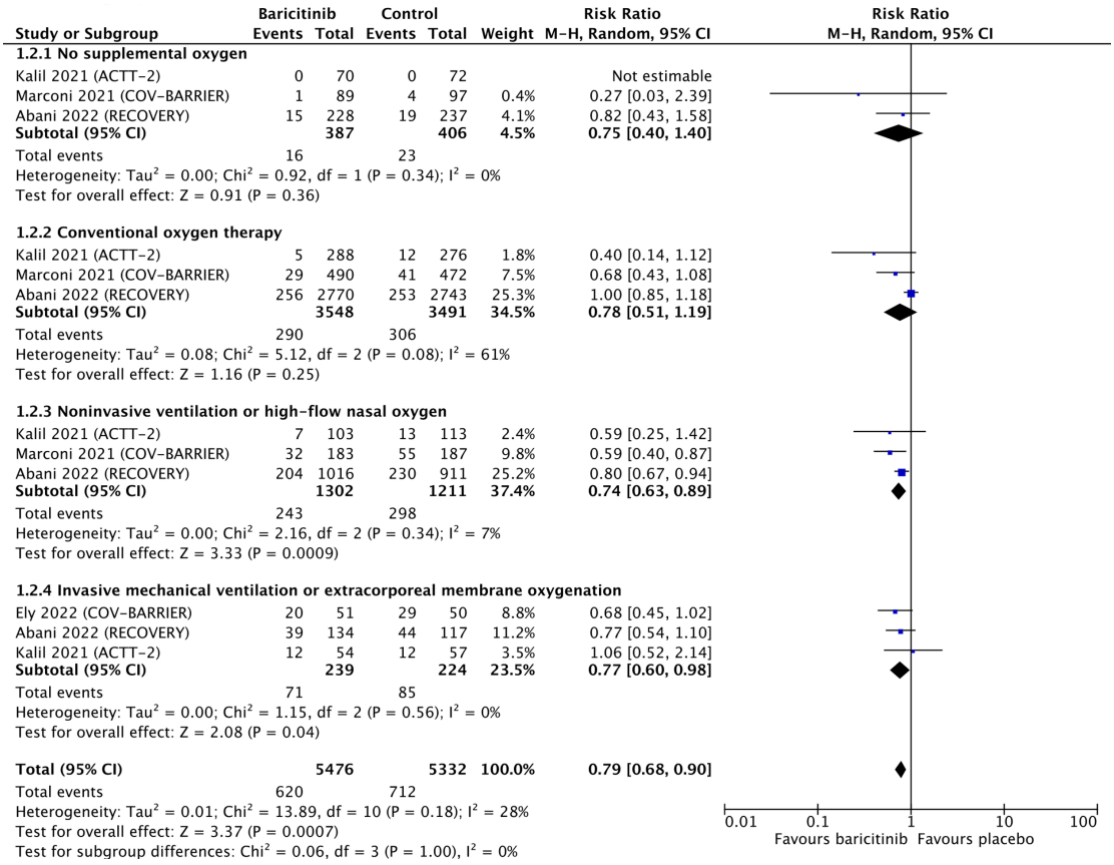

Figure 7. Subgroup analysis on all-cause mortality based on baseline respiratory support.

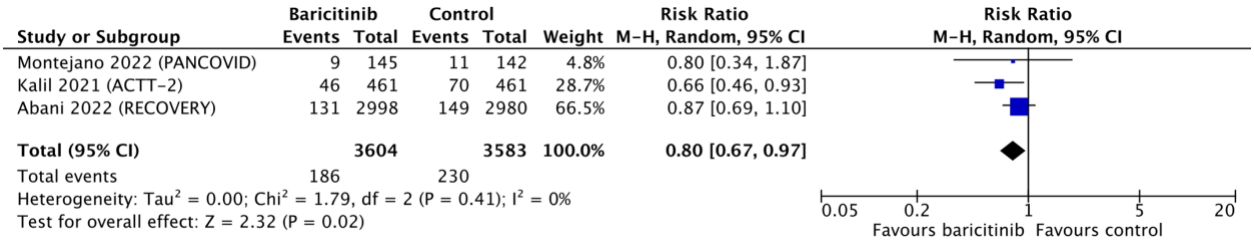

Figure 8. Effect of baricitinib on receipt of invasive mechanical ventilation.

