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Clinical efficacy and safety of Janus kinase inhibitors for COVID-19: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: This systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to investigate the clinical efficacy and safety of Janus kinase (JAK) inhibitors for COVID-19 patients.

Methods: PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched from inception to July 12, 2021. RCTs comparing the clinical efficacy and safety of JAK inhibitors with a placebo or standard care in treating COVID-19 patients were included. The primary outcome was all-cause mortality rate at day 28.

Results: Three RCTs were included in this meta-analysis. The all-cause mortality rate at day 28 was lower among the patients receiving JAK inhibitors than among the controls (4.1% [28/647] versus 7.0% [48/684], OR, 0.57; 95% CI, 0.36–0.92, $I^2 = 0$). The clinical recovery rate was higher among the patients receiving JAK inhibitors than among the controls (85.1% (579/680) versus 80.0% [547/684], OR, 1.45; 95% CI, 1.09–1.93, $I^2 = 0$). Additionally, the use of JAK inhibitors was associated with a shorter time to recovery than among the controls (MD, -2.84; 95% CI, -5.56 to -0.12; $I^2 = 50\%$). The rate of invasive mechanical ventilation (MV) was lower in the patients who used JAK inhibitors than among the controls. Finally, no significant difference was observed between the patients who used JAK inhibitors and the controls in the risk of any adverse events (OR, 0.92; 95% CI, 0.64–1.34; $I^2 = 33\%$) and serious adverse events (OR, 0.80; 95% CI, 0.45–1.44; $I^2 = 46\%$).

Conclusions: JAK inhibitors can lead to a better clinical outcome of hospitalized COVID-19 patients, and they are a safe agent in the treatment of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become the biggest threat to global public health since first being identified at the end of 2019 [1]. As of June 18, 2020, there have been more than 176 million confirmed cases of COVID-19, including more than 3.8 million deaths, reported to the World Health Organization (WHO) [2]. Even with the implementation of massive vaccination programs for prevention since the end of 2020, many new cases are being reported daily. Although more than 80% of patients infected with SARS-CoV-2 could be asymptomatic or present as mild disease, more than 15% of patients

could progress to severe or even critical illness [3,4]. In addition to the initial management with combined anti-SARS-CoV-2 monoclonal antibodies for non-hospitalized individuals and anti-viral agents for hospitalized COVID-19 patients, further anti-inflammation agents including corticosteroids and anti-interleukin-6 are key treatment for patients requiring high-flow oxygen/noninvasive ventilation therapy with the evidence of clinical progression or increased markers of inflammation [5,6].

Janus kinase (JAK) inhibitors can downregulate the JAK/signal transducer and activator of transcription protein signaling pathways and decrease cytokine concentrations, and therefore they have been proposed as a potential therapies to mitigate the immune response and

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prevent a hyperinflammatory state, which may further improve clinical outcomes of hospitalized COVID-19 patients [7–10]. The clinical uses of JAK inhibitors, including ruxolitinib, baricitinib, and tofacitinib for COVID-19 patients have been reported in many observational studies [11–18], in which adding JAK inhibitors could help resolve a hyperinflammatory state, improve respiratory function, reduce mortality, and increase survival discharge for patients with SARS-CoV-2 infections. Although two meta-analyses [19,20] assessed the efficacy of JAK inhibitors on the clinical outcomes of COVID-19 patients, cohort studies or non-randomized controlled trials (RCTs) comprised more than half of the included studies, and only two RCTs [21,22] were included in these two meta-analyses. Recently, a large RCT investigating the usefulness of tofacitinib for hospitalized COVID-19 was reported [23]. To provide robust and up-to-date evidence of the clinical efficacy and safety of JAK inhibitors for COVID-19 patients, we conducted this systematic review and meta-analysis of RCTs.

2. Methods

2.1. Study search and selection

We searched the PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases for relevant articles from inception to July 12, 2021. The following search terms were used: “Janus kinase inhibitors,” “COVID-19,” “SARS-CoV-2,” “randomized,” and “trial.” Only RCTs that assessed the clinical efficacy and safety of JAK inhibitors in the treatment of patients with COVID-19 were included. We also manually searched for additional eligible articles from the reference lists of relevant articles. Studies were included if they met the following criteria: (1) examined patients with COVID-19; (2) used a JAK inhibitor as the intervention; (3) used a placebo or other comparators as controls; (4) was designed as an RCT; and (5) reported clinical efficacy and risk of adverse events (AEs) as study outcomes. Reviews or meta-analysis studies, studies without adequate data for outcome analysis, non-RCTs, post-hoc analysis studies, and poster or conference abstracts were excluded. The following data including year of publication, study design, the regimen of the JAK inhibitor, clinical outcomes, and risk of AEs were extracted from each included study. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [24]. The protocol of the study was registered on the PROSPERO database (267247). Two authors (CYC & WCC) were responsible for searching and examining the risk of bias in each study. When they had different opinions, a third author (CKH) helped resolve the issue.

