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

ARTICLE IN PRESS
+ MODEL
Journal of Microbiology, Immunology and Infection xxx (xxxx) xxx

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.e-jmii.com

Original Article

Oral Janus kinase inhibitors for treating hospitalized patients with COVID-19: An updated systematic review and meta-analysis of randomized controlled trials

Hung-Jen Tang [a], Teng-Song Weng [b], Yu-Hung Chen [c,**], Chien-Ming Chao [c,*]

[a] *Department of Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[b] *Department of Pharmacy, Chi Mei Medical Center, Liouying, Taiwan*
[c] *Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, Tainan, Taiwan*

Received 17 May 2022; received in revised form 23 July 2022; accepted 3 August 2022
Available online ■ ■ ■

KEYWORDS
COVID-19;
Janus kinase inhibitors;
Mechanical ventilation;
Mortality

Abstract *Objectives:* This study investigated the clinical efficacy and safety of oral Janus kinase inhibitors (JAKis) in the treatment of hospitalized patients with COVID-19.
Methods: The PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases were searched for relevant articles written before January 29, 2022. Only randomized controlled trials (RCTs) that assessed the clinical efficacy and safety of oral JAKis in patients with COVID-19 were included.
Results: In the pooled analysis of the 7 RCTs, the all-cause 28-day mortality rate in the study group receiving JAKis was significantly lower than that in the control group (9.4% [183/1941] vs. 10.9% [184/1687], risk ratio [RR] = 0.69, 95% confidence interval [CI], 0.58–0.81, I^2 = 0%). In addition, the risk of 14-day mortality was in the study group was lower than that in the control group (RR = 0.65, 95% CI, 0.46–0.92, I^2 = 0%). Finally, the study group and the control group exhibited similar risks of any adverse events (RR = 0.96, 95% CI, 0.89–1.04, I^2 = 0%).
Conclusions: Oral JAKis can significantly reduce the risk of death among patients with COVID-19. In addition, JAKis are tolerable for hospitalized patients with COVID-19.

* Corresponding author.
** Corresponding author. Department of Pharmacy, Chi Mei Medical Center, Liouying, Taiwan.
E-mail address: ccm870958@yahoo.com.tw (C.-M. Chao).

https://doi.org/10.1016/j.jmii.2022.08.005

Please cite this article as: H.-J. Tang, T.-S. Weng, Y.-H. Chen et al., Oral Janus kinase inhibitors for treating hospitalized patients with COVID-19: An updated systematic review and meta-analysis of randomized controlled trials, Journal of Microbiology, Immunology and Infection, https://doi.org/10.1016/j.jmii.2022.08.005

Introduction

Since the first outbreak of coronavirus disease 2019 (COVID-19) toward the end of 2019, the COVID-19 pandemic has rapidly become one of the most devastating global problems.[1,2] As of May 3, 2022, 511,965,711 cases of SARS-CoV-2 infections and 6,240,619 COVID-19-related deaths have been confirmed and reported by the World Health Organization.[3] Patients with SARS-CoV-2 infections could exhibit protean clinical manifestations, ranging from asymptomatic to severe acute respiratory distress syndrome (ARDS).[4] Moreover, some patients who have recovered from acute SARS-CoV-2 infections continue to suffer from long COVID-19 or post-acute sequelae of COVID-19.[5] The severity of COVID-19 is significantly associated with a dysregulated immune response and excessive release of proinflammatory agents, resulting in cytokine storm.[6,7] Therefore, in addition to limited direct antiviral agents against SARS-CoV-2, such as remdesivir, molnupiravir, and nirmatrelvir plus ritonavir,[8–10] repurposing anti-inflammation therapy is considered a promising therapeutic approach for patients with COVID-19.

Several systemic anti-inflammatory and immunomodulatory agents, including corticosteroids and interleukin-6 blockade, exhibit a survival benefit for hospitalized patients with COVID-19.[11,12] Additionally, Janus kinase inhibitors (JAKis), which can ameliorate the inflammatory response and enhance antibody production, have been predicted (with the use of artificial intelligence algorithms) to be a potential therapeutic option against COVID-19.[13–15] Several randomized controlled trials (RCTs) have investigated the clinical efficacy of JAKis, including baricitinib, ruxolitinib, tofacitinib, and nezulcitinib, in the treatment of patients with COVID-19,[16–20] and several meta-analyses have assessed their effects based on these RCTs.[21–23] Since the publication of the last of these meta-analyses, one more RCT[24] and two more clinical trials[26,26] have reported relevant findings. Therefore, we conducted this study to provide updated information regarding the usefulness of JAKis in the treatment of hospitalized patients with COVID-19.

Material and methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines,[27] and the study protocol is registered in PROSPERO under number CRD42022307914. This meta-analysis did not require the approval of an institutional review board because the sources of the analyzed data are public and the analysis does not make the data individually identifiable.

