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.

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Original article

The use of Janus Kinase inhibitors in hospitalized patients with COVID-19: Systematic review and meta-analysis

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ABSTRACT

Background: The evidence of using JAK inhibitors among hospitalized patients with COVID-19 is conflicting. The systematic review and meta-analysis aimed to address the efficacy of Janus Kinase (JAK) Inhibitors in reducing risk of mortality among hospitalized patients with COVID-19.

Methods: Several electronic databases, including PubMed, EuropePMC, and the Cochrane Central Register of Controlled Trials, with relevant keywords "COVID-19″ AND ("JAK inhibitor" OR "Ruxolitinib" OR "Tofacitinib" OR "Fedratinib" OR "Baricitinib") AND ("Severe" OR "Mortality"), were used to perform a systematic literature search up to December 11, 2020. All studies pertinent to the predetermined eligibility criteria were included in the analysis. Our outcome of interest was all types of mortality, clinical improvement, and clinical deterioration. Dichotomous variables of our outcomes of interest were analyzed using Maentel-Haenszel formula to obtain odds ratios (ORs) and 95% confidence intervals (CI) with random-effects modeling regardless of heterogeneity.

Results: Five studies with a total of 1190 patients and were included in this systematic review and meta-analysis. The use of JAK inhibitors was associated with a reduced risk of mortality (OR 0.51, 95% CI 0.28–0.93, P = 0.02; I^2: 7.8%, P = 0.354) and clinical improvement (OR 1.76, 95% CI 1.05–2.95, P = 0.032; I^2: 26.4%, P = 0.253). The use of JAK inhibitors was not associated with a reduced risk of clinical deterioration (OR 0.58, 95% CI 0.28–1.19, P = 0.136; I^2: 24.1%, P = 0.267).

Conclusion: The use of JAK inhibitors was significantly associated with a reduced risk of mortality, and clinical improvement in hospitalized patients with COVID-19.

1. Introduction

Although the advent of promising COVID-19 vaccine seems could end this catastrophe by developing antibodies to prevent COVID-19 infection, treatment options for hospitalized patients with COVID-19 are still urgently needed to be addressed,[1] especially in high-risk patients who are at greater risk of developing severe or critical COVID-19.[2–4] The only effective treatment for severe COVID-19 by far is dexamethasone,[5] while others turn out to be inconclusive and might be inefficacious.[6]

Hyperinflammatory state induced by severe COVID-19, which is characterized by massive cytokine release and increased of pro-inflammatory markers, is a critical condition that may culminate into acute respiratory distress syndrome (ARDS), fatal thrombosis, and multi-organ failure.[7–9] Drugs that act to inhibit cytokine production are proposed to be beneficial in rescuing immense cytokine derangements in

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severe COVID-19. Janus Kinase (JAK) inhibitors presents as attractive therapeutic strategy, as this type of medication could deter intracellular signalling pathway in cytokine productions.

The evidence of using JAK inhibitors among hospitalized patients with COVID-19 is conflicting. Ruxolitinib, one of the JAK inhibitors, has previously been reported in a non-randomized trial to be efficacious in reducing mortality among hospitalized patients with severe COVID-19.[10] D'Alessio et al. showed significantly higher overall survival among COVID-19 patients receiving ruxolitinib [Hazard ratio (HR) for overall survival 4.65, 95% CI 1.65–12.7; p = 0.0034].[10] Remarkably, Kalil et al. reported insignificant mortality reduction using a combination of JAK inhibitors with remdesivir in a multi-center randomized controlled trial (HR 0.65; 95% CI, 0.39–1.09); though, accelerated clinical improvement was documented [Odds ratio (OR) 1.3; 95% CI, 1.0–1.6].[11] Therefore, this systematic review was aimed to assess the efficacy of JAK inhibitors in terms of clinical outcome, including mortality, clinical improvement, and clinical deterioration among hospitalized COVID-19 patients.

2. Methods

The protocol of this study is registered in PROSPERO (CRD42021228844).