2.2. Outcome measurements

The primary outcome was all-cause mortality at day 28. The secondary outcomes were all-cause mortality at day 14, the rate and the time to recovery, the use of respiratory support, the length of hospital stay and risk of AEs.

2.3. Data analysis

The Cochrane risk-of-bias tool [25] and GRADEpro Guideline Development Tool (<https://community.cochrane.org/help/tools-and-software/grade-pro-gdtwre>) were used to assess the quality of the included RCTs and their associated risk of bias. Statistical analyses were performed using Review Manager (version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark). The degree of heterogeneity was evaluated using Q statistics generated from the χ^2 test, and the I^2 measure was used to assess statistical heterogeneity. Heterogeneity was defined as significant when $p < 0.10$ or $I^2 > 50\%$. A fixed-effects model was used when the data were homogeneous, and a random-effects model was used when the data were heterogeneous. The pooled odds ratios (ORs), mean difference (MD) and 95% confidence intervals (CIs) were calculated for outcome analysis.

3. Results

3.1. Study selection

The search of the online databases yielded a total of 895 studies, of which 149 duplicate studies were excluded. In addition, 684 studies were judged to be irrelevant after screening the titles, abstracts, and publications with no full text available. Furthermore, 59 studies were excluded after the full text of 62 articles was screened. Finally, three RCTs [21–23] were included in this meta-analysis (Fig. 1 and Supplemental Table S1).

3.2. Study characteristics

The three included RCTs comprised one phase 2 trial [21] and two phase 3 trials [22,23]. All RCTs were multicenter studies that focused on adult patients (Table 1). Ruxolitinib, baricitinib, and tofacitinib were evaluated in each RCT, respectively. In addition, vitamin C and a placebo were used as controls in the first and second RCTs, respectively. Overall, 1363 patients hospitalized with COVID-19 were included in the intention-to-treat population of this meta-analysis. Among the 680 patients who were treated with a JAK inhibitor, 21 received ruxolitinib, 515 received baricitinib, and 44 received tofacitinib. In addition to the unclear risk of reporting bias for Guimarães et al.’s study [23] and unclear risk of detection and reporting bias for Cao et al.’s study [21], most of the included studies had a low risk of bias in each domain (Fig. 2).

3.3. Clinical efficacy

The all-cause mortality rate at day 28 among the patients receiving JAK inhibitors was 4.1% (28/647), which was significantly lower than that of the control group (7.0%, 48/684) (OR, 0.57; 95% CI, 0.36–0.92, $I^2 = 0$, Fig. 3 and table 2). In addition, the use of JAK inhibitors was associated with a numerically lower all-cause mortality rate at day 14 than in the control group (1.5% [10/649] versus 3.1% [21/684]), but the difference did not reach statistical significance (OR, 0.48; 95% CI, 0.23–1.02, $I^2 = 0$). The clinical recovery rate among the patients receiving JAK inhibitors was 85.1% (579/680), which was significantly higher than that in the control group (80.0%, 547/684) (OR, 1.45; 95% CI, 1.09–1.93, $I^2 = 0$, Fig. 4). Additionally, the use of JAK inhibitors was associated with a shorter time to recovery than in the control group (MD, –2.84; 95% CI, –5.56 to –0.12; $I^2 = 50\%$). The rate of invasive mechanical ventilation (MV) was lower in the users of JAK inhibitors than in the control group (OR, 0.62; 95% CI, 0.43–0.89, $I^2 = 0$, Fig. 5). Compared to the control group, the use of JAK inhibitors was associated with a shorter duration of MV or extra corporeal membrane oxygenation (ECMO) (MD, –1.46; 95% CI, –2.74 to –0.18; $I^2 = 64\%$) and length of hospital stay (MD, –1.20; 95% CI, –2.01 to –0.39; $I^2 = 0\%$).

3.4. Risk of adverse event

No significant difference was observed between the patients who received JAK inhibitors and the control group in the risk of any AEs (OR, 0.92; 95% CI, 0.64–1.34; $I^2 = 33\%$), including anemia, lymphocytopenia, liver dysfunction, hypokalemia, nausea, decreased appetite and hypertension (Fig. 6A). A similar trend was observed in the risk of serious AEs (OR, 0.80; 95% CI, 0.45–1.44; $I^2 = 46\%$), including acute kidney injury, acute respiratory failure, acute heart failure, shock, secondary infection, sepsis and septic shock (Fig. 6B).