Search strategy

A systematic literature search of relevant studies published up to January 29, 2022, was conducted using the PubMed, Embase, and Cochrane Central Register of Controlled Trials databases and clinicaltrials. gove. We used the following search terms, including "Baricitinib," "Olumiant," "Tofacitinib," "Xeljanz," "Ruxolitinib," "Jakafi," "Jakavi," "SARS-CoV-2 virus," and "COVID-19." Reference lists from the studies selected through electronic searching were manually searched to identify additional relevant studies.

Study selection

Two investigators (TSW and YHC) independently screened the titles and the abstracts for eligibility and reviewed the full texts of potentially eligible studies. In the case of disagreement, a third investigator (HJT) was responsible for establishing a consensus. Only RCTs comparing the clinical efficacy and safety of JAKis with placebo or standard of care in hospitalized patients with COVID-19 were included in this review. Clinical efficacy included mortality, clinical improvement, and the requirement of mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO). Safety was defined as the risk of adverse events (AEs). We manually searched for additional eligible articles cited in the reference lists of the identified articles. The inclusion criteria was (1) examination of hospitalized patients with COVID-19; (2) use of oral JAKis as the experimental drug; (3) use of placebo or standard of care for comparison; and (4) availability of clinical data for analysis. Exclusion criteria included in vitro studies, case reports, case series, post hoc analysis studies, posters or conference abstracts, and studies without available data for outcome analysis.

Data extraction and outcome measurement

The following data were extracted from each included study: year of publication, study design, study patients, JAKi regimen, clinical outcomes, and risk of adverse events (AEs). Data extraction and quality assessment were conducted independently by TSW and YHC. Any discrepancies were resolved through discussion and, if necessary, evaluation by third investigator (HJT).

The primary outcome was all-cause 28-day mortality, and the secondary outcomes were 14-day mortality, rate of clinical improvement, time of clinical improvement, requirement of MV or ECMO, and risk of AEs.

Assessment of risk of bias

Two investigators (SHL and CMC) independently assessed the risk of bias for each of the included studies using the Cochrane risk-of-bias tool 2.0.[28] Disagreements were resolved through discussion and consensus with a third investigator (CMC).

Statistical aanalysis

Statistical analyses were performed with Review Manager (version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity in the results of the trials was assessed using the $\chi 2$ test and is expressed in terms of I^2 index values.[29] The pooled risk ratios (RRs) or mean differences (MDs) and 95% confidence intervals (CIs) were calculated for outcome analysis using a random-effects model.

Results

Search results

The search of the online databases yielded a total of 683 studies (n = 428 from PubMed; n = 130 from Embase; n = 71 from Cochrane library; n = 54 from ClinicalTrial.gov) (Appendix 1). Among these studies, 152 duplicate studies were excluded. We deemed 472 of the studies irrelevant after screening the titles and abstracts and discovering that we could not access the full texts of the publications. After screening the full texts of 59 of the articles, we excluded 52 of the studies. Finally, seven studies[16–19,24–26] fulfilling the inclusion criteria were included in our meta-analysis (Fig. 1).

Study characteristics

Among the seven included RCTs, five[17–19,25,26] employed double-blind designs. Four of the RCTs[17,18,25,26] were multinational studies, and the remaining three were conducted in India,[24] Brazil,[19] and China.[16] One of the studies[24] was a single center study; the other six[16–19,25,26] were multicenter studies. Three JAKis (baricitinib, ruxolitinib, and tofacitinib) were used as interventions in the included studies. Three, two, and two studies evaluated the clinical efficacy of ruxolitinib,[16,25,26] baricitinib,[17,18] and tofacitinib,[19,24] respectively. All of the studies involved hospitalized patients with COVID-19. One of the studies focused on moderate COVID-19,[24] three focused on moderate-to-severe COVID-19,[17–19] and three focused only on severe COVID-19.[16,25,26] A total of 3631 patients (n = 1944 in the study group, n = 1687 in the control group) were included in the meta-analysis (Table 1). Fig. 2 presents the results of the assessment of risk of bias in each domain for each study. Murugesan et al.'s study[24] was open-label design, however, it did not affect the outcome analysis. Therefore, we considered this study[24] exhibited some concerns of randomization and the associated overall bias. All the other six included RCTs[16–19,25,26] exhibit a low risk of bias.

Primary outcome

In the pooled analysis of the RCTs, the all-cause 28-day mortality rate in the study group receiving JAKis was significantly lower than that in the control group, and low heterogeneity was observed among the studies (9.4% [183/1941] vs. 10.9% [184/1687], RR = 0.69, 95% CI, 0.58–0.81, I^2 = 0%, Fig. 3). In the leave-one-out sensitivity test to assess the confounding effect of each study, these results remained unchanged.

