Effect of JAK Inhibitors on the Risk of Death in Patients with Moderate to Severe COVID-19: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: The pathophysiology of COVID-19 involves a signalling pathway based on the Janus kinases (JAKs) and the signal transducer and activator of transcription (STAT) family of proteins. As such, there has been growing interest in exploring JAK inhibitors as potential therapeutic agents for this disease.

Objective: To provide a comprehensive summary of the efficacy of JAK inhibitors in the treatment of COVID-19 through a systematic review and meta-analysis.

Data Sources: A systematic literature search was conducted in multiple electronic databases (PubMed, Scopus, and the Cochrane Central Register of Controlled Trials) and preprint repositories, without language restrictions, to identify relevant studies published up to December 31, 2023.

Study Selection and Data Extraction: The primary outcome of interest was all-cause mortality. Randomized controlled trials (RCTs) investigating the administration of JAK inhibitors in patients with COVID-19 were included.

Data Synthesis: Through the systematic literature search, a total of 20 RCTs meeting the inclusion criteria were identified. A random-effects model was employed to estimate the pooled odds ratio for death with administration of a JAK inhibitor relative to non-administration of such an agent, with 95% confidence interval. Meta-analysis of these trials revealed a significant reduction in mortality among patients with COVID-19 who received JAK inhibitors relative to those who did not receive these agents (pooled odds ratio 0.70, 95% confidence interval 0.58–0.84).

Conclusions: The results of this systematic review and meta-analysis suggest that JAK inhibitors, specifically baricitinib, may address the urgent need for effective treatments in the ongoing COVID-19 pandemic by reducing the risk of death among affected patients. However, further research, including larger-scale RCTs, is needed to establish the efficacy and safety of other JAK inhibitors in the treatment of COVID-19 and to generate more robust evidence regarding their use in this specific patient population.

Keywords: baricitinib, COVID-19, JAK inhibitor, mortality, ruxolitinib

RÉSUMÉ

Contexte : La physiopathologie de la COVID-19 implique une voie de signalisation basée sur les Janus kinases (JAK) et les protéines STAT (pour *signal transducer and activator of transcription* en anglais, soit, les protéines transductrices de signal et activatrices de transcription). C'est pourquoi l'étude des inhibiteurs de JAK en tant qu'agents thérapeutiques potentiels pour cette maladie suscite un intérêt croissant.

Objectif : Fournir un résumé complet de l'efficacité des inhibiteurs de JAK dans le traitement de la COVID-19 grâce à une revue systématique et une méta-analyse.

Sources des données : Une recherche systématique de la littérature a été menée dans plusieurs bases de données électroniques (PubMed, Scopus et le Cochrane Central Register of Controlled Trials) et dans les référentiels de prépublications, sans restrictions linguistiques, pour identifier les études pertinentes publiées jusqu'au 31 décembre 2023.

Sélection des études et extraction des données : Le principal résultat d'intérêt était la mortalité, toutes causes confondues. Des essais contrôlés randomisés (ECR) portant sur l'administration d'inhibiteurs de JAK chez des patients atteints de COVID-19 ont été inclus.

Synthèse des données : Grâce à la recherche documentaire systématique, un total de 20 ECR répondant aux critères d'inclusion ont été identifiés. Un modèle à effets aléatoires a été utilisé pour estimer le rapport de cotes groupé de décès avec l'administration d'un inhibiteur de JAK par rapport à la non-administration d'un tel agent, avec un intervalle de confiance de 95 %. La méta-analyse de ces essais a révélé une réduction significative de la mortalité chez les patients atteints de COVID-19 ayant reçu des inhibiteurs de JAK par rapport à ceux n'ayant pas reçu ces agents (rapport de cotes groupé 0,70, intervalle de confiance à 95 % 0,58-0,84).

Conclusions : Les résultats de cette revue systématique et méta-analyse indiquent que les inhibiteurs de JAK, en particulier le baricitinib, pourraient répondre au besoin urgent de traitements efficaces dans le cadre de la pandémie de COVID-19 en cours en réduisant le risque de décès parmi les patients touchés. Cependant, des recherches supplémentaires, y compris des ECR à plus grande échelle, sont nécessaires pour établir l'efficacité et l'innocuité d'autres inhibiteurs de JAK dans le traitement de la COVID-19 et pour générer des éléments probants plus solides concernant leur utilisation dans cette population de patients en particulier.