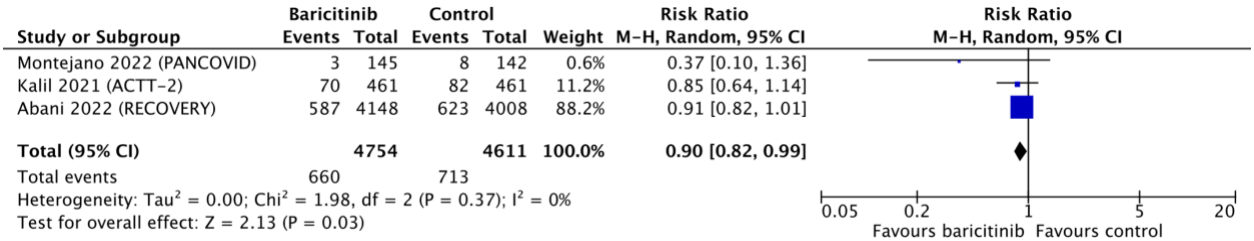

Figure 9. Effect of baricitinib on receipt of noninvasive ventilation.

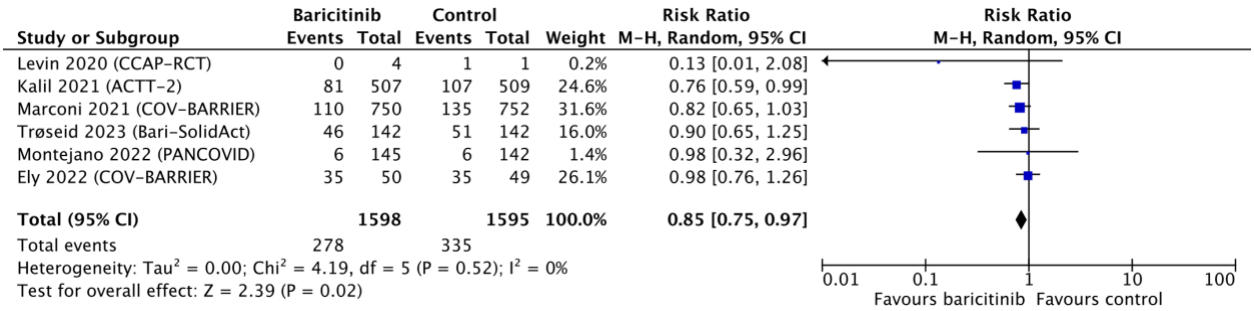

Figure 10. Proportion of patients who experienced serious adverse events comparing baricitinib to control.

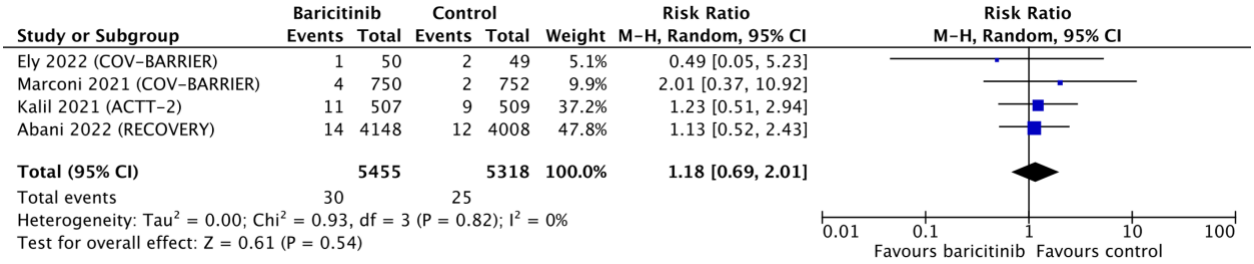

Figure 11. Occurrence of DVT comparing baricitinib to control.