In the subgroup analysis of the two RCTs that used baricitinib as the study drug,[17,18] the mortality rate in the study group was significantly lower than that in the control group (RR = 0.63, 95% CI, 0.48–0.81, I^2 = 0%). In the subgroup analysis of the studies using either of the other two JAKis as the study drug, the mortality rate in the study group was also lower than that in the control group; however, the difference did not reach statistical significance (tofacitinib: RR = 0.50, 95% CI, 0.16–0.61; ruxolitinib: RR = 0.78, 95% CI, 0.46–1.30, I^2 = 15%). In the subgroup analysis of the three RCTs[17–19] focusing on patients with moderate-to-severe COVID-19, the mortality rate in the study group was significantly lower than that in the control group (RR = 0.62, 95% CI, 0.48–0.80, I^2 = 0%). In the subgroup analysis of the studies focusing on patients with severe COVID-19, the mortality rate in the study group was lower than that in the control group; however, the

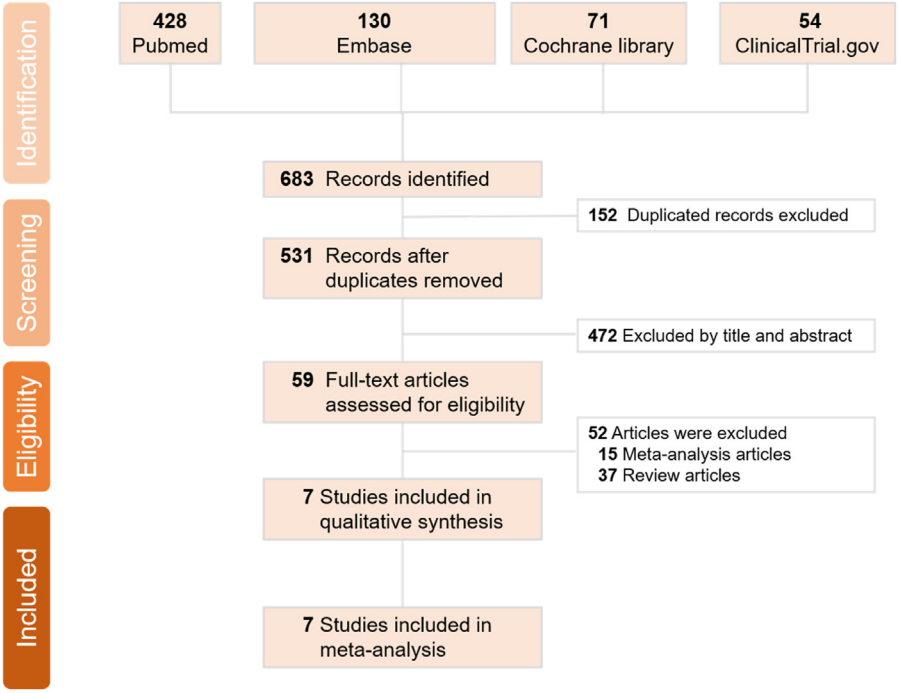

Figure 1. Algorithm for screening and identifying studies.

Table 1 Characteristics of included studies.

Author, year	Study design	Study period	Study sites	Participants	Regimen of Janus kinase inhibitor	Comparator	No of patients	
							Study group	Control group
Baricitinib								
Kalil et al.[17]	Randomized double-blind, placebo-controlled trial	Between May 8, 2020 and July 1, 2020.	67 centers in 8 countries	Hospitalized adults with moderate-to-severe COVID-19	4 mg daily dose for 14 days or until hospital discharge (plus remdesivir)	Placebo plus remdesivir	515	518
Marconi et al.[18]	Randomized double-blind, placebo-controlled trial	Between June 11, 2020, and Jan 15, 2021	101 centers in 12 countries	Hospitalized adults with moderate-to-severe COVID-19	4 mg daily for 14 days or until hospital discharge	Placebo	764	761
Tofacitinib								
Guimarães et al.[19]	Randomized, double-blind, placebo-controlled trial	Between September, 2020 and December, 2020	15 sites in Brazil	Hospitalized adults with moderate-to-severe COVID-19	10 mg twice daily for 14 days or until hospital discharge	Placebo	144	145
Murugesan et al.[24]	open-labeled randomized controlled study	Between October, 2020 and December 2020	1 center in India	Hospitalized adults with moderate COVID-19	10 mg twice daily for 14 days	SOC	50	50
Ruxolitinib								
Cao et al.[16]	Randomized single-blind trial	Between February 9 and February 28, 2020	3 hospitals in China	Adult patients with severe COVID-19	5 mg twice daily	Vitamin C	20	21
NCT04362137 (RUXCOVID)[25]	randomized, double-blind, placebo-controlled	Between May, 2020 and October, 2020	61 centers in 12 countries	Patients aged ≥12 years with COVID-19 associated cytokine storm	5 mg twice daily for 14 days or possible extension of 28 days	placebo	287	145
NCT04377620 ((RUXCOVID-DEVENT)[26]	randomized, double-blind, placebo-controlled	Between May 2020 and February 2021	33 centers in US and Russia	Patients with COVID-19-associated ARDS requiring MV	5 mg or 1 mg twice daily	placebo	77 (15-mg) 87 (5-mg)	47

ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; SOC, standard of care.