Mots-clés : baricitinib, COVID-19, inhibiteur de JAK, mortalité, ruxolitinib

INTRODUCTION

The Janus kinases (JAKs) encompass a group of protein tyrosine kinases that interact with the cytoplasmic domain of both type 1 and type 2 transmembrane cytokine receptors, facilitating signal transduction. Upon binding of a cytokine or growth factor ligand to its receptor, JAKs are activated and catalyze the phosphorylation of specific tyrosine residues on the receptor molecule. This phosphorylation event serves as a key trigger for downstream signalling events, leading to the activation and nuclear translocation of the signal transducer and activator of transcription (STAT) family of proteins. Once in the nucleus, activated STATs act as transcription factors, modulating the expression of target genes involved in diverse cellular processes. The JAK/STAT signalling pathway thus plays a pivotal role in mediating cytokine and growth factor–induced cellular responses, including immune regulation, hematopoiesis, and inflammation.[1]

The JAKs consist of 4 distinct isoforms: JAK1, JAK2, JAK3, and TYK2. Each isoform selectively associates with specific cytokine receptors, enabling cell signalling cascades. JAK1 is involved in the signalling of receptors activated by various interleukins (ILs) (IL-6, IL-10, IL-11, IL-19, IL-20, and IL-22), as well as interferons alfa, beta, and gamma.[2] JAK2 plays a crucial role in mediating cell signalling through receptors activated by hormone-like cytokines, including granulocyte–macrophage colony-stimulating factor (GM-CSF).[3] JAK3 is primarily responsible for facilitating cell signalling by means of receptors activated by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.[4] In contrast, TYK2 can associate with JAK1, JAK2, or another TYK2 molecule, participating in the cell signalling of receptors activated by IL-12, IL-23, and type 1 interferons.[5] Through their specific pairings with cytokine receptors, these JAK isoforms contribute to diverse cellular signalling processes and mediate crucial immune responses.

In the context of COVID-19, the JAK/STAT pathway is a crucial aspect of its immune response. It becomes particularly significant when a dysregulated immune response, known as a cytokine storm, occurs.[6] The JAK/STAT pathway is responsible for transmitting signals from cytokines released during the infection, leading to the activation of immune responses and inflammation. Overactivation of this pathway can contribute to the severe inflammation and tissue damage seen in some cases of COVID-19, making it a potential therapeutic target for managing the disease.[7] Given the substantial involvement of the JAK/STAT signalling pathway in the pathophysiology of COVID-19, there has been growing interest in exploring JAK inhibitors as potential therapeutic agents for this disease. Baricitinib, ruxolitinib, and tofacitinib are among the JAK inhibitors that have been repurposed for the treatment of COVID-19.[8] Multiple randomized controlled trials (RCTs) have been conducted to assess the efficacy of JAK inhibitors in COVID-19 treatment.

In this systematic review and meta-analysis of RCTs, our objective was to provide a comprehensive summary of the overall therapeutic efficacy of JAK inhibitors in the management of COVID-19, while critically evaluating the available evidence. Importantly, this work offers new perspectives on the efficacy of JAK inhibitors in COVID-19 treatment by including RCTs not analyzed in earlier reviews. We deliberately excluded observational studies from our analysis, such that our study focused exclusively on RCTs. We adopted this approach to ensure a higher level of evidence consistency and to generate a more robust and reliable understanding of the therapeutic potential of JAK inhibitors in the management of COVID-19.

METHODS

This study was conducted according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (https://www.prisma-statement.org/). The systematic literature search was conducted by 2 independent investigators (C.S.K., S.S.H.), who rigorously explored multiple scholarly databases, specifically PubMed, Scopus, and the Cochrane Central Register of Controlled Trials, as well as preprint repositories, specifically SSRN and medRxiv. The search, which encompassed the entire available literature up to December 31, 2023, employed a comprehensive set of carefully selected keywords and medical subject headings (MeSH): "COVID-19", "SARS-CoV-2", "novel coronavirus disease", "JAK inhibitor", "ruxolitinib", "baricitinib", "tofacitinib", "pacritinib", "upadacitinib", "filgotinib", "peficitinib", "TD-0903", "randomized", "controlled trial", and "clinical trial". Additionally, we examined the ClinicalTrials.gov registry to identify any ongoing clinical trials investigating the use of JAK inhibitors in the treatment of COVID-19 and reviewed the results available from these trials.

