Original Article

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Evaluation of the effects of baricitinib in patients with acute respiratory distress syndrome: a pilot, randomized, double-blind, placebo-controlled clinical trial

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Running title: baricitinib in ARDS

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Abstract

Introduction: Despite advances in supportive care, acute respiratory distress syndrome (ARDS) remains a major cause of mortality and morbidity in critically ill patients. The lack of effective pharmacological treatments underscores the necessity for novel, evidence-based therapies. Investigating baricitinib's potential to improve outcomes could address unmet needs and transform management strategies in this serious condition.

Material and methods: This double-blind, placebo-controlled clinical trial enrolled 20 patients with ARDS at Imam Reza Hospital, Tabriz, using convenience sampling. Participants were randomly assigned to two groups and received either baricitinib or a placebo. All patients received standard supportive care throughout hospitalization. Demographic and clinical data were collected from medical records and bedside interviews. Outcomes were assessed over 28 days, with both clinical and laboratory markers.

Results: Significant differences were observed in arterial oxygenation (SpO_2/FiO_2, P=0.009), and reduced need for advanced respiratory support (P<0.05) for the intervention group. Although hospital stay was longer (P<0.05), ICU mortality was lower in the intervention group (P<0.05). Kaplan-Meier analysis revealed a higher survival probability with baricitinib, with mortality rates of 30% for baricitinib versus 50% in the control group.

Conclusion: The findings of this study demonstrate that baricitinib administration in patients with ARDS led to significant improvements in oxygenation, reduced need for advanced respiratory support, and lower ICU mortality compared to the control group, despite a longer hospital stay.

Keywords: Baricitinib, Acute Respiratory Syndrome, Mortality, ICU.

Introduction

ARDS remains one of the most challenging medical complications in contemporary medicine.[1] It affects a broad spectrum of patients, including those suffering from severe viral infections such as influenza, SARS, MERS, and most recently, COVID-19, thereby imposing a considerable burden on healthcare systems worldwide.[2] Other etiologies for ARDS include bacterial pneumonia, septic shock, direct lung injury, acute pancreatitis, chest trauma, and inhalation of toxic chemicals.[3] The hallmark of this syndrome is the disruption of the alveolar-capillary barrier, increased vascular permeability within the lung tissue, and the accumulation of fluid in the interstitial and alveolar spaces. These pathophysiological changes lead to significant impairment in gas exchange, refractory hypoxemia, and, ultimately, respiratory failure and high mortality rates.[3,4] Clinically, ARDS is divided into three phases: the initial exudative phase, the subacute proliferative phase, and the chronic fibrotic phase. In the exudative phase, severe inflammation and fluid leakage into the alveolar space develop, which is associated with hypoxia refractory to oxygen therapy and a significant decrease in the ventilatory lung capacity. In the proliferative phase, activated inflammatory cells begin to repair the membrane damage, but this phase is also associated with the risk of fibrotic tissue formation. Ultimately, the fibrotic stage leads to persistent fibrosis of the lungs in some patients, which severely impairs respiratory ability.[3]

The central pathology of ARDS involves an exaggerated and dysregulated inflammatory response in the lungs. This hyperactive immune reaction, typically triggered by overactivation of immune cells (including neutrophils, macrophages, and T-lymphocytes), the excessive release of inflammatory mediators, and an imbalance in tissue immune homeostasis, results in widespread cellular damage and the destruction of pulmonary parenchyma.[5] During the COVID-19 pandemic, it became increasingly evident that many patients with severe respiratory illness developed a cytokine storm syndrome, which substantially determines disease severity and prognosis in ARDS.[6,7]

Despite recent advances in supportive care—including mechanical ventilation, oxygen therapy, and prone positioning—there is still no definitive pharmacological treatment for ARDS, and the associated mortality remains alarmingly high.[8] Various pharmacological strategies have been

explored, including corticosteroids, antiviral agents, immunomodulators, and targeted biological therapies. Their results have often been inconsistent, with many therapies facing important limitations in efficacy and safety.[9,10] Current guidelines, based on moderate-quality evidence, recommend administering corticosteroids to critically ill adult patients with ARDS.