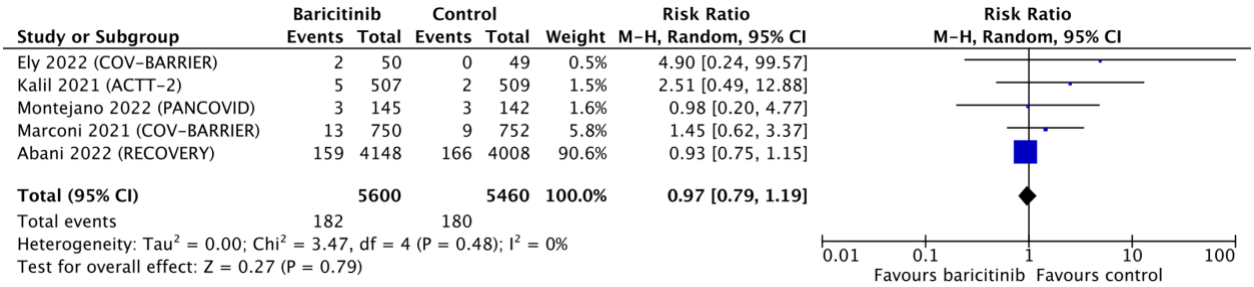

Figure 12. Occurrence of PE comparing baricitinib to control.

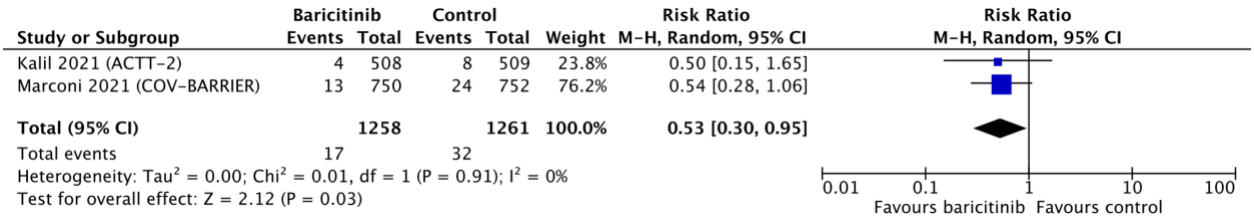

Figure 13. Occurrence of septic shock among patients receiving baricitinib and control.