The 2 investigators (C.S.K., S.S.H.) independently screened the retrieved references on the basis of study titles and abstracts. Articles that appeared potentially eligible underwent a full-text review. Disagreements during the screening process were resolved through discussions with the third investigator (D.S.R.) until consensus was reached.

For inclusion in the analysis, we considered RCTs evaluating mortality outcomes in hospitalized patients with COVID-19 and comparing the use of JAK inhibitors with non-use of JAK inhibitors. Nonrandomized trials and single-arm trials were excluded.

The primary outcome of interest was all-cause mortality. Both investigators (C.S.K., S.S.H.) independently assessed each included study and extracted relevant characteristics. The risk of bias in the included trials was evaluated using version 2 of the Cochrane risk-of-bias tool for RCTs (RoB 2).[9]

The meta-analysis was conducted using the random-effects model to estimate the pooled odds ratio for all-cause mortality, comparing the use of JAK inhibitors with non-use of JAK inhibitors. The analysis generated 95% confidence intervals to assess the precision of the findings. Heterogeneity among the included studies was evaluated using I^2 statistics and the χ^2 test, with significant heterogeneity defined as I^2 greater than 50% and a p value less than 0.10, respectively. All statistical computations were performed using Meta XL software, version 5.3 (EpiGear International).

RESULTS

Our systematic literature searches yielded a total of 1599 hits, from which 975 unique articles were identified after initial screening. Of these, 20 RCTs met the inclusion criteria and were included in our analysis.[10-29] Appendix 1 presents a visual representation of the study selection process, outlining the flow of studies from initial retrieval to final inclusion. Among these trials, 8 were conducted in multiple countries,[11,12,14,16,17,20,21,28] whereas each of the remaining trials was conducted in a single country, specifically Brazil,[15] China,[13] the United States,[18,23] the United Kingdom,[10,19] Spain,[22,24,25] Iran,[26] Greece,[27] and Italy.[29]

Table 1 presents an overview of the characteristics of the included RCTs and the comprehensive evaluation of overall risk of bias according to the RoB 2 tool. Detailed information on the risk associated with each domain can be found in Appendix 2. Among the analyzed trials, 10 exhibited a low risk of bias across all evaluated domains.[11,12,15,16,18,20,21,23,28,29] However, the remaining 10 trials raised some concerns in terms of the overall risk of bias.[10,13,14,17,19,22,24-27]

The 20 included trials each used a different JAK inhibitor for treatment. In 11 trials,[10-12,16,19,20,22,24,26-28] baricitinib was administered orally at a daily dose of 4 mg for up to 14 days or until hospital discharge. Four trials[13,17,18,25] involved oral administration of ruxolitinib at a dose ranging from 5 to 15 mg twice daily for 14 days. Two trials[14,21] employed nezulcitinib, which was administered by inhalation at various doses (1 mg, 3 mg, or 10 mg) once daily for up to 7 days. In 2 trials,[15,29] tofacitinib was administered orally at a dose of 10 mg twice daily for up to 14 days or until hospital discharge. In the trial reported by Cafardi and others,[23] pacritinib was administered orally at a dose of 200 mg twice daily for 14 days.

The meta-analysis of the 20 included trials[10-29] yielded compelling evidence to support the use of JAK inhibitors in reducing the risk of death among patients with COVID-19. The pooled odds ratio (Figure 1) showed a significant and favourable effect (odds ratio 0.72, 95% confidence interval [CI] 0.60–0.87), indicating a substantial mortality benefit associated with JAK inhibitor treatment. These findings provide robust evidence to reject the null hypothesis of no significant difference in mortality outcomes, considering the available sample size.

The subgroup analysis specifically focusing on the 11 trials that investigated the use of baricitinib[10-12,16,19,20,22,24,26-28] revealed a notable reduction in mortality rates (Figure 1; pooled odds ratio 0.75, 95% CI 0.63–0.90) relative to those who did not receive baricitinib. These findings provide robust evidence supporting the conclusion that the administration of baricitinib is associated with a significant decrease in mortality among patients with COVID-19. Conversely, the subgroup analysis of the 4 trials[13,17,18,25] that used ruxolitinib showed a trend toward lower mortality rates (Figure 1; pooled odds ratio 0.69, 95% CI 0.27–1.75) compared with non-administration of ruxolitinib, although the evidence did not reach statistical significance at the current sample size.