2.1. Study eligibility criteria

The inclusion criteria were as follows: (1) Experimental studies (either non-randomized or randomized studies), (2) in hospitalized adults patients (>18 years old) with confirmed COVID-19 based on reverse transcriptase - polymerase chain reaction (RT-PCR) test, and (3) receiving JAK inhibitors (either ruxolitinib, tofacitinib, fedratinib, or baricitinib), and (4) with our clinical outcomes of interest. Our main outcome of interest was all types of mortality, including in-hospital mortality and 14- or 28-days (30-days) mortality. Additional secondary outcome were clinical improvement and clinical deterioration. Clinical improvement was defined as being discharged or reduction of oxygen requirements after the last treatment dose. Clinical deterioration was defined as intensive care unit (ICU) admission, new use of invasive mechanical ventilation (MV), and or extra-corporeal membrane oxygenation (ECMO). Observational studies and research on pediatric patients (<18 years old) were excluded from this study.

2.2. Search strategy

Several electronic databases, including PubMed, EuropePMC, and the Cochrane Central Register of Controlled Trials, with relevant keywords "COVID-19″ AND ("JAK inhibitor" OR "Ruxolitinib" OR "Tofacitinib" OR "Fedratinib" OR "Baricitinib") AND ("Severe" OR "Mortality"), were used to perform a systematic literature search from the date of inception up to December 11, 2020. Any duplicate records were removed after obtaining the initial results. By screening the title and abstracts, potential articles were then sorted. Afterwards, the full texts of the remaining articles were assessed for relevance based on eligibility criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was carried out as the core protocol in this study.

2.3. Data collection and risk of bias assessment

Three authors independently performed a systematic search of studies, assessed study inclusion, extracted data, and assessed risk of bias. A pre-built form was used by the authors for data collection, including name of authors, study design and location, total samples, age, intervention, outcome, and key findings of the study. Randomized controlled trials (RCT) were assessed using Cochrane risk-of-bias tool for randomized trials (RoB 2),[12] while ROBINS-I tool was used for non-randomized experimental studies.[13] Rob 2 is a risk of bias tool which assess bias in RCT based on several domains, including bias due to randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and reporting bias.[12] The ROBINS-I tool also measures risk of bias in multi-dimensional approach which includes bias in confounding factors, selection bias, bias in measurement of intervention, bias in deviations from intervention, missing data, bias in measurement of outcome, and reporting bias.[13] Any results disagreement between authors will be determined through discussion.

2.4. Data synthesis and statistical analysis

Meta-analysis of included studies was conducted using STATA 16 (StataCorp LLC, Texas, US). Dichotomous variables of our outcomes of interest were analyzed using Maentel-Haenszel formula to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Random-effects models were used for pooled analysis regardless of heterogeneity. P values were two-tailed, and statistical significance was set at ≤ 0.05. Heterogeneity between studies was analyzed using I^2 (I^2) statistics with a value of >50% or *P*-values <0.10 suggesting significant heterogeneity. Small study effects were assessed with Egger test.

3. Results

3.1. Study selection and characteristics of included studies

There were 1470 records from our initial searches, which was reduced to 1395 after duplicates removal. We excluded 1376 records after title and abstract screening. After assessing 19 full-texts of the remaining articles for eligibility, 14 articles were excluded from the final analysis. The exclusion were due to observational studies (n = 4), case reports (n = 5), review articles (n = 4), and not reporting the use of JAK inhibitors (n = 1). Thereby, five studies with a total of 1190 patients included in this systematic review and meta-analysis [Fig. 1].[10,11,14–16] Three studies were considered non-randomized experimental studies, while the remaining were RCTs. Ruxolitinib and baricitinib were the only JAK inhibitors used in these trials. The characteristics of the included studies are shown in Table 1.