4. Discussion

In this meta-analysis, three RCTs [21–23] were reviewed to compare the use of JAK inhibitors (ruxolitinib, baricitinib, and tofacitinib) with a placebo or vitamin C in terms of efficacy and safety in the treatment of hospitalized COVID-19 patients. Overall, JAK inhibitors could help

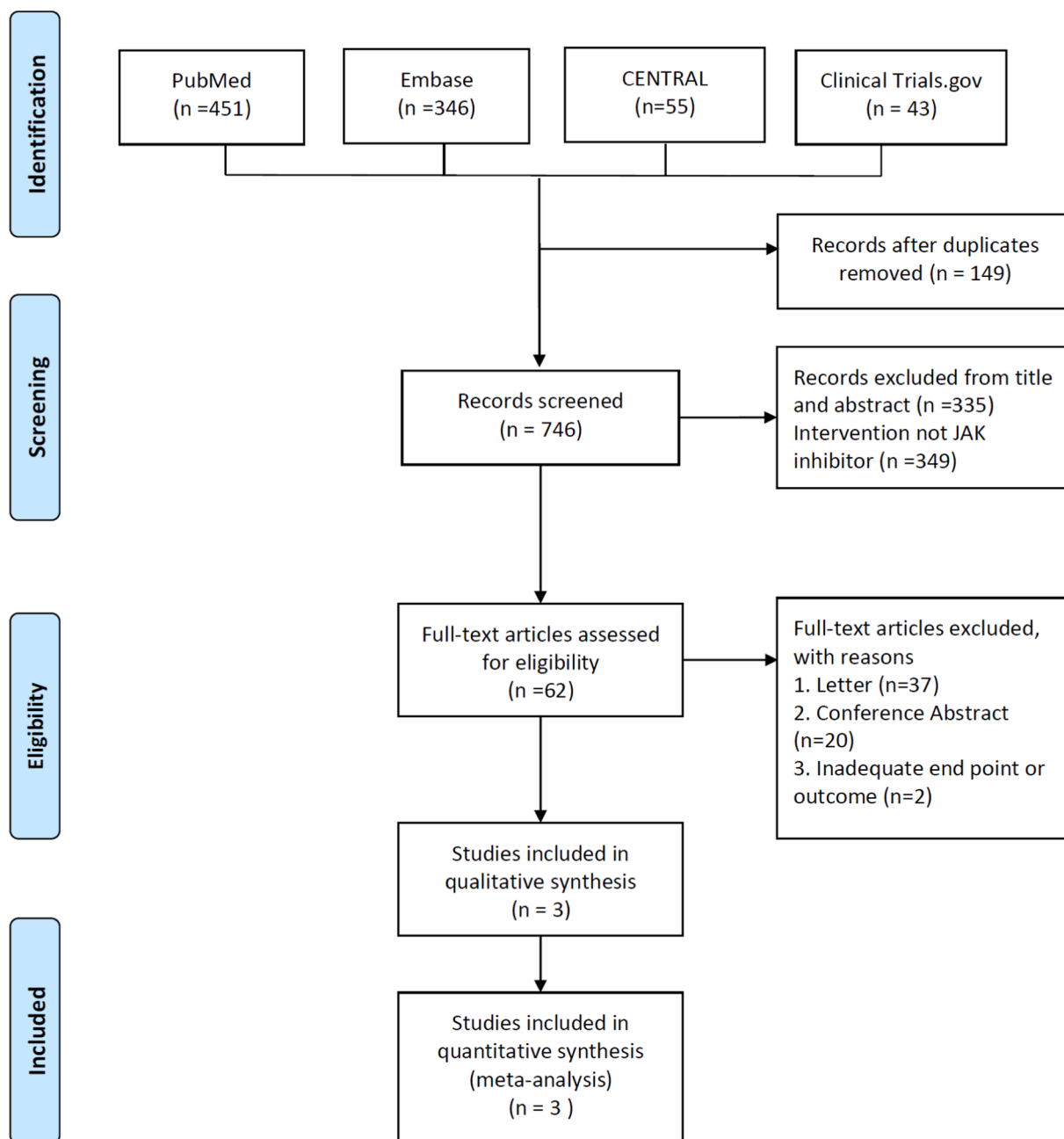


Fig. 1. Algorithm of study selection. CENTRAL, Cochrane Central Register of Controlled Trials.