Baricitinib, an oral selective inhibitor of Janus kinase 1 and 2 (JAK1/JAK2), was initially developed for the treatment of rheumatoid arthritis refractory to conventional regimens.[11] The JAK/STAT signaling pathway plays a key role in the regulation of numerous immune and inflammatory processes, including the expression of several cytokines involved in ARDS pathogenesis.[12] It has been hypothesized that inhibition of this pathway might mitigate hyperinflammatory responses, lower cytokine production, reduce migration of inflammatory cells, and ultimately improve microvascular disturbances and respiratory function in ARDS.[13]

In addition to its well-established action via JAK/STAT inhibition, preclinical evidence suggests that baricitinib may also downregulate the expression of viral entry receptors, such as AP2, on pulmonary cells, thereby potentially limiting viral invasion and replication in the respiratory tract.[14] These properties have garnered significant interest in baricitinib as a potential therapeutic option not only for autoimmune conditions but also for hyperinflammatory respiratory disorders such as COVID-19-induced ARDS.[15]

Several preliminary clinical studies and randomized controlled trials in hospitalized COVID-19 patients have shown promising outcomes with baricitinib, including reduced duration of hospitalization, improved oxygenation parameters, and lower mortality rates.[16,17] However, the existing evidence remains mixed, and concerns regarding safety—such as increased risk of secondary infections, thromboembolic events, and hematological abnormalities—as well as variable efficacy across different patient populations, continue to challenge its widespread adoption. Therefore, rigorous evaluation of the clinical impact of baricitinib in patients with ARDS, particularly through large randomized controlled trials, is essential to clarify its real therapeutic potential and safety profile.[18]

The present study was designed to assess the clinical efficacy and safety of baricitinib in patients diagnosed with ARDS and provide the scientific and medical community with updated, evidence-

based insights that could contribute to improved management and reduced burdens associated with this life-threatening condition.

Material and methods

Study Design: This research was conducted as a double-blind, placebo-controlled clinical trial at Imam Reza Hospital in Tabriz, Iran, from September 6, 2023, to March 2024.

Sampling: This study was conducted as a pilot, in which 20 patients diagnosed with ARDS were enrolled using a convenience sampling method, according to the predefined inclusion and exclusion criteria.

Eligibility Criteria: Adult patients aged 18 to 80 years with mild to moderate pneumonia-related ARDS who required oxygen therapy ($PaO_2/FiO_2 < 300$ mmHg) and were able to maintain a prolonged prone position were included in the study.

Exclusion criteria: unwillingness to participate, a recent history of baricitinib use, known hypersensitivity to baricitinib, and the presence of comorbid conditions, including infectious or immunosuppressive diseases, HIV infection, hepatic or renal disorders, and acquired immunodeficiency syndrome.

Randomization: In this study, simple random allocation was used. A list of numbers from 1 to 20 was generated and randomly divided. Upon enrollment, each patient was assigned one of these numbers according to the order of their admission. Based on the pre-established list, patients with even numbers were allocated to the intervention group, while those with odd numbers were assigned to the control group. To achieve allocation concealment, the numbers were written on individual cards and placed inside sealed envelopes. The envelopes were thoroughly sealed and stored in a box. As each participant entered the study, one envelope was opened sequentially, revealing the group assignment for that individual.

Blinding: The medication and placebo were provided to patients in identical, coded packaging. Neither the participants nor the clinical staff were aware of the group assignments. Outcome data were recorded under headings “A” and “B” without indicating the type of treatment received. Thus, double-blinding was maintained throughout the study.

Procedures and Data Collection: At the beginning of the study, demographic and clinical information for each participant was assessed and recorded in a structured data collection form. All patients received standard supportive care, which included fluid restriction, mechanical ventilation, and inhaled vasodilators (used only in cases of refractory hypoxemia and not as routine), as well as corticosteroid administration (dexamethasone 8 mg twice daily for five days) and other supportive therapies. Demographic and clinical data, as well as information on prescribed medications, were gathered through both review of medical records and direct bedside interviews.

Baricitinib and placebo tablets were identical in appearance, color, and size, and were provided to patients in identical packaging. Baricitinib was administered orally at a dose of 4 mg daily for 14 days or until hospital discharge, whichever occurred first. Patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min received a reduced dose of 2 mg once daily. The placebo was administered according to the same dosage schedule as the active drug. All patients continued to receive standard supportive care in the trial hospital throughout the study period.

Patients were followed up for 28 days. The primary composite endpoint was the proportion of participants in the baricitinib group compared to the placebo group who progressed to require high-flow oxygen or non-invasive ventilation, invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or who died by day 28. Laboratory markers, including LDH and CRP, were measured in both groups. Pre-specified key secondary outcomes evaluated from days 1 to 28 included: all-cause mortality, proportion of participants discharged from the hospital on days 4, 7, 10, and 14, number of ventilator-free days, time to recovery, duration of hospitalization, and the proportion of participants who improved their oxygen saturation from below 94% to 94% or higher between baseline and days 4, 7, 10, and 14.