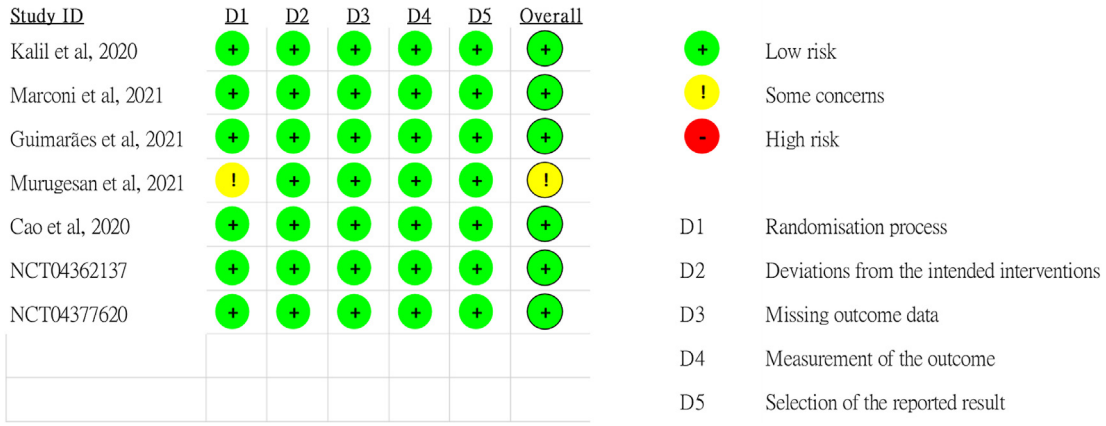

Figure 2. Risk of bias summary.

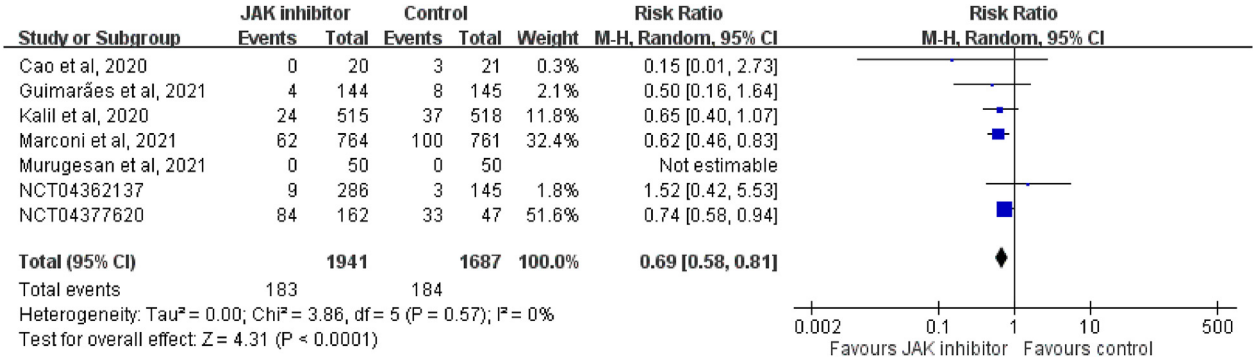

Figure 3. Forest plot of 28-day all-cause mortality rate.

difference did not reach statistical significance (tofacitinib: RR = 0.78, 95% CI, 0.46–1.30, I^2 = 15%). In the subgroup analysis of the six multicenter studies,[16–19,25,26] the mortality rate in the study group was significantly lower mortality than that in the control group (RR = 0.69, 95% CI, 0.58–0.81, I^2 = 0%).

Secondary outcomes

In the pooled analysis of the six RCTs[16–19,24,25] that reported the 14-day mortality, the risk of death in the study group was lower than that in the control group (RR = 0.65, 95% CI, 0.46–0.92, I^2 = 0%, Fig. 4). The rate of clinical improvement in the study group was significantly higher than that in the control group (RR = 1.04, 95% CI, 1.00–1.08, I^2 = 18%, Fig. 5). In addition, the average time to clinical improvement in the study group was significantly shorter than that in the control group (MD = −1.35, 95% CI, −2.57 to −0.13, I^2 = 60%, Fig. 6). In the pooled analysis of four RCTs,[16,17,19,25] the use of MV in the study group was significantly lower than that in the control group (RR = 0.72, 95% CI, 0.53–0.97, I^2 = 0%). A similar trend (RR = 0.64, 95% CI, 0.50–0.84, I^2 = 0%) was observed in the use of MV or ECMO in the pooled analysis of four RCTs.[16–19]

The risk of AEs was similar between the study group and the control group (RR = 0.96, 95% CI, 0.89–1.04, I^2 = 0%,

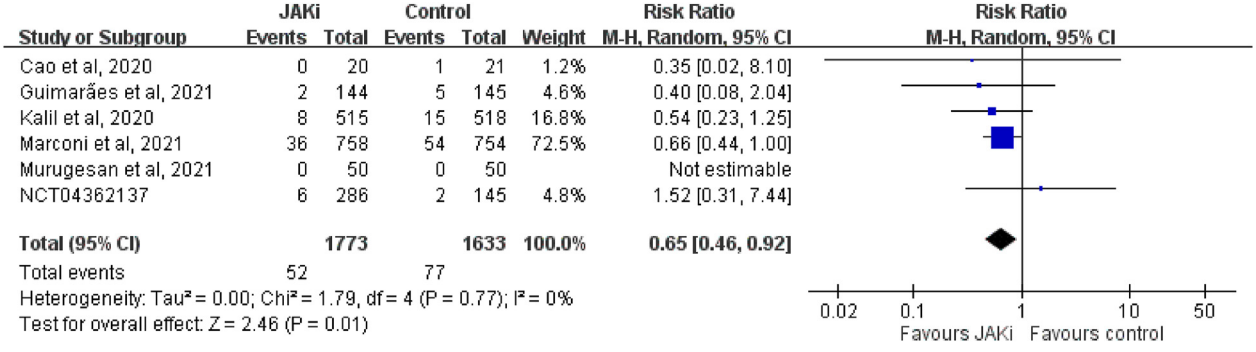

Figure 4. Forest plot of 14-day all-cause mortality rate.