3.2. JAK inhibitors, mortality, and clinical improvement

The use of JAK inhibitors was associated with a reduced risk of mortality (OR 0.51, 95% CI 0.28–0.93, P = 0.02; I^2: 7.8%, P = 0.354) [Fig. 2] and clinical improvement (OR 1.76, 95% CI 1.05–2.95, P = 0.032; I^2: 26.4%, P = 0.253) [Fig. 3]. Significantly reduced serum C-reactive protein levels after JAK inhibitors administration were reported in two studies.[10,15] Moreover, significantly faster time to lymphocyte recovery and higher percentage of CT Scan improvement after treatment were seen in the other study.[14]

3.3. JAK inhibitors and clinical deterioration

The use of JAK inhibitors was not associated with a reduced risk of clinical deterioration (OR 0.58, 95% CI 0.28–1.19, P = 0.136; I^2: 24.1%, P = 0.267) [Fig. 4].

3.4. JAK inhibitors and secondary infection

There were no incidence of new infection or secondary infection among patients receiving JAK inhibitors in three studies.[10,14,15] Remarkably, Kalil et al. reported higher incidence of new infection in patients not receiving JAK Inhibitors (5.9% vs 11.2%, Mean Diff −5.3%; 95% CI -8.7 to −1.9; P = 0.003),[11] which was similarly reported by Cao et al. (9.5% vs 0%).[14]

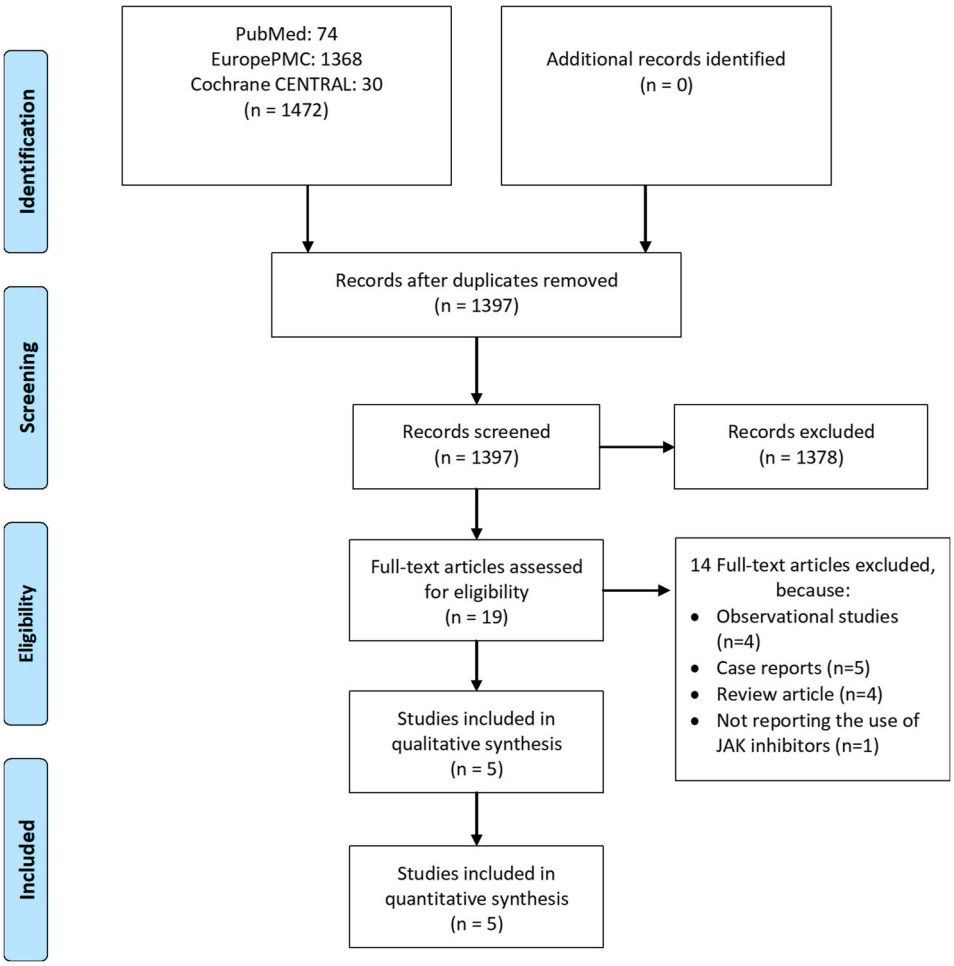

Fig. 1. Study flow diagram.