improve the clinical outcomes of COVID-19 patients, as supported by the following evidence: First, the patients who received JAK inhibitors had a significantly lower mortality rate at day 28 than the control group. Second, the patients who received JAK inhibitors had a higher clinical recovery rate and shorter time to recovery than the control group. Third, the patients who received JAK inhibitors had a lower rate of MV use, shorter duration of MV or ECMO, and a shorter length of hospital stay than the control group. These findings are in line with those of previous meta-analyses [19,20]. In one meta-analysis, which enrolled six observational studies, three clinical trials and two RCTs, Chen et al. demonstrated that the use of JAK inhibitors, including ruxolitinib and baricitinib, decreased the use of invasive MV (relative risk [RR], 0.63; 95% CI, 0.47–0.84) and had a borderline impact on the rate of intensive care unit admission (RR, 0.24; 95% CI, 0.06–1.02) [19]. In addition, the RRs of death were significantly lower for both drugs (RR, 0.42; 95% CI, 0.30–0.59), for ruxolitinib (RR, 0.33; 95% CI, 0.13–0.88) and for

baricitinib (RR, 0.44; 95% CI, 0.31–0.63) [19]. In another meta-analysis including three non-randomized trials and two RCTs, Wijaya et al. demonstrated that the use of JAK inhibitors (ruxolitinib and baricitinib) was associated with reduced risks of mortality (OR, 0.51; 95% CI 0.28–0.93) and clinical improvement (OR, 1.76; 95% CI 1.05–2.95) [20]. In contrast to these two meta-analyses [19,20], we only included RCTs and we also included an extra JAK inhibitor (tofacitinib). In summary, these findings indicate that JAK inhibitors could be a promising therapeutic option in the treatment of adult patients hospitalized with COVID-19.

The rationale of our findings supporting the repurposing of JAK inhibitors to improve the treatment strategies for COVID-19 could be explained by the following mechanisms. Much evidence has shown that severe COVID-19 patients might present with an exaggerated immune response, characterized by increased interleukin (IL)-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon- γ (IFN γ),

Table 1
Characteristics of the included studies.

	Study design	Study period	Study site	Study subjects	Intervention	Controls	No of patients		No (%) of patients receiving steroid		Primary outcome
							Study group*	Sontrol group*	Study group*	Control group*	
Cao et al, 2020	Prospective, multicenter, single-blind, randomized controlled phase II trial	Between February 9 and 28, 2020	3 hospitals in China	Adult patients with severe COVID-19	Ruxolitinib 5 mg twice a day plus standard of care	Vitamin C 100 mg twice a day plus standard of care	20	21	14 (70.0)	15 (71.4)	Time to clinical improvement and improvement rate of follow-up CT scans
Kalil et al, 2020	Double-blind, randomized, placebo-controlled trial	Between May 8, and July 1, 2020.	67 sites in 8 countries	Hospitalized adults with moderate to severe COVID-19	Baricitinib 4 mg daily for 14 days or until hospital discharge and remdesivir	Placebo and remdesivir	515	518	NA	NA	Time to recovery
Guimarães et al, 2021	Randomized, double-blind, placebo-controlled, parallel-design trial	Between September 16, 2020, and March 1, 2021	15 sites in Brazil	Hospitalized adults with moderate to severe COVID-19	Tofacitinib 10 mg twice daily for 14 days or until hospital discharge	Placebo	144	145	114 (79.2)	113 (77.9)	Occurrence of death or respiratory failure

*Intention-to-treat population.

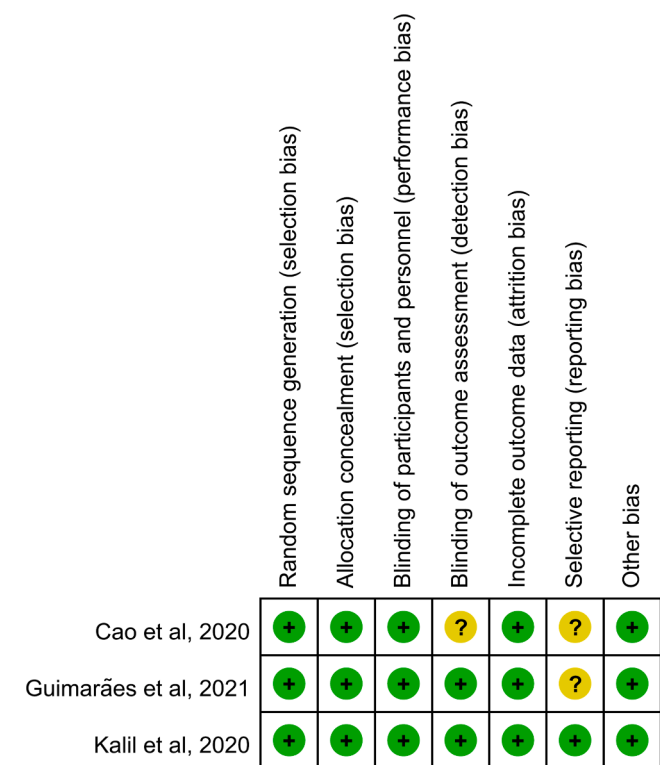


Fig. 2. Summary of risks of bias in each domain.

