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Original Article

Evaluation of the Effects of Baricitinib in Patients with Acute Respiratory Distress Syndrome: A Pilot, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Mehdi Nurmohammad Ahari[1], Shadi Ziaie[1], Ata Mahmoodpoor[2], Hassan Soleimanpour[3], Hamed Valizadeh[4], Fariba Pourkarim[5], Saman Chaparzadeh[4], Hadi Hamishehkar[6,5*]

[1]Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Tuberculosis and Lung Disease Research Center of Tabriz University of Medical Sciences, Tabriz, Iran
[5]Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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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.

Methods: This double-blind, placebo-controlled clinical trial enrolled 20 patients with ARDS at Imam Reza Hospital, Tabriz. 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 and 60 days, with both clinical and laboratory markers.

Results: Intervention group showed a greater improvement in the arterial oxygenation (PaO_2/FiO_2 ratio) versus the placebo group but there was no significant difference between the two groups from the baseline through day 14 ($P=0.37$). Significant difference was observed in the reduced need for advanced respiratory support ($P<0.05$) for the intervention group compared to the placebo group. Although hospital stay was longer ($P<0.05$), intensive care unit (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 improvements in oxygenation, reduced need for advanced respiratory support, and lower ICU mortality compared to the control group, despite a longer hospital stay.

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

***Corresponding Author:** Hadi Hamishehkar, Email: hamishehkar@gmail.com

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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 and 60 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 or 60. Laboratory markers, including lactate dehydrogenase (LDH) and C-reactive protein (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 platelet count, lymphocyte count, CRP, LDH, and PaO_2/FiO_2 ratio), 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 final analysis was performed on 20

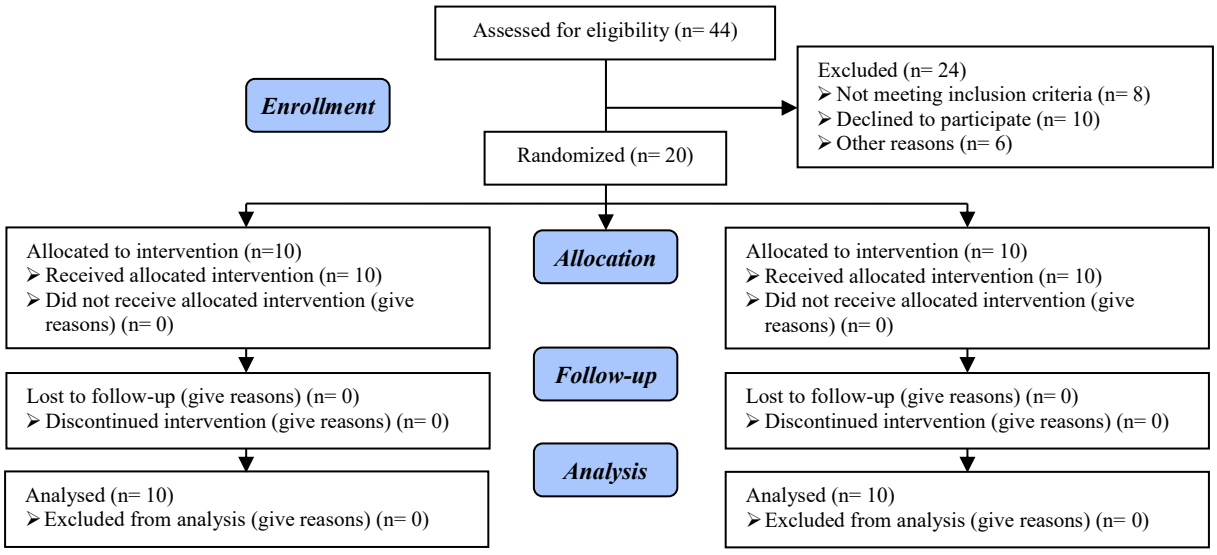


Figure 1. CONSORT flowchart diagram of the clinical trial

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 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

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 (×10³/μL)	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 (×10³/μL)	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	$P=0.322$	$P=0.474$	
PaO_2/FiO_2 ratio	Day 1	88.5±41.0	72.4±36.1	0.51
	Day 4	95.2±40.9	121.2±65.3	0.56
	Day 7	95.1±37.8	126.0±19.6	0.32
	Day 10	104.9±51.4	130.1±44.7	0.47
	Day 14	107.1±40.8	180.5±125.2	0.37
	Overall	$P=0.28$	$P=0.27$	

between group 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 ($P=0.009$). 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. Intervention group showed a greater improvement in the PaO_2/FiO_2 ratio versus the placebo group but there was no significant difference between the two groups (day 1: $P=0.51$; day 4: $P=0.56$; day 7: $P=0.32$; day 10: $P=47$; day 14: $P=0.37$) (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 the PaO_2/FiO_2 ratio was 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 lymphocyte counts between the two groups, likely reflecting decreased immune cell activation and controlled inflammatory responses in the intervention group.[22]

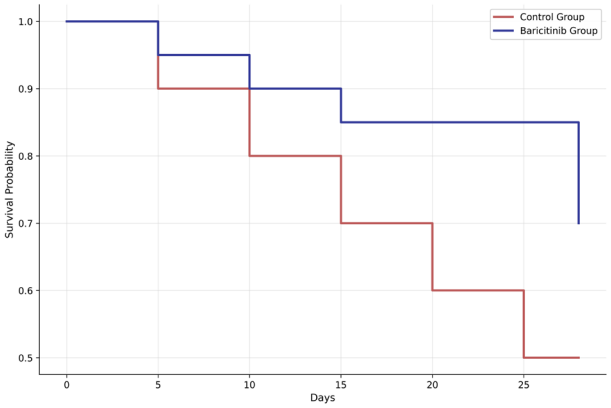


Figure 2. Kaplan-Meier survival curve comparing mortality between the baricitinib and control groups over a 28-day follow-up period

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

Interestingly, elevated levels of CRP at the early treatment stages likely reflect acute immune activation. With continued treatment with baricitinib 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 and minimizing cellular injury.[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.[12]

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.[28,29]

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.[30] 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.[32] 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.[33]

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.[34]

Limitations of 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 improvements in oxygen supplementation needs and significant 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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Authors' Contribution

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

Competing Interests

The authors declare no competing interests.

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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