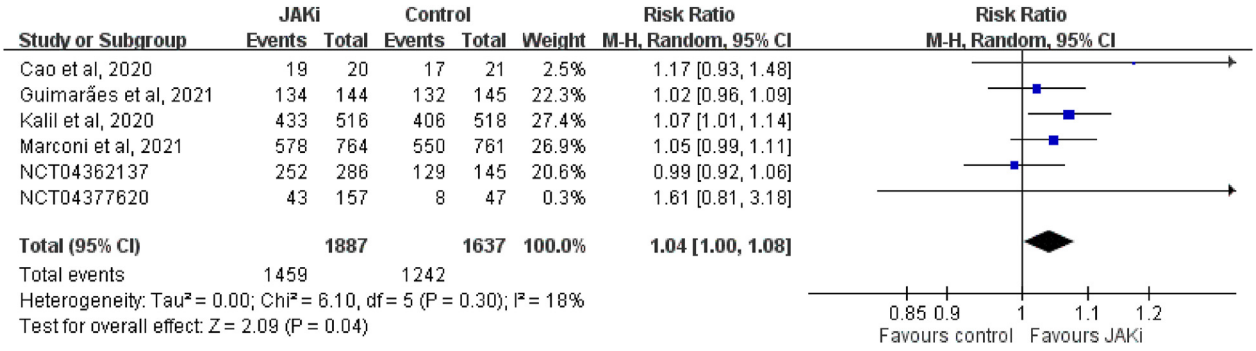

Figure 5. Forest plot of clinical improvement rate.

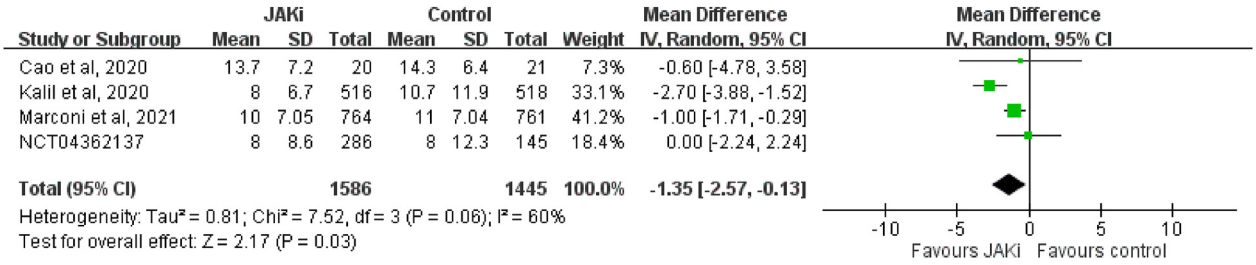

Figure 6. Forest plot of time to clinical improvement.