Statistical Analysis: Continuous variables were described using mean and standard deviation, while categorical variables were summarized as frequencies and percentages. Data distribution was assessed and found to be normal. Accordingly, comparisons between groups were performed using the independent samples t-test for quantitative variables and the chi-square

test for qualitative variables. In all analyses, a p-value of less than 0.05 was considered statistically significant. Additionally, for variables measured repeatedly across different time points within each group (including white blood cell count, platelet count, lymphocyte count, C-reactive protein, lactate dehydrogenase, SpO_2/FiO_2 ratio, and PaO_2), a linear mixed-effects model was applied to evaluate within-subject changes over time.

Ethical Considerations: This thesis received ethical approval from the Ethics Committee at Tabriz University of Medical Sciences (ID: IR.TBZMED.PHARMACY.REC.1402.030) on August 13, 2023, and was subsequently registered in the Iranian Registry of Clinical Trials (IRCT20231017059748N3). To ensure confidentiality and privacy, each patient was assigned a unique code, and all personal information and medical records remained strictly confidential with the research team. Vulnerable groups, such as children under 18 years, patients over 80 years old, and pregnant women, were excluded from the study. Participants could withdraw from the study at any time without any obligation. For illiterate individuals or those unable to provide informed consent due to incapacity, first-degree relatives were involved in the consent process; patients were excluded if this was not possible. All participants continued to receive standard heart failure therapy and were not deprived of any essential treatment at any stage of the study.

Results

Adult patients aged 18 to 80 years with mild to moderate pneumonia-related ARDS who required oxygen therapy ($PaO_2/FiO_2 < 300$ mmHg) were included in the study. The CONSORT flowchart diagram of the clinical trial is shown in Figure 1. A total of 44 patients were identified. Among them, 24 were excluded based on the predefined exclusion criteria, and the final analysis was performed on 20 participants.

No statistically significant differences were observed between the intervention and control groups in terms of baseline demographic and clinical characteristics. The mean age, body mass index (BMI), and D-dimer levels were comparable between groups ($P > 0.05$). The prevalence of obesity, smoking, diabetes, ischemic heart disease, hypercholesterolemia, and asthma did not differ significantly between the two groups (all $P > 0.05$). In both arms, the distribution of gender was also similar, indicating effective randomization and group balance (Table 1).

Levels of C-reactive protein (CRP) were significantly higher in the intervention group than in the placebo group on day 1 (P = 0.041). However, CRP levels were continuously decreasing in the intervention group after initiation of baricitinib, and CRP levels were lower in the intervention group than in the control group, indicating the effective anti-inflammatory effects of baricitinib. No significant intergroup differences were observed on days 7 or 14 (P = 0.859 and P = 0.744, respectively) (Table 2).

No statistically significant differences were found in platelet counts between the intervention and control groups on Days 1, 4, 7, or 14 (all $P > 0.05$). Interestingly, on Day 10, platelet levels were significantly elevated in the intervention group compared to the control group (P = 0.009). Lactate dehydrogenase (LDH) levels were significantly higher in the intervention group than in the control group on Day 1 (P = 0.001), Day 7 (P = 0.001), and Day 14 (P = 0.005), indicating a persistent and significant intergroup difference at these time points (Table 2).

The lymphocyte count showed statistically significant differences between the groups at all measured intervals (Day 1: P = 0.045; Day 4: P = 0.035; Day 7: P = 0.045; Day 10: P = 0.014; Day 14: P = 0.006), with the intervention group generally exhibiting lower values. At every time point, the SpO_2/FiO_2 ratio was markedly higher in the intervention group than in the control group, and these differences were statistically significant (Day 1: P = 0.009; Day 4: P = 0.008; Day 7: P = 0.002; Day 10: P = 0.001; Day 14: P = 0.001). The intervention group maintained significantly higher arterial oxygen pressure (PaO_2) values than the control group at every measured interval (Day 1: P = 0.014; Day 4: P = 0.013; Day 7: P = 0.001; Day 10: P = 0.009; Day 14: P = 0.001) (Table 2).

Comparison of clinical outcomes between the two study groups with ARDS demonstrated that patients in the intervention group experienced significantly more days with oxygen saturation levels of at least 94% on room air and more days without the need for supplemental oxygen compared to the control group ($P < 0.01$ for both variables). Additionally, the intervention group achieved a greater number of days with a respiratory rate below 20 breaths per minute ($P < 0.01$). The need for high-flow oxygen or non-invasive ventilation, as well as the requirement for intubation, was notably lower in the intervention group ($P < 0.05$ for both). Although the median length of hospital stay was longer in the intervention group ($P < 0.05$), ICU mortality was lower

than in the control group ($P < 0.05$), indicating a potential benefit of the intervention in terms of respiratory outcomes and survival (Table 3).

Based on the results of the Kaplan-Meier survival analysis, the probability of survival in the control group declined more steeply, with the mortality rate reaching 50% (5 out of 10 patients) by the end of the follow-up period. In contrast, the mortality rate in the baricitinib group was 30% (3 out of 10 patients) at the end of the study (Figure 2). The divergence between the survival curves was evaluated using the log rank test, which indicated a statistically significant difference between the groups (log rank $P = 0.04$).