3.5. Risk of bias

Two of the non-randomized trials were assessed with serious overall risk of bias, which mainly owing to the domain of bias due to deviation from intended interventions. One of the RCT was considered low risk of bias, while some concern in the risk of bias was considered in the other study due to non-blinded measurements of outcome by the treating physician. The risks of bias of the included studies were depicted in Tables 2 and 3. The small study effects, as shown by the Egger test, were not significant for mortality, clinical improvement, and clinical deterioration (P = 0.812, P = 0.580, and P = 0.645), respectively.

4. Discussion

This current meta-analysis of experimental studies showed that the use of JAK inhibitors was significantly associated with a reduced risk of mortality, and clinical improvement in hospitalized patients with COVID-19. Overall, the safety consideration regarding secondary infection among patients receiving JAK inhibitors was not a concern in all studies. Our findings was supported by previous meta-analysis which reported a significantly lower odds of mortality among patients receiving JAK inhibitors (OR 0.12; 95% CI, 0.03–0.39; p = 0.0005).[17] The core difference between this study and the previous meta-analysis by Walz et al. was the inclusion of non-experimental studies. We only included experimental studies (non-observational) in order to provide stronger evidence. Despite the difference in study inclusion criteria, the findings of both studies supported the evidence in using JAK inhibitors among hospitalized patients with COVID-19, especially in terms of clinical improvement and reduction of mortality.

Interestingly, the use of JAK inhibitors was not significantly associated with a reduced risk of clinical deterioration which we defined as the ICU admission, new use of invasive MV, and or ECMO, in this study; though, the trend was toward a reduced risk. Hypothetically, this was due to the zero events in the specific outcome of intervention group in two studies. Further inclusion of RCT with higher samples and number of events and/or outcome might enlighten this issue.

The JAKs are families of receptor-associated tyrosine kinase comprising of JAK1, JAK2, JAK3, and tyrosine kinase-2 (TYK2).[18] They are all associated with a particular dependent cytokine such as IFN-a, IFN-b, IFN-g, IL-2, IL-4, IL-6, and IL-7 to activate signal transducer and activators of transcription (STATs).[18,19] Their pivotal role as signalling pathways in cellular survival, proliferation, differentiation, and immigration, provides an ideal therapeutic target for numerous immune, inflammatory, and hematopoietic diseases.[20] As of today, JAK inhibitors have been approved for wide range of diseases, including rheumatoid arthritis, psoriasis, atopic dermatitis, ulcerative colitis, myelofibrosis, polycythemia vera, and essential thrombocytosis.[21]

Several reports have suggested cytokine release syndrome or hypercytokinemia is associated with COVID-19 disease severity through the hyperinflammatory state.[8,22–24] A recent study from China had shown IL-6 as the predictor of fatality in COVID-19 patients, convincing that viral-induced hyper inflammation as the leading cause of mortality.[25,26] Numerous cytokines in COVID-19 patient use one discrete intracellular signalling pathway mediated by JAKs to confer multiple biological functions such as immune regulation, lymphocyte growth and differentiation, and oxidative stress.[27] Therefore, JAK inhibitors are

Table 1
Characteristics of included studies.