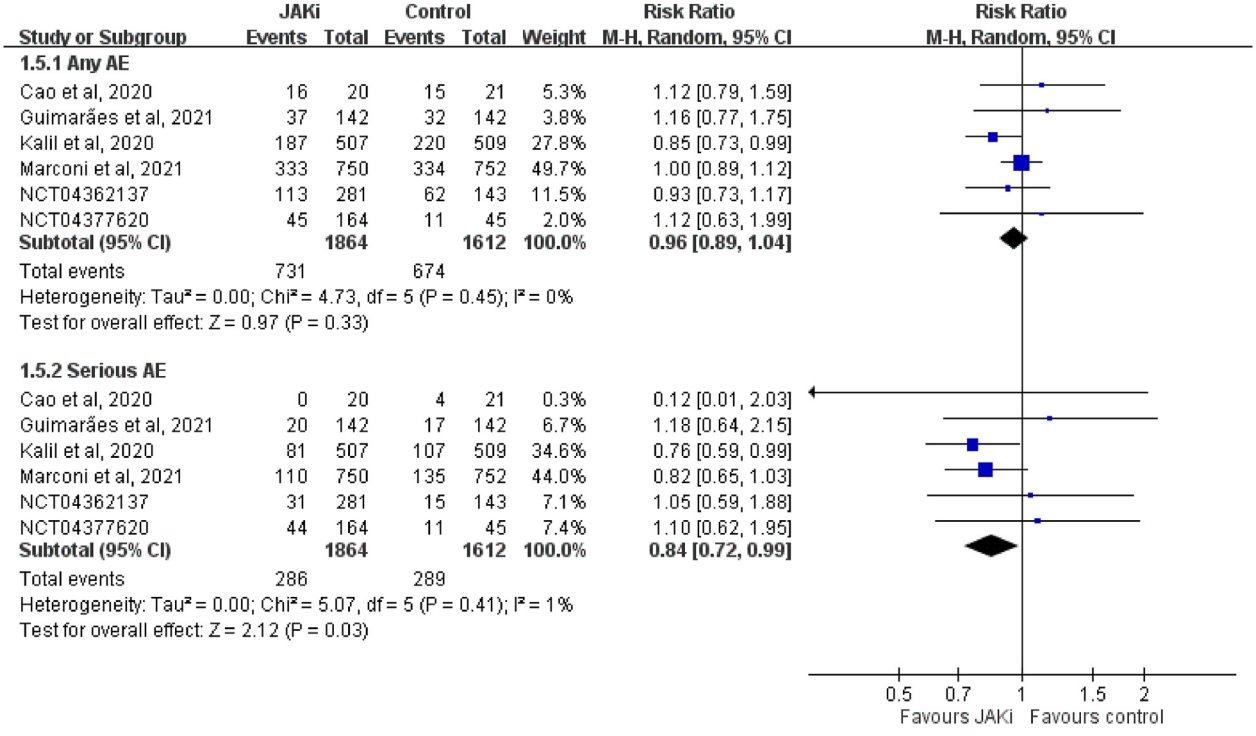

Figure 7. Forest plot of the risk of adverse events (AEs).

Fig. 7); however, the risk of serious AEs in the study group was lower than that in the control group (RR = 0.84, 95% CI, 0.72–0.99, I^2 = 1%, Fig. 7) (see Fig. 6). The study group and the control group exhibited similar risks of infection (RR = 0.94, 95% CI, 0.75–1.17, I^2 = 0%), sepsis (RR = 0.83, 95% CI, 0.62–1.12, I^2 = 0%), and septic shock (RR = 0.61, 95% CI, 0.36–1.04, I^2 = 0%).

Discussion

This meta-analysis was conducted to assess the clinical efficacy and safety of using JAKis (baricitinib, tofacitinib, and ruxolitinib) to treat hospitalized patients with COVID-19. The results revealed that the study group (patients who

received JAKis) exhibited more favorable clinical outcomes than did the control group, which was supported by the following evidence. First, the all-cause 28-day mortality rate was significantly (31%) lower in the study group than in the control group. Second, this trend remained unchanged in the leave-one-out sensitivity test. Third, the trend was similar across various subgroups defined according to the type of JAKis used, disease severity of COVID-19, and study design. Fourth, the 14-day mortality rate was 35% lower in the study group than in the control group. Finally, the study group had a higher clinical improvement rate, a shorter time to clinical improvement, and a lower rate of MV or ECMO use than did the control group. In addition, the included RCTs exhibited low heterogeneity ($I^2 < 50\%$). Our findings are in line with previous meta-analyses[21,22] of four or five RCTs involving less than 3000 patients. However, our analysis included seven RCTs with a total of 3631 patients and could therefore more effectively verify the clinical effectiveness of JAKis. In summary, our findings indicate that JAKis can significantly reduce the risk of mortality and improve the clinical outcomes of patients with COVID-19, thereby aiding patients and health-care professionals in the fight against COVID-19.

The clinical benefit of JAKis in the treatment of patients with COVID-19 can be explained as follows. Severe COVID-19 may be caused by a dysregulated immune response or cytokine storm, which is characterized by the uncontrolled secretion of many proinflammatory cytokines, including interleukin (IL)-I, IL-2, IL-6, IL-10, IL-18, and IL-33; tumor necrosis factor-α; interferon-γ; and macrophage inflammatory protein 1α.[30–32] JAKis can target and downregulate JAK1, JAK2, JAK3, and tyrosine kinase-2 (TYK2), thereby attenuating hyperinflammatory responses.[33] In this meta-analysis, three JAKis — baricitinib, tofacitinib, and ruxolitinib — were evaluated. Baricitinib and ruxolitinib are selective inhibitors of JAK1/JAK2, and tofacitinib is a selective inhibitor of JAK 1/JAK3, with functional selectivity for JAK2. Baricitinib exhibits additional potential to impair the cellular viral entry of SARS-CoV-2.[15,34] Although the effectiveness of JAKis was consistently demonstrated in this meta-analysis, the clinical efficacy of different JAKis could vary, and additional RCTs are warranted to clarify their differences in clinical practice.

Beyond clinical efficacy, we also assessed the tolerability of JAKis. Overall, the patients who received JAKis did not exhibit a higher risk of any AEs or serious AEs than did the patients in the control group. Furthermore, the use of JAKis did not increase the patients' risk of infection, sepsis, or septic shock. These findings are consistent with those of previous studies[11,12,21–23] and indicate that JAKis are safe for use in the treatment of patients with COVID-19.