DISCUSSION

The mortality benefits observed in patients with COVID-19 treated with JAK inhibitors may be attributed to the ability of these agents to prevent the phosphorylation of key cytokines involved in the inflammatory signalling pathway. For example, baricitinib reversibly inhibits JAK1 and JAK2, moderately inhibits TYK2, and modestly inhibits JAK3 (and can thus be considered a pan-JAK inhibitor).[30] This inhibitory action allows for the inhibition of cytokines such as IL-6, IL-10, IL-2, IL-7, and GM-CSF, which are implicated in the cytokine storm that may be observed in COVID-19. In contrast, tofacitinib, another pan-JAK inhibitor, reversibly inhibits JAK1 and JAK3 and to a lesser extent inhibits JAK2 and TYK2, thereby inhibiting the signalling of cytokines IL-2, IL-7, IL-6, and IL-10.[31] Ruxolitinib acts as a JAK1/2 inhibitor, inhibiting the signalling of cytokines such as IL-6, IL-10, and GM-CSF.[32] Pacritinib, a selective JAK2 inhibitor, inhibits GM-CSF signalling. The inhaled JAK inhibitor TD-0903 is designed to target all JAK isoforms (JAK1, JAK2, JAK3, TYK2).[14]

The mortality benefits of JAK inhibitors may also be attributed to their antiviral properties. Baricitinib, in particular, exhibits high-affinity inhibition of numb-associated kinases—AP2-associated protein kinase 1 and cyclin G-associated kinase—which are crucial regulators of clathrin-mediated viral endocytosis.[33] This inhibition may prevent the entry of SARS-CoV-2 into alveolar type II epithelial cells. Notably, this specific mechanism is unique to baricitinib among the JAK inhibitors, explaining why the mortality benefits were not observed with other JAK inhibitors in our analysis.

In terms of safety, the trials included in our analysis did not reveal notable risks of co-infections or venous thromboembolism associated with the short-term use of JAK inhibitors in patients with COVID-19. However, the relatively small sample sizes of these trials may have limited the

TABLE 1 (part 1 of 3). Characteristics of Included Studies

Study (Year)	Design	Country	Age (Years) (Median or Mean)	Severity of COVID-19	JAKi Regimen (Intervention)	Comparator Regimen (Control)	Morality Events (*n*/*N*, %)		Risk of Bias[a]
							JAKi Users	Non–JAKi Users	
Hall et al. (2023)[10]	Randomized controlled, open-label trial	United Kingdom	JAKi users: 61.4 Non-JAKi users: 59.9	Moderate to severe	Baricitinib (4 mg once daily orally for up to 14 days or until hospital discharge) + standard of care	Standard of care (corticosteroids, remdesivir, interleukin-6 receptor blocker)	24/137 (17.5)	21/145 (14.5)	Some concerns
Marconi et al. (2021)[11]	Randomized, double-blind, placebo-controlled trial	Global (12 countries)	JAKi users: 57.8 Non-JAKi users: 57.5	Severe (requirement for baseline oxygen support or non-invasive ventilation but not invasive ventilation)	Baricitinib (4 mg once daily orally for up to 14 days or until hospital discharge) + standard of care	Placebo + standard of care (remdesivir, corticosteroids)	62/764 (8.1)	100/761 (13.1)	Low
Kalil et al. (2021)[12]	Randomized, double-blind, placebo-controlled trial	Global (8 countries)	JAKi users: 55.0 Non-JAKi users: 55.8	Moderate to severe	Baricitinib (4 mg once daily orally for up to 14 days or until hospital discharge) + remdesivir	Placebo + remdesivir (200 mg loading dose on day 1, followed by 100 mg once daily on days 2 through 10 or until hospital discharge or death)	24/515 (4.7)	37/518 (7.1)	Low
Cao et al. (2020)[13]	Randomized, single-blind, placebo-controlled trial	China	JAKi users: 63.0 Non-JAKi users: 64.0	Severe (requirement for baseline oxygen support or non-invasive ventilation but not invasive ventilation)	Ruxolitinib (5 mg twice daily orally); duration not specified	Vitamin C 100 mg twice daily orally + standard of care (umifenovir/oseltamivir, antibiotics, corticosteroids)	0/20 (0)	3/21 (14.3)	Some concerns
Singh et al. (2021)[14]	Randomized, double-blind, placebo-controlled trial	Global (3 countries)	JAKi users: 52.8 (10-mg arm) to 62.0 (3-mg arm) Non-JAKi users: 54.2	Severe (requirement for supplemental oxygen to maintain $SpO_2 > 90\%$)	Nezulcitinib (1 mg, 3 mg, or 10 mg once daily by inhalation for up to 7 days; loading doses administered on day 1 for 2 lowest maintenance doses [1 and 3 mg])	Placebo	1/19 (5.3)	2/6 (33.3)	Some concerns
Guimarães et al. (2021)[15]	Randomized, double-blind, placebo-controlled trial	Brazil	JAKi users: 55.0 Non-JAKi users: 57.0	Moderate to severe	Tofacitinib (10 mg orally twice daily for up to 14 days or until hospital discharge) + standard of care	Placebo + standard of care (corticosteroids, antibiotics, anticoagulants, oseltamivir)	4/144 (2.8)	8/145 (5.5)	Low
Ely et al. (2022)[16]	Randomized, double-blind, placebo-controlled trial	Global (4 countries)	JAKi users: 58.4 Non-JAKi users: 58.8	Severe (requirement for invasive mechanical ventilation or extracorporeal membrane oxygenation)	Baricitinib (4 mg once daily orally for up to 14 days or until hospital discharge) + standard of care	Placebo + standard of care (corticosteroids, antivirals, vasopressors)	20/51 (39.2)	29/50 (58.0)	Low