Discussion

The findings of this study indicate that baricitinib administration in patients with ARDS resulted in improvements in clinical and laboratory parameters compared to the placebo group. Statistical analyses demonstrated that parameters such as the SpO_2/FiO_2 ratio and arterial oxygen pressure (PaO_2) were consistently higher in the intervention group, indicating improved gas exchange and pulmonary function.

One of the most notable results was the reduction in the need for advanced respiratory support, including high-flow oxygen and non-invasive ventilation, as well as a decreased requirement for intubation, in the baricitinib group. This effect can likely be attributed to the drug's modulation of inflammatory responses and inhibition of the interleukin-6 and JAK-STAT pathways.[19] As a selective JAK inhibitor, baricitinib downregulates cytokines such as IL-6, which play a pivotal role in the hyperinflammatory state seen in ARDS.[20] The improved respiratory status in the intervention group supports prior experimental evidence of baricitinib's anti-inflammatory and immunomodulatory activity.[21]

Another plausible mechanism underpinning these favorable outcomes may involve the inhibition of leukocyte and lymphocyte aggregation and migration in lung tissue. The study's data showed significant differences in leukocyte and lymphocyte counts between the groups, likely reflecting

decreased immune cell activation and controlled inflammatory responses in the intervention group.[22]

Interestingly, elevated levels of CRP and LDH at the early treatment stages in the intervention group likely reflect acute immune activation before the full therapeutic effect of baricitinib. With continued treatment and increased JAK-STAT pathway inhibition, a progressive reduction in these markers became evident, especially toward the late phases of the study, further confirming the anti-inflammatory properties of the drug. Statistically significant declines in CRP, along with favorable LDH trends, suggest a positive impact on minimizing cellular injury and systemic inflammation.[23,24]

Furthermore, the marked difference in survival rates between the two arms highlights the potential role of baricitinib in reducing mortality among ARDS patients. Kaplan-Meier survival analysis revealed a mortality rate nearly twice as high in the control group compared to those receiving baricitinib. This difference could plausibly be explained by the prevention of cytokine storm and subsequent reduction in acute lung injury through the attenuation of pivotal inflammatory mediators such as IL-6 and interferon-gamma.[25] By dampening cytokine production, baricitinib may alleviate pulmonary edema and alveolar injury, thus improving chances of survival.[26]

Additionally, patients in the intervention group maintained adequate blood oxygenation ($SpO_2 \geq 94\%$) for more days and required supplemental oxygen for fewer days compared to controls. These findings are likely attributable to improved alveolar-capillary function secondary to baricitinib-induced reduction in pulmonary inflammation.[27] By inhibiting the migration and activation of macrophages and neutrophils, baricitinib likely impedes excessive cytokine secretion, preventing further alveolar damage and enhancing gas exchange.[28]

Significant differences in lymphocyte and platelet counts also suggest that baricitinib can modulate cellular immunity and coagulation balance in affected patients. The observed increase in platelet count on day 10 in the baricitinib group may reflect controlled inflammation and prevention of critical illness progression. Lower lymphocyte counts in the intervention arm are

indicative of a controlled immune suppression that reduces hyperinflammation without exposing patients to the risks of profound immunosuppression and secondary infection.[29,30]

The observed reduction in the need for mechanical ventilation and ICU mortality in the intervention group likely stems from baricitinib's direct effects on reducing lung inflammation, improving gas exchange, and preventing the escalation of acute respiratory distress.[31] These findings are consistent with previous studies supporting the beneficial effects of JAK inhibitors in managing severe COVID-19.[32]

Given the statistically significant improvements in clinical and laboratory outcomes—including enhanced oxygenation, reduced need for respiratory support, and better survival prospects—baricitinib appears to exert multifaceted effects extending beyond immunomodulation.[33] The drug's main mechanism likely revolves around indirect inhibition of the JAK-STAT pathway and downregulation of key inflammatory cytokines, although stabilization of immune homeostasis, reduction of capillary leakage, and protection of cell viability may also play contributory roles.[34]

Also, the results of recent meta-analysis showed that baricitinib can reduce the duration of invasive ventilation and mortality in patients with ARDS.[35]

Moreover, by controlling the endocrine-like actions of cytokines, baricitinib may support both quality of life and disease trajectory, potentially reducing the likelihood of escalation to more invasive interventions.[36]

Limitations of the study

This study had some limitations. First, the sample size was relatively small, which may limit the generalizability of the results. Second, the study's follow-up period was limited. Therefore, clinical trials with larger sample sizes and longer follow-up are suggested for future studies.