However, this study has some limitations. First, the numbers of studies on each JAKi, as well as the numbers of patients in each study, were limited. Only 289 and 674 of the patients received tofacitinib and ruxolitinib, respectively. By contrast, 2558 patients were involved in the study focusing baricitinib. Therefore, we found that only baricitinib was associated with a significant survival benefit, whereas tofacitinib and ruxolitinib could have been associated with marginal effects. Second, because the disease severity of COVID-19 varied among the included RCTs, we could not determine which populations may consistently benefit from JAKis. Therefore, more large-scale RCTs are required to evaluate the clinical efficacy of each inhibitor in the treatment of patients with COVID-19 of different severities.

In conclusion, JAKis can significantly reduce the risk of mortality, enhance clinical improvement, and prevent the need for MV or ECMO among patients with COVID-19. In addition, JAKis are tolerable for hospitalized patients with COVID-19.

Ethical approval

Not required.

Funding

This paper was not funded.

Declaration of competing interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, patents received or pending, and royalties.

Acknowledgments

This study was supported by Chi Mei Medical Center, Liouying (CLFHR11039).

References

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents* 2020;**55**:105924.
2. Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. *Int J Antimicrob Agents* 2020;**55**:105946.
3. World Health Organization. https://covid19.who.int/. [Accessed 3 May 2022].
4. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. *J Microbiol Immunol Infect* 2020;**53**:404—12.
5. Proal AD, VanElzakker MB. Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. *Front Microbiol* 2021;**12**:698169.

6. Vora SM, Lieberman J, Wu H. Inflammasome activation at the crux of severe COVID-19. *Nat Rev Immunol* 2021;**21**:694—703.
7. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;**395**:1033—4.
8. Vangeel L, Chiu W, De Jonghe S, Maes P, Slechten B, Raymenants J, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *Antivir Res* 2022;**198**:105252.
9. Drożdżal S, Rosik J, Lechowicz K, Machaj F, Szostak B, Przybyciński J, et al. An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment. *Drug Resist Updates* 2021;**59**:100794.
10. Lai CC, Chao CM, Hsueh PR. Clinical efficacy of antiviral agents against coronavirus disease 2019: a systematic review of randomized controlled trials. *J Microbiol Immunol Infect* 2021;**54**:767—75.
11. Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, Spiga F, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA* 2021;**326**:499—518.
12. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;**324**:1330—41.
13. Ravid JD, Leiva O, Chitalia VC. Janus kinase signaling pathway and its role in COVID-19 inflammatory, vascular, and thrombotic manifestations. *Cells* 2022;**11**:306.
14. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 2020;**20**:400—2.
15. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020;**395**:e30—1.
16. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020;**146**:137—46. e3.
17. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;**384**:795—807.
18. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med* 2021;**9**:1407—18.
19. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* 2021;**385**:406—15.
20. Singh D, Bogus M, Moskalenko V, Lord R, Moran EJ, Crater GD, et al. A phase 2 multiple ascending dose study of the inhaled pan-JAK inhibitor nezulcitinib (TD-0903) in severe COVID-19. *Eur Respir J* 2021;**58**:210067.
21. Lan SH, Wang CK, Chang SP, Lu LC, Hung SH, Lin WT. Janus kinase inhibitors for hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials. *Expert Rev Anti Infect Ther* 2021;**20**:773—9.
22. Chen CY, Chen WC, Hsu CK, Chao CM, Lai CC. Clinical efficacy and safety of Janus kinase inhibitors for COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Int Immunopharm* 2021;**99**:108027.
23. Patoulias D, Doumas M, Papadopoulos C, Karagiannis A. Janus kinase inhibitors and major COVID-19 outcomes: time to forget the two faces of Janus! A meta-analysis of randomized controlled trials. *Clin Rheumatol* 2021;**40**:4671—4.
24. Murugesan H, Cs G, Nasreen HS, Santhanam S, M G, Ravi S, et al. An evaluation of efficacy and safety of tofacitinib, a JAK Inhibitor in the management of hospitalized patients with mild to moderate COVID-19 - an open-label randomized controlled study. *J Assoc Phys India* 2022;**69**:11—2.
25. *ClinicalTrials.gov*. https://clinicaltrials.gov/ct2/show/NCT04362137. [Accessed 29 January 2022].
26. *ClinicalTrials.gov*. https://clinicaltrials.gov/ct2/show/NCT04377620. [Accessed 29 January 2022].
27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol* 2021;**134**:103—12.
28. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.
29. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557—60.
30. Soy M, Keser G, Atagündüz P. Pathogenesis and treatment of cytokine storm in COVID-19. *Turk J Biol* 2021;**45**:372—89.
31. Morris G, Bortolasci CC, Puri BK, Marx W, O'Neil A, Athan E, et al. The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all? *Cytokine* 2021;**144**:155593.
32. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med* 2020;**383**:2255—73.
33. Luo W, Li YX, Jiang LJ, Chen Q, Wang T, Ye DW. Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19. *Trends Pharmacol Sci* 2020;**41**:531—43.
34. Stebbing J, Krishnan V, de Bono S, Ottaviani S, Casalini G, Richardson PJ, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. *EMBO Mol Med* 2020;**12**:e12697.