TABLE 1 (part 2 of 3). Characteristics of Included Studies

Study (Year)	Design	Country	Age (Years) (Median or Mean)	Severity of COVID-19	JAKi Regimen (Intervention)	Comparator Regimen (Control)	Morality Events (*n*/*N*, %)		Risk of Bias[a]
							JAKi Users	Non–JAKi Users	
Han et al. (2022)[17]	Randomized, double-blind, placebo-controlled trial	Global (12 countries)	JAKi users: 56.4 Non-JAKi users: 56.9	Moderate to severe	Ruxolitinib (5 mg twice daily orally for 14 days) + standard of care	Placebo + standard of care (antivirals, corticosteroids, heparin, anticoagulants, antiemetics, calcineurin inhibitors, azole fungal prophylaxis, broad-spectrum antibiotics, narcotics, and sedatives)	9/286 (3.1)	3/145 (2.1)	Some concerns
Rein et al. (2022)[18]	Randomized, double-blind, placebo-controlled trial	United States	JAKi users: 63.6 Non-JAKi users: 62.5	Severe (requirement for mechanical ventilation)	Ruxolitinib (5 mg or 15 mg twice daily orally for 14 days) + standard of care	Standard of care	84/164 (51.2)	33/47 (70.2)	Low
RECOVERY (2022)[19]	Randomized controlled, open-label trial	United Kingdom	JAKi users: 58.5 Non-JAKi users: 57.7	Any severity	Baricitinib (4 mg once daily orally for up to 10 days or until hospital discharge) + standard of care	Standard of care (antivirals, corticosteroids, hydroxychloroquine, antibiotics, tocilizumab/ sarilumab, ASA, colchicine, casirivimab+imdevimab)	513/4148 (12.4)	546/4008 (13.6)	Some concerns
Trøseid et al. (2023)[20]	Randomized, double-blind, placebo-controlled trial	Global (10 countries)	JAKi users: 59.0 Non-JAKi users: 60.0	Severe (SpO_2 < 90% on room air, SpO_2 90%–94% with a downward trend and/or signs of respiratory distress, need for oxygen by non-invasive ventilation/ continuous positive airway pressure, high-flow oxygen or non-rebreather mask, or need for mechanical ventilation or extracorporeal membrane oxygenation)	Baricitinib (4 mg once daily orally for up to 14 days or until hospital discharge) + standard of care	Placebo + standard of care	14/139 (10.1)	18/136 (13.2)	Low
Belperio et al. (2023)[21]	Randomized, double-blind, placebo-controlled trial	Global (7 countries)	Not reported	Severe (requirement for supplemental oxygen to maintain SpO_2 > 90%)	Nezulcitinib (6 mg loading dose, followed by 3 mg once daily by inhalation for up to 7 days)	Placebo	6/106 (5.7)	13/104 (12.5)	Low
Montejano et al. (2023)[22]	Randomized controlled, open-label trial	Spain	JAKi users: 68.0 Non-JAKi users: 67.0	Moderate to severe (SpO_2 < 95% with increase in at least one inflammatory biomarker)	Baricitinib (4 mg once daily orally for up to 14 days) + dexamethasone	Dexamethasone	3/145 (2.1)	7/142 (4.9)	Some concerns