macrophage inflammatory protein 1 α (MIP1A), and tumor necrosis factor- α (TNF- α) [26–29]. In contrast, JAK inhibitors targeting JAK1, JAK2, JAK3, and tyrosine kinase-2 (TYK2) can downregulate these cytokines to further decrease inflammatory responses [27,28,30]. In addition, baricitinib (a JAK1/2 inhibitor) may affect the cellular viral entry of SARS-CoV-2 through potential inhibitory effects on AP2-associated protein kinase 1 and cyclin G-associated kinase [31,32]. Moreover, fedratinib, a highly selective JAK2 inhibitor, inhibits the expression of IL-17 in murine T helper 17 (Th17) cells and suggests a possible role for JAK2 selective inhibitors in blocking Th17-associated cytokine activation in COVID-19 management [33]. Although all of these findings support the use of JAK inhibitors for COVID-19 patients, further studies are needed to validate these hypotheses in clinical practice.

Finally, this meta-analysis assessed safety issues associated with the use of JAK inhibitors. We did not find an association between the use of JAK inhibitors and a higher risk of AEs and serious AEs compared to the controls. Although infection remains a serious concern when using JAK inhibitors among patients with rheumatoid arthritis [34–36], the risk of secondary infection, sepsis and septic shock was similar between the patients who received JAK inhibitors and the control groups in this meta-analysis. Based on this limited evidence, JAK inhibitors could be a safe agent in the treatment of COVID-19 patients. However, further studies are warranted to confirm our findings.

This meta-analysis had several limitations. First, the numbers of studies and patients were small, especially for each JAK inhibitor. Moreover, the finding of the meta-analysis was determined according to the weight of the studies, and Kalil’s study [22] has the biggest weight. Therefore, our findings should be interpreted cautiously and further large scales study is warranted to validate our findings. Second, the

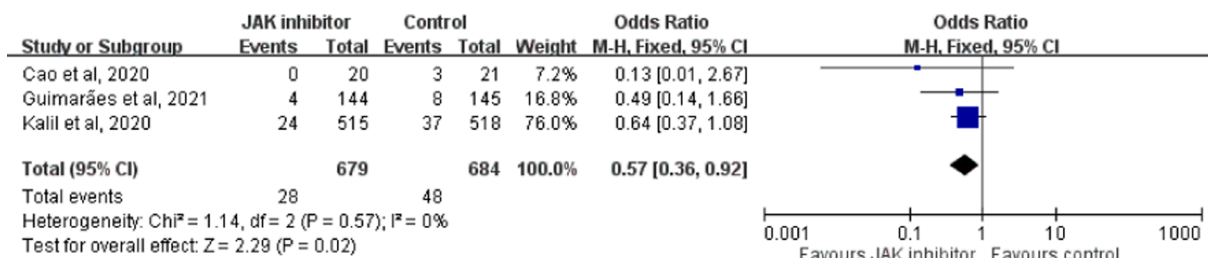


Fig. 3. Forest plot of the comparison of all-cause mortality rate at day 28 between the patients who received JAK inhibitors and the control group.

Table 2
Grading of evidence.

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With controls	With Janus kinase inhibitors		Risk with controls	Risk difference with Janus kinase inhibitors
Outcome 1363 (3 RCTs)	serious	not serious	not serious	not serious	none	⊕⊕⊕x MODERATE	48/684 (7.0%)	28/679 (4.1%)	OR 0.57 (0.36 to 0.92)	70 per 1,000	29 fewer per 1,000 (from 44 fewer to 5 fewer)

CI: Confidence interval; OR: Odds ratio.

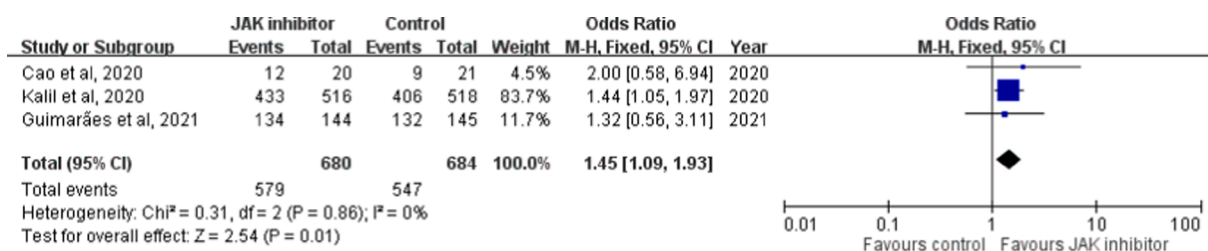


Fig. 4. Forest plot of the comparison of clinical recovery rate between the patients who received JAK inhibitors and the control group.