No	Authors	Study Design/ Location	Total Samples (Intervention vs Control)	Age (Mean or Median)	Intervention (JAK Inhibitors)	Outcome	Result/Key Findings (Intervention vs Control)	Secondary/New Infection (Intervention vs Control)	Overall Risk of Bias
1	D'Alessio et al.[10]	Non-randomized trial, single center, Italy	75 (32 vs 43) 100% Severe COVID-19	67.5 vs 67.8	Ruxolitinib 5 mg BID (7 days), then 5 mg OD (10 days) + Methylprednisolone 1 mg/kg IV (3 days), followed by 0.5 mg/kg IV (5 days), then oral prednisone (tapered over 2 weeks)	1. Clinical recovery without mechanical ventilation 2. Admission to ICU for MV 3. Death 4. Reduction of inflammatory response	**Clinically recovered:** 75% (24/32) vs 63% (27/43) **ICU (+MV):** 16% (5/32) vs 13.9% (6/43) **Mortality:** 9% (3/32) vs 30% (13/43) **Overall Survival:** HR 4.65 (95% CI 1.65–12.7; p = 0.0034) **Reduction Inflammatory Response:** 28/32 (87%) vs 10/43 (23%), p = 0.0001	None	Serious
2	Cantini et al.[15]	Non-randomized trial, single center, Italy	24 (12 vs 12) Moderate COVID-19 100%	63.5 vs 63	Baricitinib 4 mg/day (14 days)	1. Clinical and Laboratory parameters 2. Admission to ICU 3. Discharge at 14 days	**Clinical and Laboratory parameters:** Fever, SpO2, PaO2/FiO2, CRP, and MEWS significantly improved (p: 0.000; 0.000; 0.017; 0.023; 0.016, respectively). **Admission to ICU:** 0% (0/12) vs 33.3% (4/12), p = 0.093 **Discharge at 14 days:** 58% (7/12) vs 8% (1/12), p = 0.027	None	Serious
3	Giudice et al.[16]	Non-randomized trial, Single-Center, Italy	17 (7 vs 10) 100% Severe COVID-19	61 vs 63.5	Ruxolitinib 10 mg BID (14 days) + Eculizumab 900 mg IV (every 7 day, up to total 3 doses)	Clinical Outcome	**Laboratory parameters: PaO2/FiO2:** 370.5 vs 246 (p = 0.0395) **ARDS:** 14.2% (1/7) vs 40.0% (4/10) **Mortality:** 14.2% (1/7) vs 10% (1/10)	None	Serious
4	Cao et al.[14]	RCT, single-blind, Multi-center, China	41 (20 vs 21) 100% Severe COVID-19	63 vs 64	Ruxolitinib 5 mg BID	1. Time to clinical improvement 2. CT Scans Improvement on Day 14 3. Time to Lymphocyte recovery 4. Invasive MV 5. Mortality 6. Viral Clearance Time	**Time to clinical improvement:** 12 vs 15 days (p = 0.147) **Clinical improvement Day 14:** 60.0% (12/20) vs 42.9% (9/21) **Clinical Deterioration:** 0% vs 19.0% (4/21), p = 0.107 **CT Scan Improvement Day 14:** 90.0% (18/20) vs 61.9% (13/21) p = 0.0495 **Time to Lymphocyte Recovery:** 5 vs 8 days (p = 0.033) **Invasive MV:**	0% (0/20) vs (9.5%) 2/21	Some Concerns

(*continued on next page*)

Table 1 (*continued*)