TABLE 1 (part 3 of 3). Characteristics of Included Studies

Study (Year)	Design	Country	Age (Years) (Median or Mean)	Severity of COVID-19	JAKi Regimen (Intervention)	Comparator Regimen (Control)	Morality Events (*n*/*N*, %)		Risk of Bias[a]
							JAKi Users	Non–JAKi Users	
Cafardi et al. (2022)[23]	Randomized, double-blind, placebo-controlled trial	United States	JAKi users: 60.0 Non-JAKi users: 59.0	Severe (almost all participants required oxygen support)	Pacritinib (400 mg orally on day 1 followed by 200 mg twice daily orally on days 2 through 14) + standard of care	Placebo + standard of care (corticosteroids, anticoagulants/ antiplatelets)	10/99 (10.1)	8/101 (7.9)	Low
Morales-Ortega et al. (2023)[24]	Randomized controlled, open-label trial	Spain	JAKi users: 55.5 Non-JAKi users: 53.7	Any severity	Baricitinib (4 mg once daily orally for 7 days) + standard of care	Standard of care (antipyretics, antibiotics, subcutaneous low-molecular-weight heparin)	0/55 (0)	2/55 (3.6)	Some concerns
Garcia-Donas et al. (2023)[25]	Randomized controlled, open-label trial	Spain	JAKi users: 62.0 Non-JAKi users: 67.0	Mild	Ruxolitinib (5 mg twice daily for 7 days, followed by 10 mg twice daily for 7 days) + standard of care	Standard of care (corticosteroids, tocilizumab, heparin)	2/46 (4.3)	1/46 (2.2)	Some concerns
Dastan et al. (2023)[26]	Randomized controlled, open-label trial	Iran	JAKi users: 69.2 Non-JAKi users: 61.3	Severe	Baricitinib (4 mg once daily orally for 14 days) + tocilizumab	Tocilizumab	0/34 (0)	2/34 (5.9)	Some concerns
Karampitsakos et al. (2023)[27]	Randomized controlled, open-label trial	Greece	JAKi users: 73.0 Non-JAKi users: 72.0	Severe ($PaO_2/FiO_2 < 200$)	Baricitinib (4 mg once daily orally for 14 days)	Tocilizumab	40/125 (32.0)	50/126 (39.7)	Some concerns
Wolfe et al. (2022)[28]	Randomized, double-blind, placebo-controlled trial	Global (5 countries)	JAKi users: 58.2 Non-JAKi users: 58.5	Severe (requirement for baseline oxygen support or non-invasive ventilation but not invasive ventilation)	Baricitinib (4 mg once daily orally for 14 days) + remdesivir	Dexamethasone + remdesivir	27/516 (5.2)	30/494 (6.1)	Low
Ferrarini et al. (2023)[29]	Randomized controlled, open-label trial	Italy	JAKi users: 60.5 Non-JAKi users: 57.9	Mild to moderate	Tofacitinib (10 mg orally twice daily for up to 14 days or until hospital discharge) + standard of care	Standard of care (dexamethasone, remdesivir, heparin)	1/58 (1.7)	0/58 (0)	Low

ASA = acetylsalicylic acid, JAKi = Janus kinase inhibitor, PaO_2/FiO_2 = ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen, SpO_2 = oxygen saturation.
[a]Risk of bias determinations are detailed in Appendix 2.