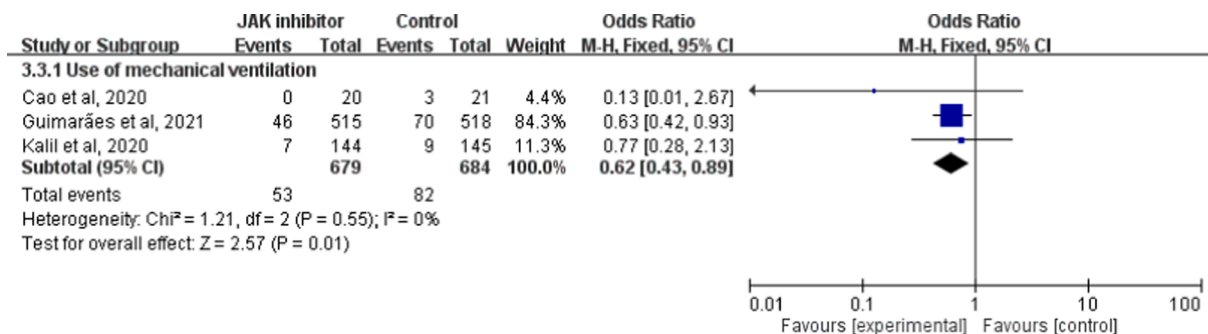


Fig. 5. Forest plot of the comparison of the risk of mechanical ventilation use between the patients who received JAK inhibitors and the control group.

regimens of standard care vary in the three included RCTs [21–23], particularly for remdesivir and corticosteroids. Remdesivir was routinely used in Kalil et al.’s study [22], but it was not used in the other two RCTs [21,23]. In Kalil et al.’s study, corticosteroids were not permitted, except when following standard indications such as adrenal insufficiency, asthma exacerbation, laryngeal edema, septic shock, and acute respiratory distress syndrome [22]. In contrast, more than 70% of the patients received corticosteroids in the two other RCTs [21,23]. Finally, only three JAK inhibitors (ruxolitinib, baricitinib and tofacitinib) were used in the included studies, so further studies are needed to

investigate the usefulness of other JAK inhibitors for COVID-19.

In conclusion, JAK inhibitors can lead to a better clinical outcome of hospitalized COVID-19 patients, and they are a safe agent in the treatment of COVID-19.

Declaration of Competing Interest

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

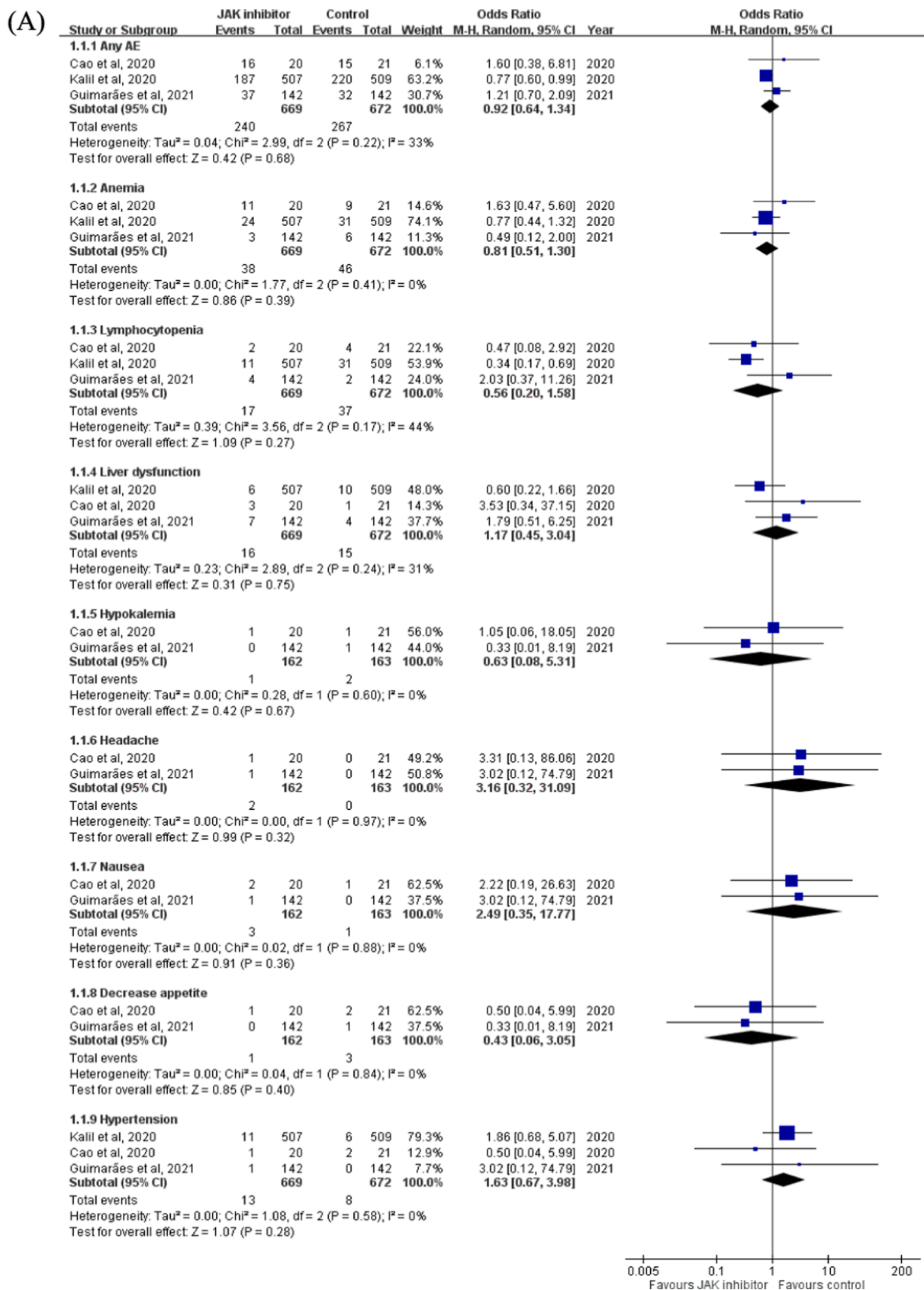


Fig. 6. Forest plots of comparisons of the risk of adverse events (A) and serious adverse events (B) between the patients who received JAK inhibitors and the control group.