No	Authors	Study Design/ Location	Total Samples (Intervention vs Control)	Age (Mean or Median)	Intervention (JAK Inhibitors)	Outcome	Result/Key Findings (Intervention vs Control)	Secondary/New Infection (Intervention vs Control)	Overall Risk of Bias
							0% vs 14.3% (3/21), p = 0.232 **Mortality:** 0% (0/20) vs 14.3% (3/21) p = 0.232) **Viral Clearance Time:** 13 vs 12 days (p = 0.649)		
5	Kalil et al.[11]	RCT, double blind, Multi-center (USA-Singapore-South Korea- Mexico, Japan, Spain, UK, Denmark)	1033 (515 vs 518) 31.7% Severe COVID-19	55.0 vs 55.8	Baricitinib 4 mg/day (14 days) 2 mg/day if eGFR <60	1. Time to recovery 2. Clinical Status at Day 15 3. Number of Days Supplemental O2 4. NIV or High Flow 5. Invasive MV or ECMO 6. Mortality 7. Adverse Events	**Median time to recovery and Clinical Recovery:** 7 vs 8 days, 84.1% (433/515) vs 78.4% (406/518), RR for recovery, 1.16; 95% CI 1.01–1.32; p = 0.03 Improvement in clinical status at day 15: OR 1.3; 95% CI, 1.0–1.6). **Supplemental Oxygen use:** 10 vs 12 days (MD -2.0 95% CI -5.2 to 1.2) **NIV or High Flow:** 4 vs 5 days (MD -1.0, 95% CI -2.9 to 0.9) **Invasive MV or ECMO:** (1) Duration of use 20 vs 25 days (MD -5.0, 95% CI -12.9 to 2.9) (2) New use 9.9% (46/461) vs 15.2% (70/461), RR 0.64, 95% CI 0.44 to 0.93) **28-day mortality:** 4.7% (24/515) vs 7.1% (37/518) HR 0.65; 95% CI, 0.39–1.09 **Serious Adverse Events:** 16.0% vs 21.0% (MD -5.0%; 95% CI, −9.8 to −0.3; p = 0.03)	5.9% (30/515) vs 11.2% (57/519), (MD -5.3%; 95% CI, −8.7 to −1.9; p = 0.003)	Low

JAK: Janus Kinase; RCT: Randomized Controlled Trials; ICU: Intensive Care Unit; MV: Mechanical Ventilation; NIV: Non-Invasive Ventilation; ECMO: Extra-Corporeal Membrane Oxygenation; SpO2: Oxygen Saturation; PaO2: Partial pressure of oxygen; FiO2: Fraction of oxygen; CRP: C-Reactive Protein; S: Modified Early Warning Score; HR: Hazard Ratio; OR: Odds Ratio; MD: Mean Difference; CI: Confidence Interval.

hypothetically capable in reducing the severity of hyperinflammatory state in COVID-19.

Among patients receiving ruxolitinib, the levels of seven cytokines—IL-6, nerve growth factor b, IL-12(p40), migration inhibitory factor, MIP-1a, MIP-1b, and VEGF—were significantly decreased in comparison to the control group.[14] Between these cytokines, IL-6 is the main proinflammatory cytokine which mediated organ dysfunction and tissue damage.[28] Targeting multiple pro-inflammatory pathways, rather than a single cytokine (e.g. IL-6), is theoretically attractive, as recent RCTs have shown unsatisfactory results of IL-6 inhibitor among hospitalized patients with COVID-19.[29,30] IL-12(p40), MIP-1a, and MIP-1b are important chemokines for recruiting activated monocytes/macrophages and other inflammatory cells to the site of infection.[31–33] VEGF plays a role in recruiting monocytes/macrophages and increasing capillary permeability syndrome that characterizes some types of viral pneumonia.[34] The inhibition of multiple pro-inflammatory cytokines in JAK inhibitors provides the rationalization of superiority in using this class of drug among hospitalized patients with COVID-19.

Baricitinib, another JAK inhibitors, can interfere with the cellular entry of SARS-CoV-2 through the inhibitory effects on the known endocytosis regulators such as AP2-associated protein kinase 1 and cyclin G-associated kinase.[35] Several studies have shown the safety and efficacy of baricitinib therapy in COVID-19 patients, with the improved clinical condition and minimal infections or hematologic adverse events.[15]

Hypothetically, anti-inflammatory drugs are beneficial in patients with COVID-19 patients only when given at the right time. An early administration could intensify viral replication, while a late treatment could worsen the immunological fatigue caused by the prolonged hypercytokinemia.[10] Siddiqi and Mehra have proposed three stages of