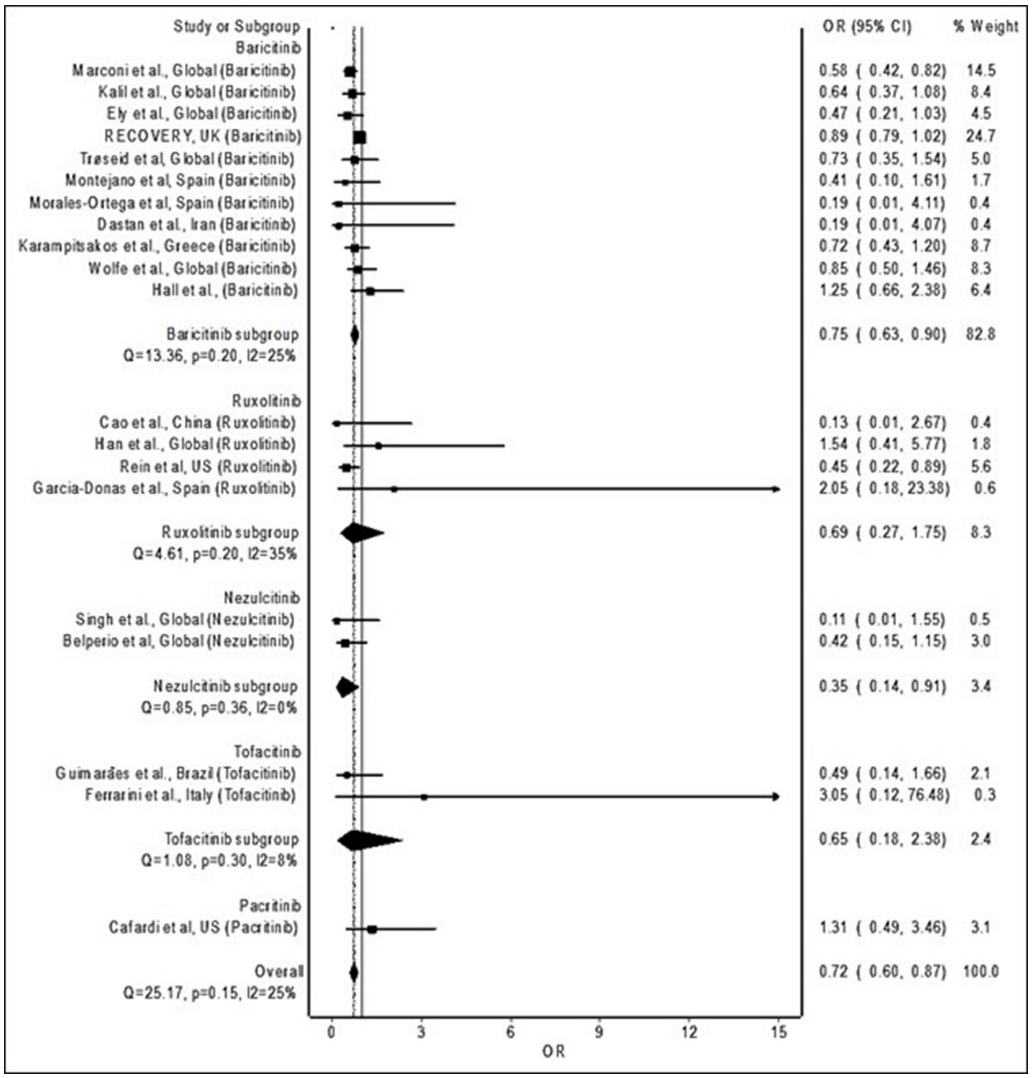

FIGURE 1. Pooled odds ratio (OR) for death with administration of Janus kinase (JAK) inhibitors relative to non-administration of JAK inhibitors in patients with COVID-19. CI = confidence interval.

detection of such adverse effects. Additionally, increased transaminase levels were observed in higher proportions of patients treated with ruxolitinib (35.0% vs 9.5%)[13] and tofacitinib (4.9% vs 2.8%)[15] relative to controls, which indicates a need for periodic monitoring of liver function.

CONCLUSION

These findings suggest that JAK inhibitors, especially baricitinib, may address the significant unmet needs in the current pandemic by reducing the risk of death in patients with COVID-19. However, larger-scale RCTs are needed to establish the efficacy and safety of other JAK inhibitors in this patient population before widespread recommendations can be made.