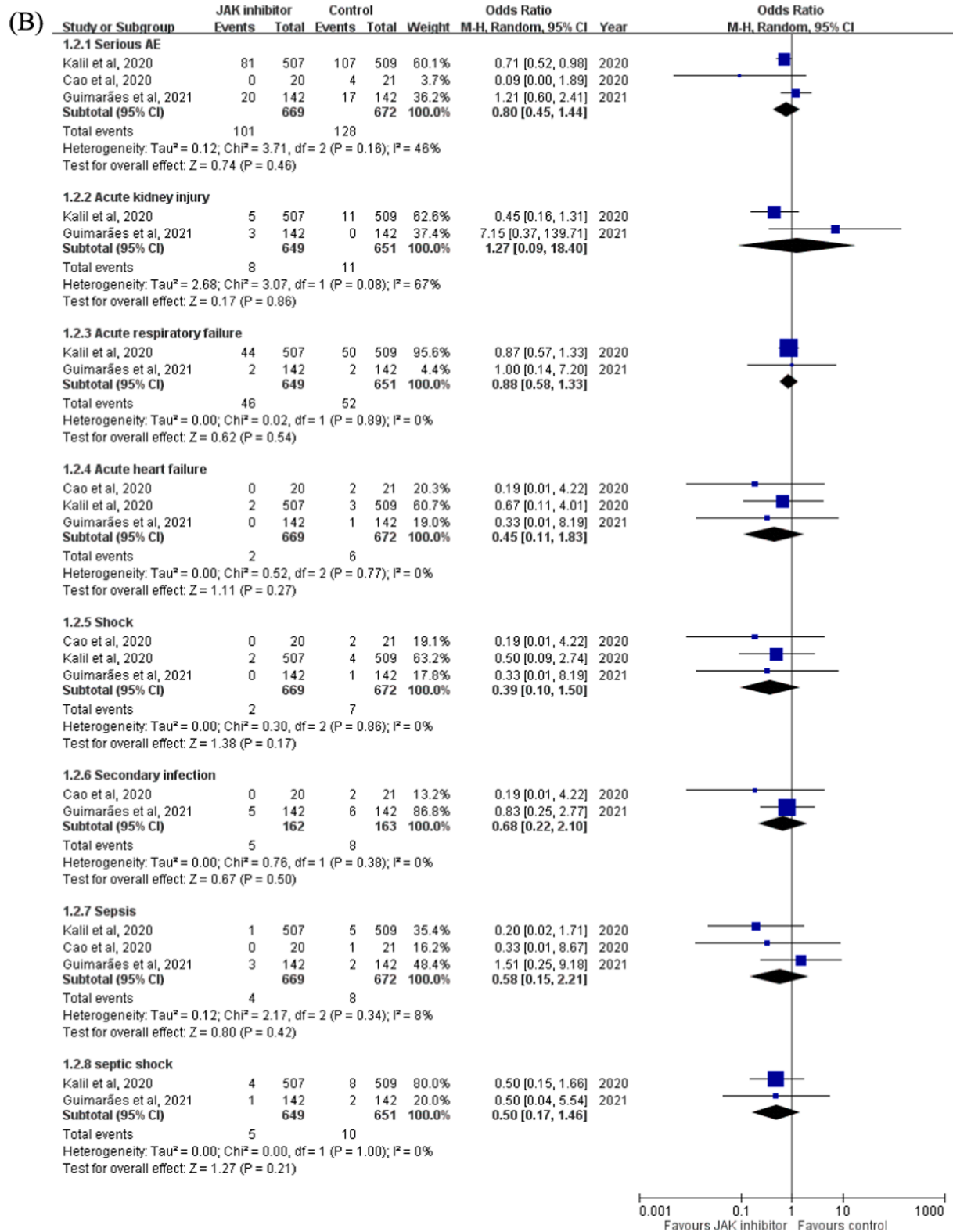


Fig. 6. (continued).

Appendix A. . Search strategy

Pubmed

1#	Search: ((janus kinase inhibitor OR JAK inhibitor) AND (SARS-CoV2 OR COVID-19)) ("janus kinase inhibitors"[Pharmacological Action] OR "janus kinase inhibitors"[MeSH Terms] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitors"[All Fields]) OR "janus kinase inhibitors"[All Fields] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitor"[All Fields]) OR "janus kinase inhibitor"[All Fields] OR ("janus kinase inhibitors"[Pharmacological Action] OR "janus kinase inhibitors"[MeSH Terms] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitors"[All Fields]) OR "janus kinase inhibitors"[All Fields] OR ("jak"[All Fields] AND "inhibitor"[All Fields]) OR "jak inhibitor"[All Fields])) AND ("SARS-CoV2"[All Fields] OR ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) Translations janus kinase inhibitor: "janus kinase inhibitors"[Pharmacological Action] OR "janus kinase inhibitors"[MeSH Terms] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitors"[All Fields]) OR "janus kinase inhibitors"[All Fields] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitor"[All Fields]) OR "janus kinase inhibitor"[All Fields] JAK inhibitor: "janus kinase inhibitors"[Pharmacological Action] OR "janus kinase inhibitors"[MeSH Terms] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitors"[All Fields]) OR "janus kinase inhibitors"[All Fields] OR ("jak"[All Fields] AND "inhibitor"[All Fields]) OR "jak inhibitor"[All Fields] COVID-19: ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR ("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])	16
#2	Therapy/Broad[filter]	100

EMBASE

1#	Search: 'janus kinase inhibitor'/exp OR 'janus kinase inhibitor' OR (('janus'/exp OR janus) AND ('kinase'/exp OR kinase) AND ('inhibitor'/exp OR inhibitor)) OR 'jak inhibitor'/exp OR 'jak inhibitor' OR (jak AND ('inhibitor'/exp OR inhibitor)) OR 'baricitinib'/exp OR baricitinib OR 'tofacinib'/exp OR tofacitinib OR 'ruxolitinib'/exp OR ruxolitinib OR 'ocelactinib'/exp OR oclacitinib OR 'peficitinib'/exp OR peficitinib OR 'filgotinib'/exp OR filgotinib OR 'fedratinib'/exp OR fedratinib	168,301
2#	Search: 'covid 19' OR covid19 OR (coronavirus AND disease) OR 'sars cov 2'	26,278
3#	#1 and #2	1052
4#	Filter: trial topic'/de	346

Cochrane central register of controlled trials

1#	Search: (janus kinase inhibitor) OR (JAK inhibitors) or Baricitinib or Tofacinib or Ruxolitinib or Oclacitinib or Peficitinib or fedratinib or filgotinib	2498
2#	Search: ((janus kinase inhibitor OR JAK inhibitor) AND (SARS-CoV2 OR COVID-19))	6297
3#	#1 and #2	55

Clinical Trials.gov

1#	janus kinase inhibitor OR JAK inhibitor AND COVID-19	43
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