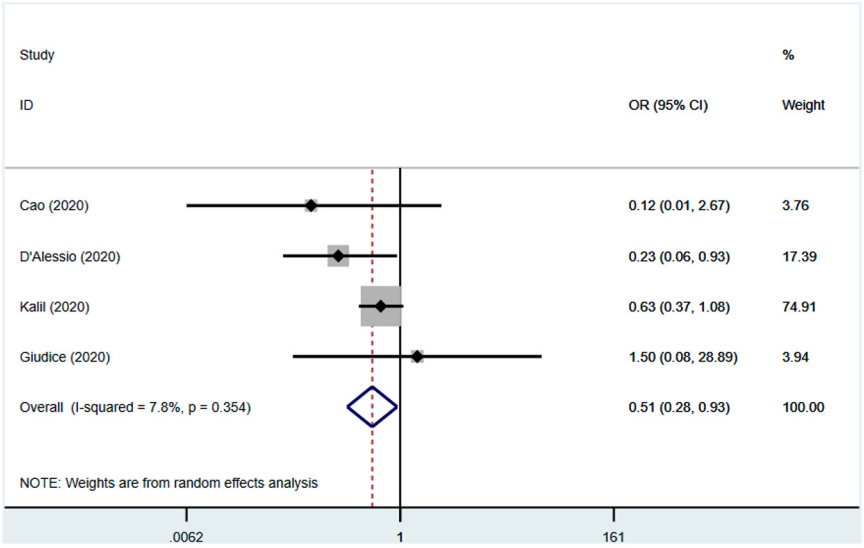

Fig. 2. Forest plot showing overall effect estimates of Janus Kinase inhibitors and risk of mortality. OR: Odds Ratio; CI: Confidence Interval.

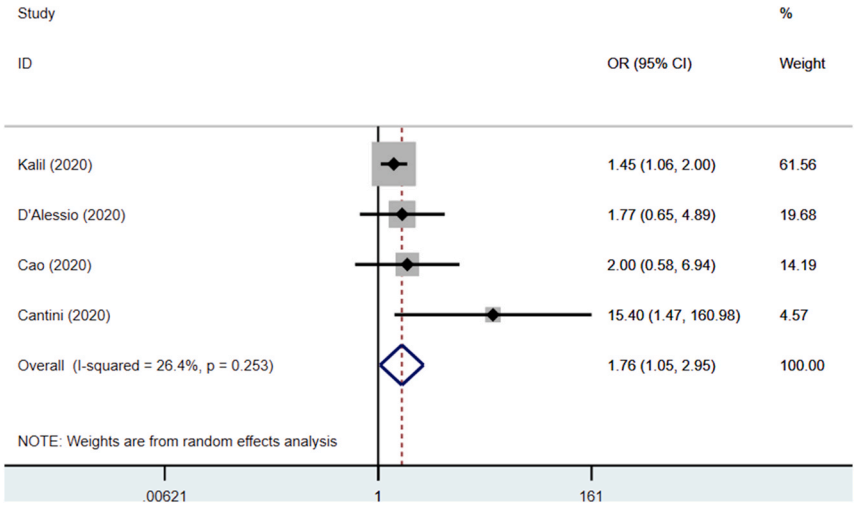

Fig. 3. Forest plot showing overall effect estimates of Janus Kinase inhibitors and risk of clinical improvement. OR: Odds Ratio; CI: Confidence Interval.

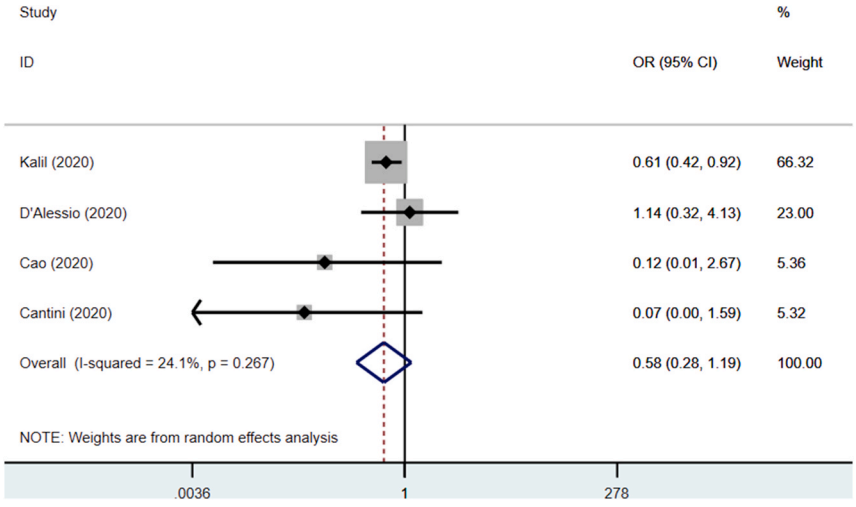

Fig. 4. Forest plot showing overall effect estimates of Janus Kinase inhibitors and risk of clinical deterioration. OR: Odds Ratio; CI: Confidence Interval.

Table 2
Risk of bias of randomized controlled trials.

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Cao et al.	Low	Low	Low	Some concerns	Low	Some concerns
Kalil et al.	Low	Low	Low	Low	Low	Low

Low risk of bias.
Some concerns.
High risk of bias.

Table 3
Risk of bias of non-randomized trials.

Study	Confounding	Selection	Measurement of intervention	Deviations from Intended Interventions	Missing Data	Measurement of outcomes	Reported results	Overall
D'Alessio et al.	Moderate	Moderate	Low	Serious	Low	Moderate	Moderate	Serious
Guidice et al.	Serious	Moderate	Low	Serious	Low	Moderate	Moderate	Serious
Cantini et al.	Moderate	Moderate	Low	Serious	Low	Moderate	Moderate	Serious

Low Risk of Bias.
Moderate Risk of Bias.
Serious Risk of Bias.

COVID-19 disease progression.[36] The third stage is defined as severe extrapulmonary systemic hyperinflammation syndrome, characterized by ARDS, systemic inflammatory response syndrome (SIRS), and impending multi-organ failure. In this phase, anti-inflammatory drugs such as JAK inhibitors may be justified before multiorgan dysfunction occurs.[36] Although the most effective timing of administration of these drugs are yet to be reported, prompt initiation within 1–2 weeks after disease onset is a sensible approach.[37]

Despite concerns about immunosuppression, secondary infections, and thrombosis with use of JAK inhibitors, all the included studies did not report any major issues regarding these adverse effects. On the contrary, lower incidence of secondary infection compared to non-intervention arm was reported in two studies. The latter effect may be associated with shorter recovery time and faster clinical improvement, reducing the risk of secondary infection.[11]

5. Limitations

This study has several limitations. There were only baricitinib and ruxolitinib in the included studies, therefore whether all JAK inhibitors provide the same benefits need further studies. There were only two RCT included in the analysis and only one RCT provided relatively large sample size. Consequently, more RCTs are still needed to further confirm these findings.

6. Conclusion

The use of JAK inhibitors was significantly associated with a reduced risk of mortality, and clinical improvement in hospitalized patients with COVID-19.

Data availability

The data used to support the findings of this study are included in the article.

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Author contribution

Indra Wijaya: Conceptualization, Methodology, Validation, Resources, Writing – Original Draft, Writing - Review & Editing, Project administration. **Rizky Andhika**: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing. **Ian Huang**: Methodology, Investigation, Data Curation, Formal Analysis, Validation, Resources, Writing – Original Draft, Writing – Review and Editing. **Aga Purwiga**: Software, Validation, Data Curation, Formal Analysis, Visualization. **Kevin Yonatan Budiman**: Writing – Original Draft, Writing – Review & Editing. Muhammad Hasan Bashari: Writing – Review and Editing, Supervision. Lelani Reniarti: Writing – Review and Editing, Supervision. **Rully Marsis Amirullah Roesli**: Writing – Review and Editing, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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