Conclusion

The findings of this study demonstrate that baricitinib administration in patients with ARDS was associated with significant improvements in oxygen supplementation needs and reduced need for advanced respiratory support. Importantly, patients receiving baricitinib exhibited a lower ICU mortality rate compared to the control group.

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Author Contributions

Mehdi Nurmohammad Ahari: Investigation, Data Curation, Writing - Original Draft. **Shadi Ziaie:** Methodology, Supervision, Writing - Review & Editing. **Ata Mahmoodpoor:** Methodology, Data Curation, Samples Analysis, Writing - Review & Editing. **Hassan Soleimanpour:** Samples Analysis, Investigation, Data Curation, Writing - Review & Editing. **Hamed Valizadeh:** Investigation, Data Curation, Writing - Review & Editing. **Fariba Pourkarim:** Investigation, Writing - Original Draft & revision. **Saman Chaparzadeh:** Writing - Original Draft & revision. **Hadi Hamishehkar:** Conceptualization, Methodology, Supervision, Writing - Review & Editing.

Ethical Approval

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.PHARMACY.REC.1402.030). It has also been submitted to the Iranian Registry of Clinical Trials (IRCT20231017059748N3). Additionally, we received consent forms from all participants.

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References

1. Synowiec A, Szczepański A, Barreto-Duran E, Lie LK, Pyrc K. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. *Clin Microbiol Rev*. 2021;34(2):e00133-20. doi: 10.1128/CMR.00133-20.

2. Wick KD, Ware LB, Matthay MA. Acute respiratory distress syndrome. *BMJ*. 2024;387:e076612. doi: 10.1136/bmj-2023-076612.

3. Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. *Lancet*. 2022;400(10358):1145-1156. doi: 10.1016/S0140-6736(22)01485-4.

4. Gorman EA, O'Kane CM, McAuley DF. Acute respiratory distress syndrome in adults: diagnosis, outcomes, long-term sequelae, and management. *Lancet*. 2022;400(10358):1157-1170. doi: 10.1016/S0140-6736(22)01439-8.

5. Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, et al. A new global definition of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2024;209(1):37-47. doi: 10.1164/rccm.202303-0558WS.

6. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet*. 2021;398(10300):622-37. doi: 10.1016/S0140-6736(21)00439-6.

7. Grotberg JC, Reynolds D, Kraft BD. Management of severe acute respiratory distress syndrome: a primer. *Crit Care*. 2023;27(1):289. doi: 10.1186/s13054-023-04572-w.

8. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MB, Antonelli M, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med*. 2023;49(7):727-759. doi: 10.1007/s00134-023-07050-7.

9. Fujishima S. Guideline-based management of acute respiratory failure and acute respiratory distress syndrome. *J Intensive Care*. 2023;11(1):10. doi: 10.1186/s40560-023-00658-3.

10. Aslan A, Aslan C, Zolbanin NM, Jafari R. Acute respiratory distress syndrome in COVID-19: possible mechanisms and therapeutic management. *Pneumonia*. 2021;13(1):14. doi: 10.1186/s41479-021-00092-9.

11. Bieber T, Feist E, Irvine AD, Harigai M, Haladyj E, Ball S, et al. A review of safety outcomes from clinical trials of baricitinib in rheumatology, dermatology and COVID-19. *Adv Ther*. 2022;39(11):4910-4960. doi: 10.1007/s12325-022-02281-4.

12. 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(12):1407-1418. doi: 10.1016/S2213-2600(21)00331-3.

13. Assadiasl S, Fatahi Y, Mosharmovahed B, Mohebbi B, Nicknam MH. Baricitinib: from rheumatoid arthritis to COVID-19. *J Clin Pharmacol*. 2021;61(10):1274-1285. doi: 10.1002/jcph.1874.

14. Ely EW, Ramanan AV, Kartman CE, de Bono S, Liao R, Piruzeli MLB, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med*. 2022;10(4):327-336. doi: 10.1016/S2213-2600(22)00006-6.

15. 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(9):795-807. doi: 10.1056/NEJMoa2031994.

16. Rubin R. Baricitinib is first approved COVID-19 immunomodulatory treatment. *JAMA*. 2022;327(23):2281. doi: 10.1001/jama.2022.9846.

17. Selvaraj V, Finn A, Lal A, Khan MS, Dapaah-Afriyie K, Carino GP. Baricitinib in hospitalised patients with COVID-19: A meta-analysis of randomised controlled trials. *EClinicalMedicine*. 2022;49:101489. doi: 10.1016/j.eclinm.2022.101489.

18. Wolfe CR, Tomashek KM, Patterson TF, Gomez CA, Marconi VC, Jain MK, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med*. 2022;10(9):888-899. doi: 10.1016/S2213-2600(22)00088-1.

19. Richardson PJ, Robinson BW, Smith DP, Stebbing J. The AI-assisted identification and clinical efficacy of baricitinib in the treatment of COVID-19. *Vaccines*. 2022;10(6):951. doi: 10.3390/vaccines10060951.

20. Paules CI, Wang J, Tomashek KM, Bonnett T, Singh K, Marconi VC, et al. A risk profile using simple hematologic parameters to assess benefits from baricitinib in patients hospitalized with COVID-19: A post hoc analysis of the adaptive COVID-19 treatment Trial-2. *Ann Intern Med*. 2024;177(3):343-352. doi: 10.7326/M23-2593.

21. Lin Z, Niu J, Xu Y, Qin L, Ding J, Zhou L. Clinical efficacy and adverse events of baricitinib treatment for coronavirus disease-2019 (COVID-19): a systematic review and meta-analysis. *J Med Virol*. 2022;94(4):1523-1534. doi: 10.1002/jmv.27482.

22. Wang Z, Chan ECY. Physiologically-Based Pharmacokinetic Modelling to Investigate Baricitinib and Tofacitinib Dosing Recommendations for COVID-19 in Geriatrics. *Clin Pharmacol Ther*. 2022;112(2):291-296. doi: 10.1002/cpt.2600.

23. Smith DP, Oechsle O, Rawling MJ, Savory E, Lacoste AM, Richardson PJ. Expert-augmented computational drug repurposing identified baricitinib as a treatment for COVID-19. *Front Pharmacol*. 2021;12:709856. doi: 10.3389/fphar.2021.709856.

24. Richardson PJ, Stebbing J. Baricitinib as the treatment of choice for hospitalised individuals with COVID-19. *EClinicalMedicine*. 2022;49:101493. doi: 10.1016/j.eclinm.2022.101493.

25. Song W, Sun S, Feng Y, Liu L, Gao T, Xian S, et al. Efficacy and safety of baricitinib in patients with severe COVID-19: A systematic review and meta-analysis. *Medicine*. 2023;102(48):e36313. doi: 10.1097/MD.0000000000036313.

26. Viermyr H-K, Tonby K, Ponzi E, Trouillet-Assant S, Poissy J, Arribas JR, et al. Safety of baricitinib in vaccinated patients with severe and critical COVID-19 sub study of the randomised Bari-SolidAct trial. *EBioMedicine*. 2025;111. doi: 10.1016/j.ebiom.2024.105511.

27. Cherian JJ, Eerike M, Bagepally BS, Das S, Panda S. Efficacy and safety of baricitinib and tocilizumab in hospitalized patients with COVID-19: A comparison using systematic review and meta-analysis. *Front Pharmacol*. 2022;13:1004308. doi: 10.3389/fphar.2022.1004308.

28. 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(12):1407-1418. doi: 10.1016/S2213-2600(21)00331-3

29. Karampitsakos T, Papaioannou O, Tsiri P, Katsaras M, Katsimpris A, Kalogeropoulos AP, et al. Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial. *Clin Microbiol Infect*. 2023;29(3):372-378. doi: 10.1016/j.cmi.2022.10.015.

30. Manoharan S, Ying Ying L. Baricitinib statistically significantly reduced COVID-19-related mortality: a systematic review and meta-analysis of five phase III randomized, blinded and placebo-controlled clinical trials. *Biol Methods Protoc*. 2024;9(1):bpae002. doi: 10.1093/biomethods/bpae002.

31. Dobosh B, Zandi K, Giraldo DM, Goh SL, Musall K, Aldeco M, et al. Baricitinib attenuates the proinflammatory phase of COVID-19 driven by lung-infiltrating monocytes. *Cell Rep*. 2022;39(11):110945. doi: 10.1016/j.celrep.2022.110945.

32. Hall FC, Cheriyan J, Cope AP, Galloway J, Wilkinson I, Bond S, et al. Efficacy and safety of baricitinib or ravulizumab in adult patients with severe COVID-19 (TACTIC-R): a randomised, parallel-arm, open-label, phase 4 trial. *Lancet Respir Med*. 2023;11(12):1064-1074. doi: 10.1016/S2213-2600(23)00376-4.

33. Zhang J, Fan X, Zhang X, Jiang F, Wu Y, Yang B, et al. Efficacy and safety of tocilizumab and baricitinib among patients hospitalized for COVID-19: a systematic review and meta-analysis. *Front Pharmacol*. 2023;14:1293331. doi: 10.3389/fphar.2023.1293331.

34. Morales-Ortega A, Farfán-Sedano AI, San Martín-López JV, Escribá-Bárcena A, Jaenes-Barrios B, Madroñal-Cerezo E, et al. Baricitinib or imatinib in hospitalized COVID-19 patients: Results from COVINIB, an exploratory randomized clinical trial. *J Med Virol*. 2023;95(2):e28495. doi: 10.1002/jmv.28495.

35. Ahari MN, Mahmoodpoor A, Soleimanpour H, Valizadeh H, Ziaie S, Hamishehkar H. Evaluation of the Effects of Baricitinib and Ruxolitinib in Acute Respiratory Distress Syndrome (ARDS) Patients: A Meta-Analysis Study. *Pharm Sci*. 2025;31(2): 127-134. doi: 10.34172/PS.024.40299.

36 - Thoms BL, Gosselin J, Libman B, Littenberg B, Budd RC. Efficacy of combination therapy with the JAK inhibitor baricitinib in the treatment of COVID-19. *SN Compr Clin Med*. 2022;4(1):42. doi: 10.1007/s42399-022-01121-4.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Control Group (N = 10)	Intervention Group (N = 10)	P Value
Age (years), Mean ± SD	41.0 ± 13.4	51.2 ± 23.2	0.635
BMI (kg/m²), Mean ± SD	25.6 ± 2.3	26.3 ± 4.4	0.774
Gender (Male)	6	8	0.125
Obesity, n (%)	8 (80%)	4 (40%)	0.069
Smoking, n (%)	4 (40%)	0 (0%)	0.078
D-dimer, Mean ± SD	1.4 ± 0.2	1.0 ± 0.4	0.112
Comorbidities:			
Diabetes, n (%)	4 (40%)	6 (60%)	0.251
Ischemic Heart Disease, n (%)	4 (40%)	0 (0%)	
Hypercholesterolemia, n (%)	8 (80%)	2 (20%)	
Asthma, n (%)	8 (80%)	4 (40%)	

Table 2: Laboratory findings in the intervention and control groups throughout the study

Variable	Study Day	Control Group (N=10)	Intervention Group (N=10)	*P* Value
CRP (mg/L)	Day 1	113.0 ± 9.0	159.1 ± 124.2	0.041
	Day 7	113.6 ± 9.8	110.6 ± 55.3	0.859
	Day 14	118.2 ± 22.5	102.7 ± 93.8	0.744
	Overall	*P* = 0.695	*P* = 0.745	

Platelets ($\times 10^3/\mu L$)	Day 1	210.3 ± 19.5	213.2 ± 45.1	0.978
	Day 4	224.3 ± 64.6	211.0 ± 53.3	0.659
	Day 7	212.0 ± 78.0	255.2 ± 102.0	0.314
	Day 10	186.5 ± 69.5	329.7 ± 49.6	0.009
	Day 14	203.5 ± 74.5	235.7 ± 56.5	0.328
	Overall	*P* = 0.411	*P* = 0.859	
LDH (U/L)	Day 1	226.7 ± 95.8	661.2 ± 207.6	0.001
	Day 7	246.9 ± 69.9	745.8 ± 274.3	0.001
	Day 14	227.6 ± 73.6	639.2 ± 468.8	0.005
	Overall	*P* = 0.526	*P* = 0.851	
Lymphocyte ($\times 10^3/\mu L$)	Day 1	10.7 ± 8.9	8.0 ± 2.2	0.045
	Day 4	13.2 ± 8.3	10.9 ± 4.2	0.035
	Day 7	14.8 ± 7.0	8.8 ± 7.8	0.045
	Day 10	13.0 ± 6.2	7.4 ± 4.9	0.014
	Day 14	12.5 ± 6.5	8.8 ± 7.0	0.006
	Overall	*P* = 0.322	*P* = 0.474	
SpO_2/FiO_2 Ratio	Day 1	40.5 ± 2.9	72.4 ± 36.1	0.009
	Day 4	39.8 ± 7.6	74.2 ± 33.2	0.008
	Day 7	47.5 ± 3.7	110.7 ± 38.1	0.002
	Day 10	49.3 ± 3.1	110.4 ± 53.5	0.001
	Day 14	37.3 ± 12.6	180.5 ± 125.2	0.001

	Overall	*P* = 0.217	*P* = 0.395	
PaO_2 (mmHg)	Day 1	32.0 ± 5.8	52.6 ± 21.7	0.014
	Day 4	30.4 ± 6.6	55.5 ± 15.1	0.013
	Day 7	29.2 ± 6.5	80.1 ± 16.2	0.001
	Day 10	31.6 ± 3.2	63.9 ± 17.2	0.009
	Day 14	31.3 ± 4.1	95.6 ± 17.8	0.001
	Overall	*P* = 0.452	*P* = 0.633	

Table 3: Comparison of clinical outcomes in patients with ARDS between study groups

Variable	**Control Group (N=10)**	**Intervention Group (N=10)**	***P* Value**
Days with oxygen saturation ≥ 94% on room air, median (IQR)	10 (8–12)	16 (14–18)	0.002
Days without the need for supplemental oxygen, median (IQR)	12 (10–14)	18 (16–20)	0.003
Days with respiratory rate < 20 breaths per minute, median (IQR)	10 (8–12)	16 (14–18)	0.001
Requirement for high-flow oxygen or non-invasive ventilation, n (%)	8 (80%)	4 (40%)	0.012
Requirement for intubation, n (%)	6 (60%)	2 (20%)	0.045
Length of hospital stay (days), median (IQR)	28 (20–36)	40 (30–48)	0.020
ICU mortality rate, n (%)	4 (40%)	2 (20%)	0.045

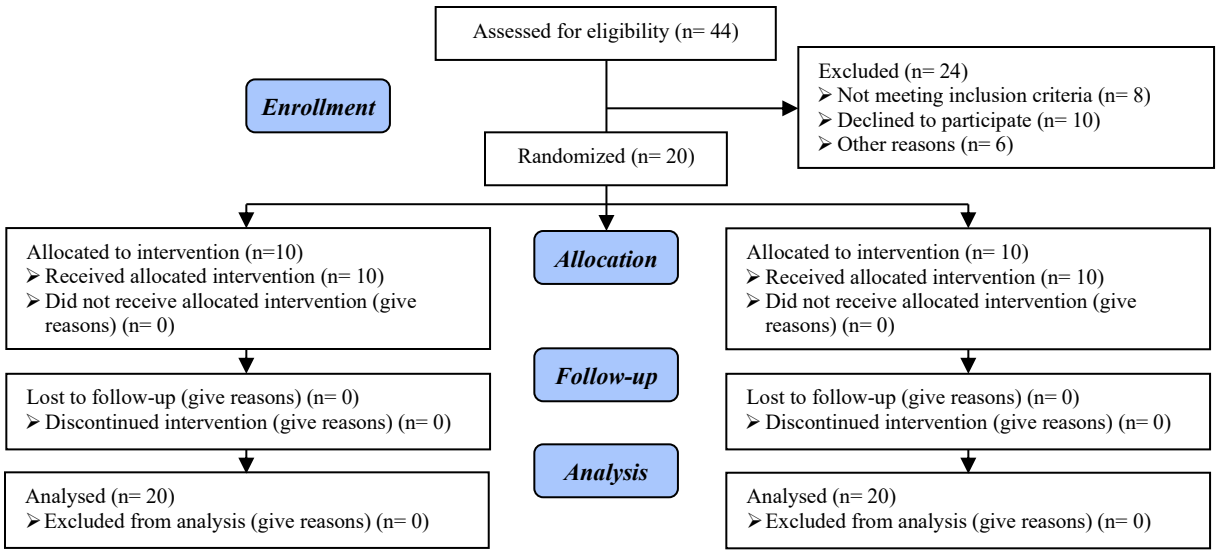

Figure 1. CONSORT flowchart diagram of the clinical trial

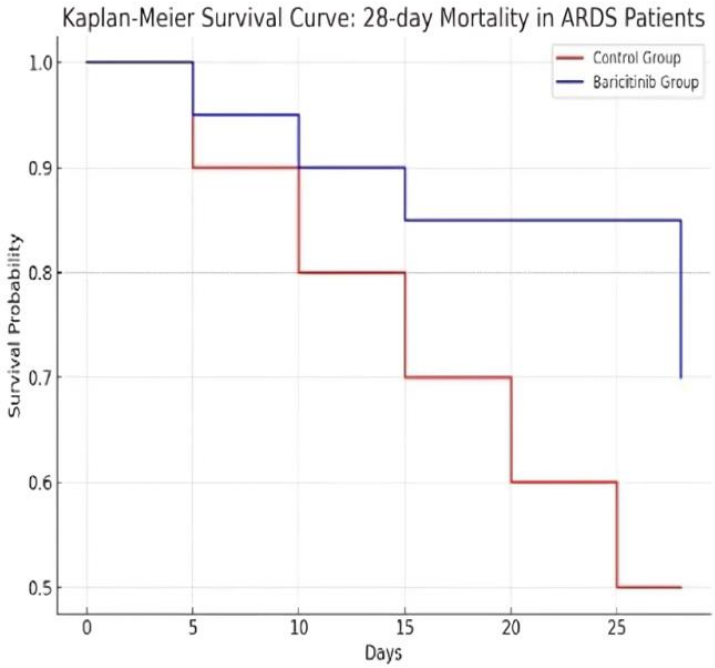

Figure 2: Kaplan-Meier survival curve comparing mortality between the baricitinib and control groups over a 28-day follow-up period