Abbreviation

AE	adverse event
ARDS	acute respiratory distress syndrome
ECMO	extracorporeal membrane oxygenation
JAKi	Janus kinase inhibitor
MV	mechanical ventilation
RCT	randomized controlled trial
SOC	standard of care

Appendix 1. Search strategy

PubMed search strategy — last searched on Jan 29, 2022		Results
#1	Search: Baricitinib or Olumiant"baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields] OR "baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields] OR "olumiant" [All Fields] TranslationsBaricitinib: "baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields]Olumiant: "baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields] OR "olumiant" [All Fields]	764
#2	Search: COVID-19 or SARS-CoV-2 virus"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]) OR ("sars cov 2" [MeSH Terms] OR "sars cov 2" [All Fields] OR "sars cov 2 virus" [All Fields]) TranslationsCOVID-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]))SARS-CoV-2 virus: "sars-cov-2" [MeSH Terms] OR "sars-cov-2" [All Fields] OR "sars cov 2 virus" [All Fields]	222,470
#3	Search: #1 and #2 ("baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields] OR ("baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields] OR "olumiant" [All Fields])) AND ("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]) OR ("sars cov 2" [MeSH Terms] OR "sars cov 2" [All Fields] OR "sars cov 2 virus" [All Fields])) TranslationsBaricitinib: "baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields]Olumiant: "baricitinib" [Supplementary Concept] OR "baricitinib" [All Fields] OR "olumiant" [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]))SARS-CoV-2 virus: "sars-cov-2" [MeSH Terms] OR "sars-cov-2" [All Fields] OR "sars cov 2 virus" [All Fields]	227
#4	Search: Tofacitinib or Xeljanz"tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "tofacitinib s" [All Fields] OR "tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "xeljanz" [All Fields] OR "tofacitinib s" [All Fields]TranslationsTofacitinib: "tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "tofacitinib's" [All Fields]Xeljanz: "tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "xeljanz" [All Fields] OR "tofacitinib's" [All Fields]	2127
#5	Search: #2 and #4 ("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	71

(*continued on next page*)

(*continued*)

PubMed search strategy — last searched on Jan 29, 2022		Results
	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]) OR ("sars cov 2" [MeSH Terms] OR "sars cov 2" [All Fields] OR "sars cov 2 virus" [All Fields])) AND ("tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "tofacitinib s" [All Fields] OR ("tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "xeljanz" [All Fields] OR "tofacitinib s" [All Fields]))TranslationsCOVID-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]))SARS-CoV-2 virus: "sars-cov-2" [MeSH Terms] OR "sars-cov-2" [All Fields] OR "sars cov 2 virus" [All Fields]Tofacitinib: "tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "tofacitinib's" [All Fields]Xeljanz: "tofacitinib" [Supplementary Concept] OR "tofacitinib" [All Fields] OR "xeljanz" [All Fields] OR "tofacitinib's" [All Fields]	
#6	Search: Ruxolitinib or Jakafi or Jakavi"ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakafi" [All Fields] OR "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakavi" [All Fields] TranslationsRuxolitinib: "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields]Jakafi: "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakafi" [All Fields]Jakavi: "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakavi" [All Fields]	2086
#7	Search: #2 and #6 ("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]) OR ("sars cov 2" [MeSH Terms] OR "sars cov 2" [All Fields] OR "sars cov 2 virus" [All Fields])) AND ("ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR ("ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakafi" [All Fields]) OR ("ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakavi" [All Fields]))TranslationsCOVID-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]))SARS-CoV-2 virus: "sars-cov-2" [MeSH Terms] OR "sars-cov-2" [All Fields] OR "sars cov 2 virus" [All Fields]Ruxolitinib: "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] Jakafi: "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakafi" [All Fields] Jakavi: "ruxolitinib" [Supplementary Concept] OR "ruxolitinib" [All Fields] OR "jakavi" [All Fields]	130
Embase search strategy — last searched on Jan 29, 2022		Results
1	**'sars cov 2 virus'** OR **'covid 19'**	203,383
2	baricitinib	2720
3	1 and 2	773
4	3 and 'randomized controlled trial topic'/de	70
5	tofacitinib	6949
6	5 and 1	286
7	6 AND 'randomized controlled trial topic'/de	20
8	ruxolitinib	7400
9	1 AND 8	422
10	#9 AND 'randomized controlled trial topic'/de	40
Cochrane Library search strategy — last searched on Jan 29, 2022		Results

(*continued*)

PubMed search strategy — last searched on Jan 29, 2022		Results
1	sars cov 2 virus	316
2	covid 19	8885
3	1 OR 2	8885
4	Baricitinib or Olumiant	523
5	3 AND 4	31
6	Tofacitinib or Xeljanz	934
7	3 and 6	17
8	Ruxolitinib or Jakafi or Jakavi	575
9	3 and 8	23
clinicaltrials.gov search strategy — last searched on Jan 29, 2022		Results
1	Condition or disease: COVID-19, Other terms: Baricitinib	25
2	Condition or disease: COVID-19, Other terms: Tofacitinib	7
3	Condition or disease: COVID-19, Other terms: Ruxolitinib	22