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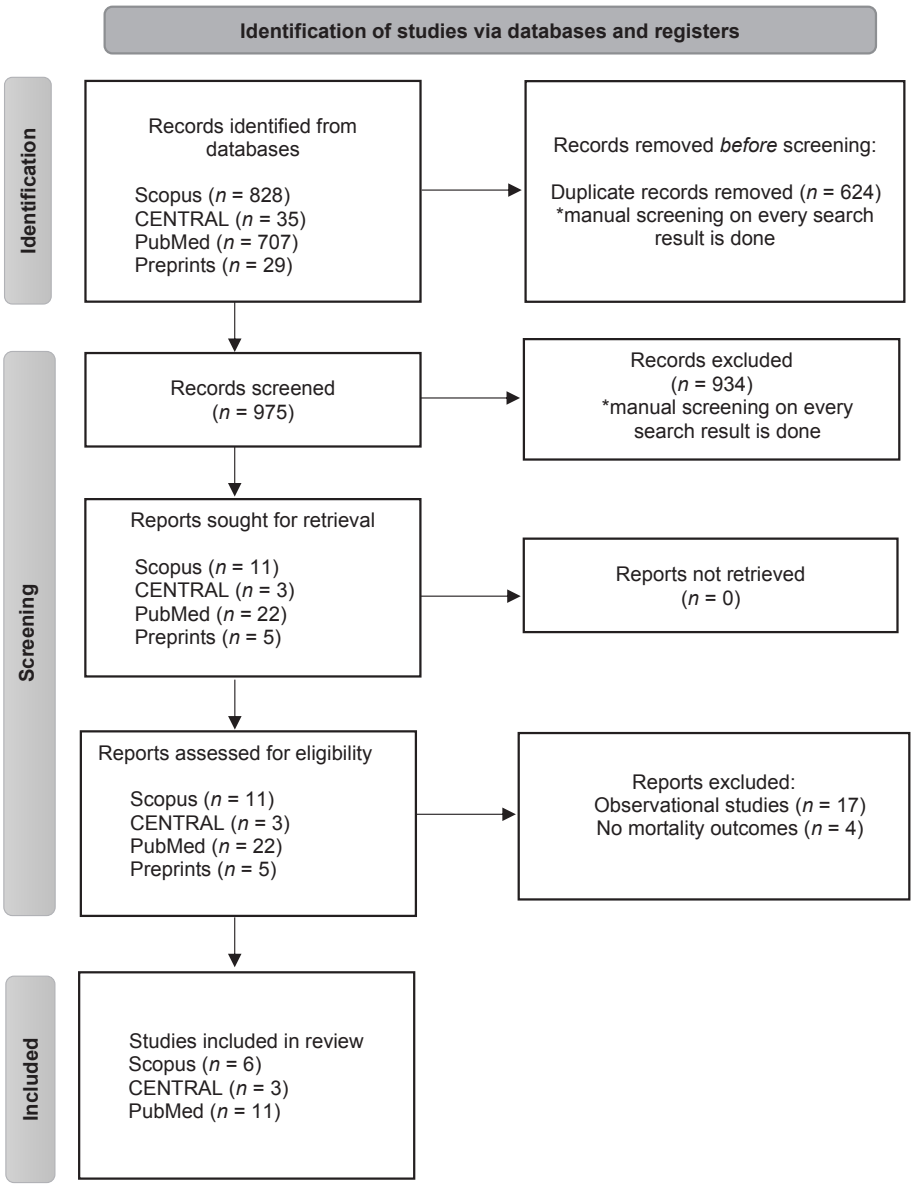
APPENDIX 1: Flow diagram of study selection.



APPENDIX 2: Risk of bias of included trials (see main article for reference list).

	Potential Source of Bias					
Study	Randomization	Deviations from Intervention	Missing Outcome Data	Measurement of Outcome	Selection of Reported Results	Overall Risk of Bias
Hall et al. (2023)[10]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Marconi et al. (2021)[11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kalil et al. (2021)[12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cao et al. (2020)[13]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Singh et al. (2021)[14]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Guimarães et al. (2021)[15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ely et al. (2022)[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Han et al. (2022)[17]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Rein et al. (2022)[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
RECOVERY (2022)[19]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Trøseid et al. (2023)[20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Belperio et al. (2023)[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Montejano et al. (2023)[22]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Cafardi et al. (2022)[23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Morales-Orgega et al. (2023)[24]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Garcia-Donas et al. (2023)[25]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Dastan et al. (2023)[26]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Karampitsakos et al. (2023)[27]	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns
Wolfe et al. (2022)[28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ferrarini et al. (2023)[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk