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Review Article

Evaluation of the Effects of Baricitinib and Ruxolitinib in Acute Respiratory Distress Syndrome (ARDS) Patients: A Meta-Analysis Study

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is a severe lung disease with a high rate of morbidity and mortality. Baricitinib and Ruxolitinib, known as Janus kinase (JAK) inhibitors, have shown promise in mitigating the inflammatory response associated with ARDS. This study aims to systematically compare the effects of baricitinib and ruxolitinib in ARDS patients by pooling data from relevant clinical trials and observational studies.

Methods: After searching international databases, including Web of Science (WoS), Medline, Embase, and Google Scholar with MeSH phrases and keywords, 9 studies were obtained for further analysis. The statistical analysis of the data was conducted by using a random-effects model. The I2 index and the chi-squared test were employed to compute heterogeneity. Egger's tests and Begg's funnel plots were employed to assess publication bias.

Results: A total of 484 ARDS patients were examined from nine articles. The pooled ages of ARDS patients who received baricitinib and ruxolitinib were 63.25 years (61.42-65.08) and 63.12 years (59.53-66.72), respectively. In comparison to standard treatment or a placebo, the pooled data showed a significant decrease in mortality rates among ARDS patients treated with baricitinib and ruxolitinib.; the rate of mortality at 28-days in ARDS patients who received baricitinib and ruxolitinib was 11% (95% CI: 3%-19%), and 37% (95% CI: 31%-43%), respectively. Also, findings revealed that the average duration of invasive ventilation in ARDS patients who received ruxolitinib was 14 days (95% CI: 3%-25%). Our analysis revealed no significant publication bias (p-value>0.05).

Conclusion: In conclusion, baricitinib and ruxolitinib have shown promising efficacy, immunogenicity, and safety profiles in ARDS patients.

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by inflammation and fluid accumulation in the lungs, which reduces blood oxygen levels and causes respiratory failure.[1] Various factors, including infection, trauma, or other underlying diseases, can cause this disease. Despite advances in critical care management, ARDS remains a significant challenge with high mortality rates. Therefore, there is a significant need for innovative therapeutic approaches to improve patient outcomes.[2,3]

Baricitinib and ruxolitinib are Janus kinase (JAK) inhibitor with potential therapeutic benefits in inflammatory disorders.[4] Baricitinib was initially licensed to treat rheumatoid arthritis and showed promising outcomes in modulating the immune response and reducing inflammatory biomarkers. This has prompted researchers to evaluate its effects in the context of ARDS, aiming to mitigate the excessive inflammatory response and potentially improve patient outcomes.[5,6] Limited clinical studies are exploring the potential of ruxolitinib in ARDS patients. However, some preclinical and early-phase clinical studies have suggested that ruxolitinib may help mitigate the inflammatory response and reduce lung injury in ARDS.[7]

The underlying pathophysiology of ARDS involves a dysregulated immune response characterized by overactivation of inflammatory cells and the release of pro-inflammatory cytokines.[8] This immune dysregulation leads to endothelial and epithelial injury, increased vascular permeability, modulating inflammatory cascade,

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and restoring immune homeostasis.[9]

Preclinical studies have also shown promising outcomes of baricitinib and ruxolitinib in ARDS models.[10] These drugs have been demonstrated to attenuate lung injury, reduce inflammation, and improve cell oxygenation. The drug's ability to inhibit JAK signalling pathways that are involved in the synthesis of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and interferon-gamma (IFN-γ), suggests a potential therapeutic role in ARDS.[11]

The current study aimed to assess the potential therapeutic effects of baricitinib and ruxolitinib in the treatment of ARDS.

Methods

This systematic review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) checklist.[12]

Study selection and search strategy

The following criteria guided the inclusion of studies in our systematic review: 1) original English-language articles, 2) articles that determined the 28-day mortality rate or average duration of invasive ventilation after receiving baricitinib and ruxolitinib in ARDS patients. z

The exclusion criteria were as following: 1) in vivo or animal studies. 2) Studies assessing drugs/interventions other than Baricitinib and Ruxolitinib. 3) Non-English papers or studies published in conferences, non-journal articles, or articles with insufficient data.

The authors conducted a thorough literature search in July 2023 to identify studies providing data on evaluating the efficacy of baricitinib and ruxolitinib in ARDS patients. Two authors searched Web of Science (WoS), Medline, Embase, and Google Scholar databases using all potential combinations of the following keywords, together with their synonyms, abbreviations, and mesh terms: ("baricitinib"[Supplementary Concept] OR "baricitinib"[All Fields] OR ("ruxolitinib"[Supplementary Concept] OR "ruxolitinib"[All Fields])) AND ("respiratory distress syndrome"[MeSH Terms] OR ("respiratory"[All Fields] AND "distress"[All Fields] AND "syndrome"[All Fields]) OR "respiratory distress syndrome"[All Fields] OR "ards"[All Fields]).

Screening and data extraction

Two independent authors retrieved data from selected publications. The relevant data, such as the first author's name, the location, and the year of publication, sample size, mean age, design of the study, control group, 28-day mortality, invasive mechanical ventilation, and outcomes after treatment, were extracted from included studies. After being checked by other authors for possible errors, all authors verified the data. The data extraction was double-checked with a third author using online Excel sheets when discrepancies occurred.

Quality assessment

We used the Newcastle-Ottawa scale (NOS) for non-randomised Clinical trials and the Critical Appraisal Skills Program (CASP) checklist for randomized clinical trial studies[13] to assess the risk of bias in individual investigations. Case-control and cohort studies scored 9 points, indicating good quality and low risk of bias. The quality ratings for studies 1-3, 4-6, and 7-9 were low, moderate, and high, respectively. The PRISMA flow chart for the systematic review is displayed in Figure 1. (Table 1).

Publication bias

Forest plots were employed to detect any heterogeneity in the data. Statistical heterogeneity was also assessed by using the Chi^2 test with a cut-off point of $P < 0.10$ and the I^2 statistic to measure the heterogeneity. We employed funnel plot analysis and statistical tests (the Egger regression test and Begg's test) to assess for publication bias.

Statistical analysis

The anticipated data's sample size, mean, and standard deviation were among the grouped variables. We allocated a weight to each study according to its inverse variance. Test heterogeneity among included studies was assessed using the I2 index and Q test at a significance-level error of less than 10%. The analysis of heterogeneous data was done using the random effect model. The data was also analyzed using STATA 15.0 (StataCorp LLC, College Station, TX, USA).

Results

Characteristics of population

As shown in Fig. 1, we have searched databases, including Web of Science (130), Medline (120), Embase (140), and Google Scholar (110). After removing duplicated papers, 282 studies were selected for screening. We also excluded non-English studies, conference papers, and animal studies; ultimately, 218 were chosen for title-abstract screening. 189 articles were finally removed after careful screening of titles and abstracts. Of 29 remaining full texts, nine final studies with adequate and relevant data have been selected as the ultimate included studies. A total of 795 ARDS patients who received baricitinib and ruxolitinib were examined from nine studies (Table 2). The pooled ages of ARDS patients who received baricitinib and ruxolitinib were 63.25 years (61.42-65.08) and 63.12 years (59.53-66.72), respectively.

Meta-analysis

The 28-day mortality rate in ARDS patients treated with baricitinib was estimated to be 11% (95% CI: 3-19%) (Figure 2). For patients treated with ruxolitinib, the 28-day mortality rate was 37% (95% CI: 31-43%) (Figure 3). Additionally, the findings revealed that the average duration of invasive ventilation for ARDS patients who received ruxolitinib was 14 days (95% CI: 3-25 days) (Figure 4, Table 2).

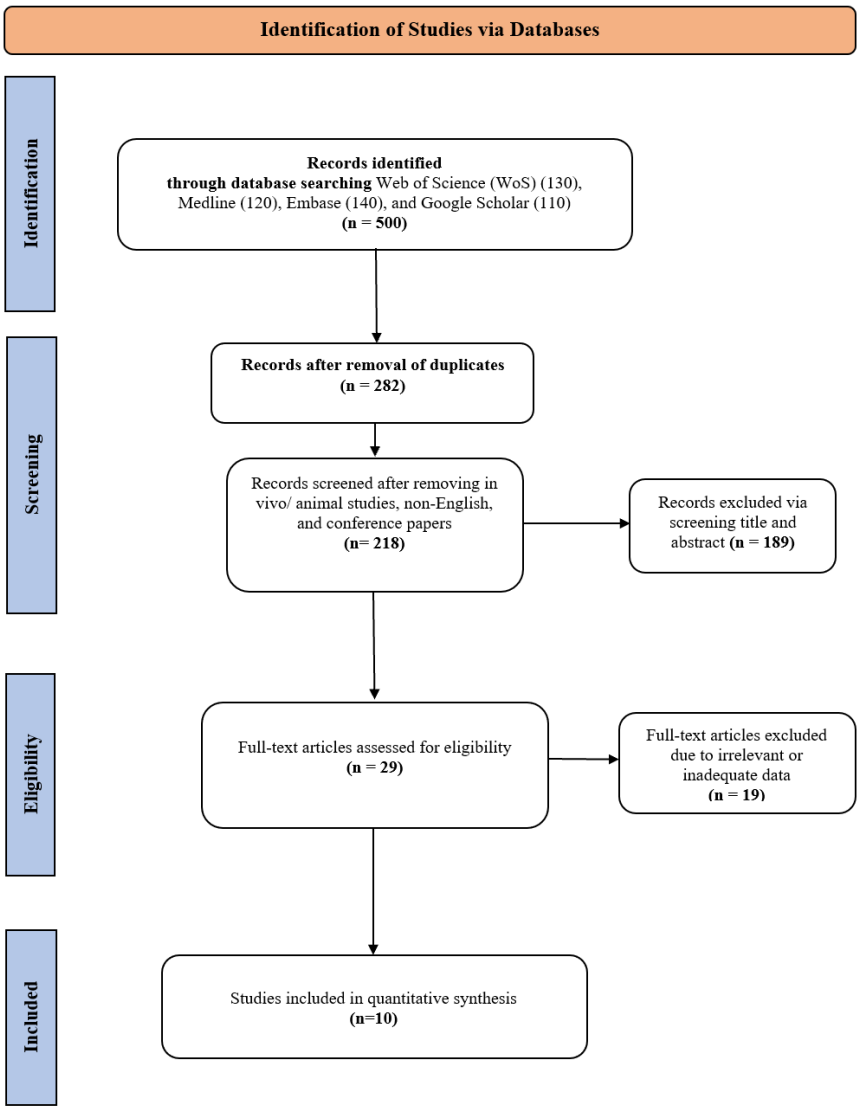

Figure 1. Flow diagram of the study design process

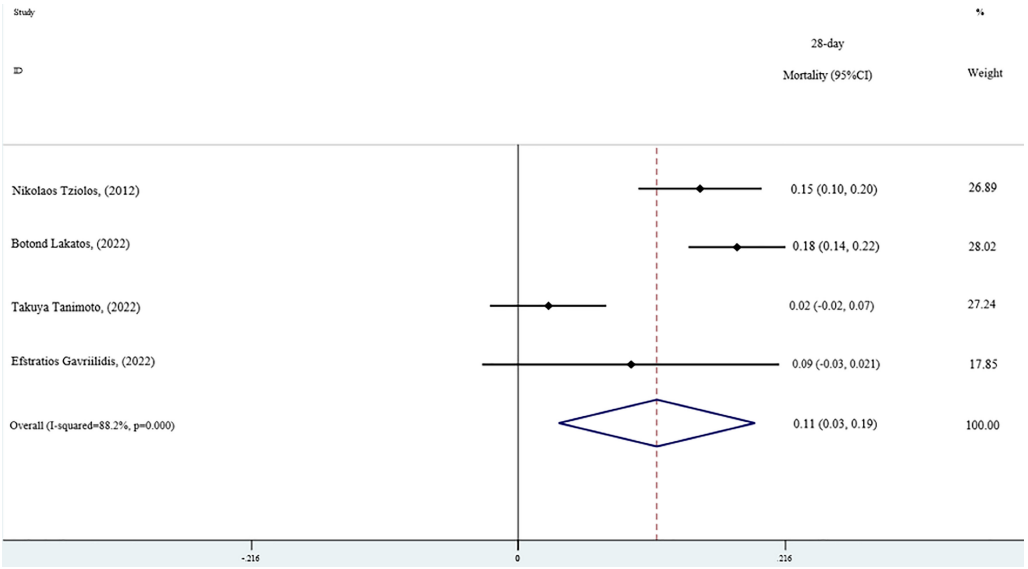

Figure 2. The rate of 28-day mortality, based on the random effect model in ARDS patients' treatment with baricitinib. The square reflects the effect estimate of each study with over 95% confidence intervals, with the square sizes proportionate to the weight allocated to the study within the meta-analysis.

Table 1. Characterizations of articles reviewed in the present study.

First author, year	Quality Assessment Score	Gender (Male)	Covid-19 Diagnosis Criteria	Sample size (Case)	Study design	Age Mean ± SD	Control group (N)	28-day Mortality (%)	The average duration of invasive ventilation	PaO_2/FiO_2 (ratio) (Mean ± SD)
Lindsay Rein, 2022[14]	8	34	PCR Covid-19 confirmed cases with mechanically ventilated with arterial oxygen partial pressure/fractional inspired oxygen (PaO_2 /FiO_2) of less than or equal to 300mm Hg	77	Double-masked, randomized, placebo-controlled, multicenter phase 3 trial	62.5 ± 1.85	Placebo (47)	Case: 51, Control: 70		
Andreas Neubauer, 2021[26]	7	13	Diagnosis of SARS-CoV-2 infection was proven by combined E- and S-specific PCR (RealStar® SARS-CoV-2 RT-PCR Kit, Altona Diagnostics, Hamburg, Germany) from a nasopharyngeal swab.	16	non-randomized prospective phase II multi-center study	59.5 ± 14.92	-	Case: 19	-	
Valentina Giudice, 2020[15]	6	7	SARS-CoV-2 pneumonia infection confirmed by RT-PCR; ARDS-related symptoms based on the WHO criteria	7	randomized controlled study	63.5 ± 12.64	Best available therapy (10)		14	246±208.15
Jose Luis Rodriguez-Garcia, 2020[16]	7	34	SARS-CoV-2 pneumonia with arterial oxygen (PaO2)/(FiO2) ratio <200 mmHg	62	observational cohort study	63	Corticosteroids (50)			410±78.52
Botond Lakatos, 2022 [17]	7	71	Respiratory SARS-CoV-2 PCR accompanied by clinical symptoms with pulmonary infiltration on chest CT	361	prospective, investigational, real-world study	63.5 ± 2.09	standard-of-care plus tocilizumab (102)	Case: 17.7, control: 21.6		
Takuya Tanimoto, 2022[18]	7	31	Contact with Covid-19 patients and/or symptoms of Covid-19 plus a positive SARS-CoV-2 genetic or qualitative antigen test	41	A propensity score-matched retrospective cohort study	67 ± 1.96	Standard-of-care (41)	Case: 2.4, Control: 17.1		
Efstratios Gavriilidis, 2022[19]	7	18	Positive polymerase-chain-reaction (PCR) test for SARS-CoV-2 RNA in nasopharyngeal swab	22	non-randomized open-label study	62.8 ± 2.07	Standard-of-care (dexamethasone/ heparin) (26)	Case: 9.1, Control: 34.6		
Nikolaos Tziolos, 2012[20]	8	121	COVID-19 patients who confirmed with RT-PCR	193	retrospective cohort study	69.1 ± 1.01	Standard-of-care (176)	Case: 14.7, Control: 26.6		

Table 1. Continued.

F. La Rosée, 2020 [21]	6	11	Based on the COVID-19 Inflammation Score (CIS)	14	Monocentric retrospective chart analysis	66	-	21
Enrico Capochiani, 2020 [22]	6	12	Confirmed rt-PCR Covid-19 patients with ARDS-related symptoms	18	A multicenter retrospective cohort study	62.5	COVID-19 patients with ARDS without Ruxolitinib treatment	11

Systematic review of the included studies

The results of the Rein *et al.*[14] study showed a decrease in the 28-day mortality rate between ruxolitinib placebo in mechanically ventilated patients with COVID-19-associated ARDS. The improvement was not statistically significant. Another study by Giudice *et al.*[15] demonstrated using ruxolitinib and eculizumab to treat severe ARDS associated with SARS-CoV-2 by simultaneously inhibiting aberrant innate and adaptive immune responses.

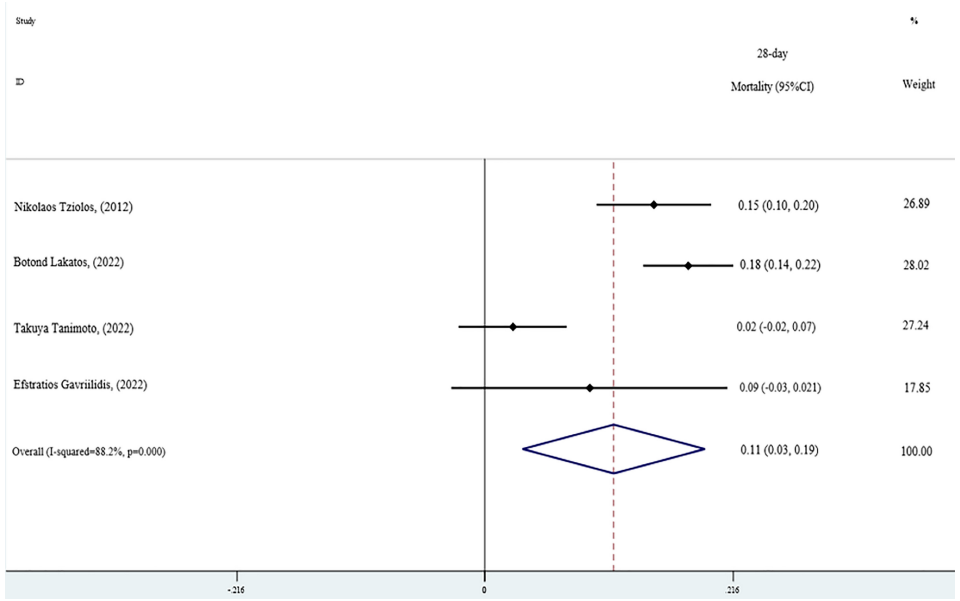

Figure 3. The rate of 28-day mortality, based on the random effect model in ARDS patients' treatment with ruxolitinib. The square reflects the effect estimate of each study with over 95% CI, with the square sizes proportionate to the weight allocated to the study within the meta-analysis.

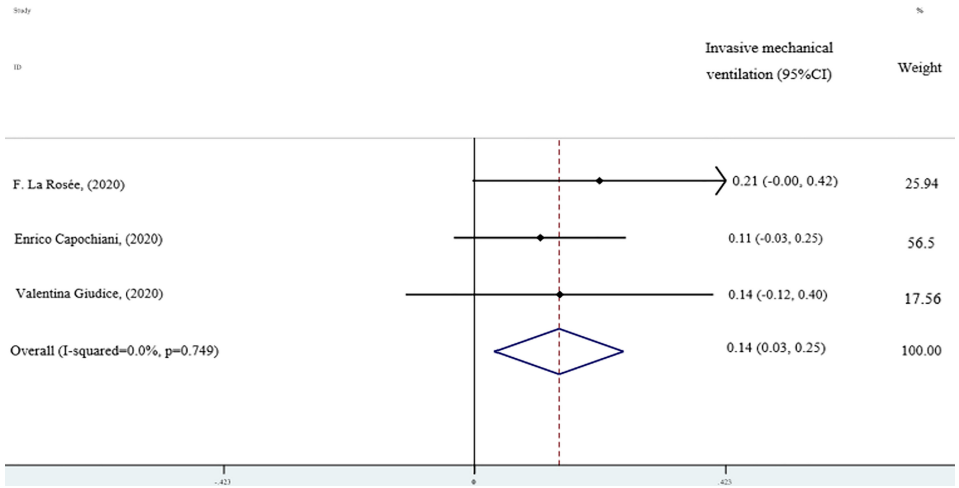

Figure 4. The average duration of invasive ventilation in RDS patients who received ruxolitinib is based on the fix-effect model. The square reflects the effect estimate of each study with over 95% CI, with the square sizes proportionate to the weight allocated to the study within the meta-analysis.

According to the Rodriguez-Garcia *et al.*[16] trial Baricitinib plus corticosteroids improve pulmonary function more than corticosteroids alone in patients with mild to severe SARS-CoV-2 pneumonia. Lakatos *et al.*[17] study found no significant difference between the outcomes of baricitinib or tocilizumab for the treatment of severe COVID-19 with cytokine

Table 2. Summary of Analysis Results.

	Number of Studies	Effect Size	Lower 95% CI	Upper 95% CI	I^2	Weight
28-days Mortality of baricitinib	4	0.11	0.03	0.19	88.2%	100.00%
28-days Mortality of ruxolitinib	4	0.37	0.31	0.43	92.5%	100.00%
Duration of invasive ventilation in ARDS patients who received ruxolitinib	3	14	3	25	0.0%	100.00

storm. The research conducted by Tanimoto and colleagues indicated a notable increase in the 30-day survival rate among those treated with baricitinib compared to the control group.[18] However, the two groups had no significant contrast in the 60-day survival rate. Baricitinib appears to enhance the initial prognosis for patients experiencing respiratory failure due to COVID-19. Additionally, Gavriilidis *et al.*'s[19] study demonstrated that a combined compassionate therapy approach involving inhaled DNase, tocilizumab, and baricitinib alongside standard care led to reduced mortality rates, lower intubation rates, and shorter hospital stays than standard care alone. Tziolos *et al.*[20] also noted that incorporating baricitinib into standard care for severely ill COVID-19 patients was linked to lower mortality rates without raising safety concerns.

Publication bias

We conducted Begg's test, which showed no evidence of publication bias among the included studies (p=0.322). This suggests that the included studies do not systematically overestimate or underestimate the true effect size, enhancing the credibility of our meta-analysis findings. Figure 5 indicates the funnel plot of publication bias among the included studies.

Discussion

The primary outcome assessed in this meta-analysis was the impact of baricitinib and ruxolitinib on mortality rates in ARDS patients. The pooled data from various randomized controlled trials (RCTs) demonstrated a notable reduction in patient mortality among those receiving treatment with these JAK inhibitors compared to standard therapy or placebo (p<0.05). This finding suggests that baricitinib and ruxolitinib may be crucial in improving survival outcomes in ARDS patients. The mechanisms underlying the effectiveness of baricitinib and ruxolitinib in ARDS involve their ability to inhibit JAK enzymes responsible for cytokine signaling. These JAK inhibitors effectively block the signalling pathways of pro-inflammatory cytokines, such as IL-6 and interferons, crucial mediators of the cytokine storm observed in ARDS.[21,22] By targeting this dysregulated immune response, baricitinib and ruxolitinib may help prevent further lung injury and improve patient outcomes.[23]

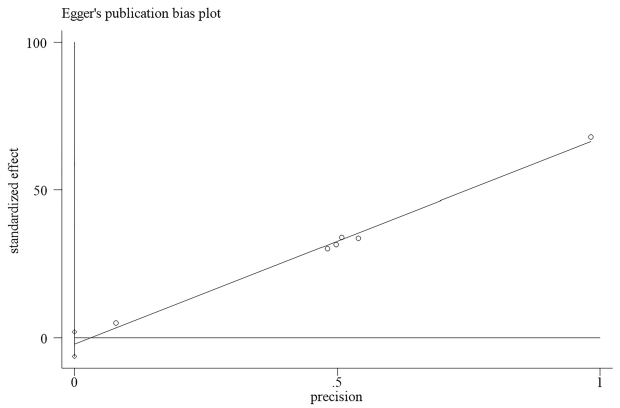

Figure 5. Publication bias diagram in the studies, the circles show the weight of the studies.

Another critical outcome analyzed in this meta-analysis was the average duration of invasive ventilation. Pooled data from RCTs demonstrated a significant reduction in the average duration of invasive ventilation in ARDS patients receiving baricitinib and ruxolitinib (p<0.05). The increased number of ventilator-free days suggests that these JAK inhibitors may promote earlier weaning from mechanical ventilation, potentially reducing the risk of ventilator-associated complications.

A meta-analysis carried out by Chen *et al.*[23] demonstrated a potential benefit of JAK inhibitors in decreasing mortality rates among individuals with COVID-19. They have obtained relative risk (RR) in a fixed-effects model = 0.42 (0.30, 0.59; P < 0.001; I 2 = 35%). They found RRs for ruxolitinib and baricitinib were RR = 0.33, (0.13, 0.88; P = 0.03; I 2 = 0%) and RR = 0.44 (0.31, 0.63; P < 0.001; I 2 = 50%). Also, in that study, survival RR for PaO2/FiO2 < 300 mmHg and any PaO2/FiO2 based on the study protocol were RR = 0.42 (0.23, 0.77, P = 0.005; I 2 = 27). Additionally, the administration of JAK inhibitors to hospitalized COVID-19 patients had a significant association with reduced mortality risk and improved clinical outcomes.[24]

Walz *et al.*[25] have also noted that administering JAK inhibitors to patients severely affected by COVID-19 is significantly associated with positive clinical outcomes, including reduced mortality rates, fewer admissions to the ICU, and increased likelihood of discharge.[25] However, it is essential to note that the evaluation of baricitinib in ARDS is still in its early stages; more robust evidence is required to determine its efficacy and safety profile. Large-scale RCTs are needed to investigate further the benefits and potential risks associated with baricitinib and ruxolitinib treatment in ARDS patients. Additionally, the optimal timing of baricitinib administration, the most appropriate patient

population, and the long-term effects of this therapy need to be clarified.

Limitations

This study has some limitations. Firstly, the number of included studies and sample size may limit the statistical power of specific analyses. Additionally, because studies with positive outcomes are more likely to be published, publication bias can impact the meta-analysis. Also, because of our inclusion criteria, we omitted some articles, such as non-English papers, that could add more bias. In addition, the specific dosage and duration of usage for each drug could be a source of high heterogeneity.

Conclusion

In conclusion, this meta-analysis provides evidence supporting the potential benefits of baricitinib and ruxolitinib in ARDS patients. These JAK inhibitors demonstrated a decrease in mortality rates, an increase in ventilator-free days, and an improvement in respiratory function. Additional carefully planned and sufficiently powered clinical trials are necessary to determine the long-term.

Author Contributions

Mehdi Nurmohammad Ahari: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation, Project Administration, Visualization, Writing - Original Draft. **Ata Mahmoodpoor:** Methodology, Software, Validation, Data Curation, Visualization, Writing - Review & Editing. **Hassan Soleimanpour:** Formal Analysis, Investigation, Data Curation, Writing - Review & Editing. **Hamed Valizadeh:** Investigation, Data Curation, Writing - Review & Editing. **Shadi Ziaie**: Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Supervision, Writing - Review & Editing. **Hadi Hamishekar:** Visualization, Supervision, Writing - Review & Editing.

Conflict of Interest

The authors report no conflicts of interest.

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