Appendix 7: GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib	standard of care	Relative (95% CI)	Absolute (95% CI)		
28-day mortality												
7	randomised trials	not serious	serious[a]	not serious	not serious	none	637/5769 (11.0%)	738/5622 (13.1%)	**RR 0.73** (0.58 to 0.90)	**35 fewer per 1,000** (from 55 fewer to 13 fewer)	⨁⨁⨁◯ Moderate	
28-day mortality among patients without baseline supplemental oxygen												
3	randomised trials	not serious	not serious	not serious	not serious	none	16/387 (4.1%)	23/406 (5.7%)	**RR 0.75** (0.40 to 1.40)	**14 fewer per 1,000** (from 34 fewer to 23 more)	⨁⨁⨁⨁ High	
28-day mortality among patients on baseline conventional oxygen therapy												
3	randomised trials	not serious	serious[b]	not serious	not serious	none	290/3548 (8.2%)	306/3491 (8.8%)	**RR 0.78** (0.51 to 1.19)	**19 fewer per 1,000** (from 43 fewer to 17 more)	⨁⨁⨁◯ Moderate	
28-day mortality among patients on baseline noninvasive ventilation or high-flow nasal oxygen												
3	randomised trials	not serious	not serious	not serious	not serious	none	243/1302 (18.7%)	298/1211 (24.6%)	**RR 0.74** (0.63 to 0.89)	**64 fewer per 1,000** (from 91 fewer to 27 fewer)	⨁⨁⨁⨁ High	
28-day mortality among patients on baseline invasive mechanical ventilation or extracorporeal membrane oxygenation												
3	randomised trials	not serious	not serious	not serious	not serious	none	71/239 (29.7%)	85/224 (37.9%)	**RR 0.77** (0.60 to 0.98)	**87 fewer per 1,000** (from 152 fewer to 8 fewer)	⨁⨁⨁⨁ High	
Receipt of invasive mechanical ventilation												
3	randomised trials	not serious	not serious	not serious	not serious	none	186/3604 (5.2%)	230/3583 (6.4%)	**RR 0.80** (0.67 to 0.97)	**13 fewer per 1,000** (from 21 fewer to 2 fewer)	⨁⨁⨁⨁ High	CRITICAL
Receipt of noninvasive ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib	standard of care	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	not serious	not serious	none	660/4754 (13.9%)	713/4611 (15.5%)	**RR 0.90** (0.82 to 0.99)	**15 fewer per 1,000** (from 28 fewer to 2 fewer)	⨁⨁⨁⨁ High	CRITICAL
Serious adverse events												
6	randomised trials	not serious	not serious	not serious	not serious	none	278/1598 (17.4%)	335/1595 (21.0%)	**RR 0.85** (0.75 to 0.97)	**32 fewer per 1,000** (from 53 fewer to 6 fewer)	⨁⨁⨁⨁ High	CRITICAL
Occurrence of septic shock												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	17/1258 (1.4%)	32/1261 (2.5%)	**RR 0.53** (0.30 to 0.95)	**12 fewer per 1,000** (from 18 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Occurrence of pulmonary embolism												
5	randomised trials	not serious	not serious	not serious	serious[c]	none	182/5600 (3.3%)	180/5460 (3.3%)	**RR 0.97** (0.79 to 1.19)	**1 fewer per 1,000** (from 7 fewer to 6 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Occurrence of deep venous thrombosis												
4	randomised trials	not serious	not serious	not serious	serious[c]	none	30/5455 (0.5%)	25/5318 (0.5%)	**RR 1.18** (0.69 to 2.01)	**1 more per 1,000** (from 1 fewer to 5 more)	⨁⨁⨁◯ Moderate	IMPORTANT
28-day mortality among pediatric patients												
1	randomised trials	not serious	not serious	not serious	extremely serious[d]	none	2/16 (12.5%)	1/17 (5.9%)	**RR 2.13** (0.21 to 21.22)	**66 more per 1,000** (from 46 fewer to 1,000 more)	⨁◯◯◯ Very Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib	standard of care	Relative (95% CI)	Absolute (95% CI)		
Receipt of mechanical ventilation among pediatric patients												
1	randomised trials	not serious	not serious	not serious	extremely serious[e]	none	2/6 (33.3%)	1/8 (12.5%)	**RR 2.67** (0.31 to 23.00)	**209 more per 1,000** (from 86 fewer to 1,000 more)	⨁◯◯◯ Very Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. There is moderate statistical heterogeneity I2=54%.
b. There is moderate statistical heterogeneity I2=61%
c. The 95% confidence interval includes important benefit and harm.
d. This subgroup analysis included a small sample size (n=33), low event rate, with extremely wide confidence intervals.
e. This subgroup analysis included a small sample size (n=14), low event rate, with extremely wide confidence intervals.

Appendix 8: Ongoing Studies

A study with immunotherapy for Moderate COVID-19 (EUCTR2020-001854-23-IT)	Ongoing
Baricitinib in hospitalized patients with COVID19 pneumonia: COVID-BAR Trial (CTRI/2021/11/037866)	Ongoing/Not yet recruiting
Clinical trial phase II to evaluate the efficacy of 3 types of treatment in patients with pneumonia by COVID-19 (EUCTR2020-001321-31-ES)	Ongoing
Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia (NCT04345289)	Ongoing/Not yet recruiting
Joint European Research on active and emerging pandemics (EUCTR2021-000541-41-NO)	Ongoing
A Study of Baricitinib (LY3009104) in Children With COVID-19 (COV-BARRIER-PEDS) (NCT05074420)	Ongoing
[Updated] Evaluation of therapeutic effect of baricitinib with severe pneumonia requiring non-invasive ventilation induced to COVID 19	Ongoing