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Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierx20

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To cite this article: Sepideh Tahsini Tekantapeh, Morteza Ghojazadeh, Ali Akbar Ghamari, Aida Mohammadi & Hassan Soleimanpour (2022) Therapeutic and anti-inflammatory effects of baricitinib on mortality, ICU transfer, clinical improvement, and CRS-related laboratory parameters of hospitalized patients with moderate to severe COVID-19 pneumonia: a systematic review and meta-analysis, Expert Review of Respiratory Medicine, 16:10, 1109-1132, DOI: 10.1080/17476348.2022.2114899

To link to this article: https://doi.org/10.1080/17476348.2022.2114899

EXPERT REVIEW OF RESPIRATORY MEDICINE
2022, VOL. 16, NO. 10, 1109–1132
https://doi.org/10.1080/17476348.2022.2114899

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META-ANALYSIS

Therapeutic and anti-inflammatory effects of baricitinib on mortality, ICU transfer, clinical improvement, and CRS-related laboratory parameters of hospitalized patients with moderate to severe COVID-19 pneumonia: a systematic review and meta-analysis

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ABSTRACT

Background: Due to the high incidence and mortality of the worldwide COVID-19 pandemic, beneficial effects of effective antiviral and anti-inflammatory drugs used in other diseases, especially rheumatic diseases, were observed in the treatment of COVID-19.

Methods: Clinical and laboratory parameters of eight included cohort studies and five Randomized Control Trials between the baricitinib group and the control group were analyzed on the first day of admission and days 7, 14, and 28 during hospitalization.

Results: According to the meta-analysis result of eight included cohort studies with 2088 patients, the Pooled Risk Ratios were 0.46 ($P < 0.001$) for mortality, 6.14 ($P < 0.001$) for hospital discharge, and the mean differences of 76.78 ($P < 0.001$) for PaO_2/FiO_2 ratio was −47.32 ($P = 0.02$) for CRP, in the baricitinib group vs. control group on the seventh or fourteenth day of the treatment compared to the first day. Based on the meta-analysis of five RCT studies with 11,825 patients, the pooled RR was 0.84 ($P = 0.001$) for mortality and 1.07 ($P = 0.014$) for patients' recovery. The mean differences were −0.80 ($P < 0.001$) for hospitalization days, −0.51($P = 0.33$) for time to recovery in the baricitinib group vs. control group.

Conclusions: Baricitinib prescription is strongly recommended in moderate to severe COVID-19.

ARTICLE HISTORY
Received 1 November 2021
Accepted 16 August 2022

KEYWORDS
COVID-19 pneumonia; baricitinib; Olumiant; cytokine release syndrome (CRS); hyperinflamation; JAK inhibitor; JAK-STAT pathway; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

1. Introduction

A newly enveloped non-segmented positive-sense Ribonucleic acid (RNA) β-coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the seventh member of the Coronaviridae family to infect humans, has caused the widespread global pandemic of the coronavirus disease (COVID-19) since December 2019 until now [1–5]. The main route of the transmission of the SARS-CoV-2 is through the respiratory tract. In order of prevalence, the most common clinical symptoms are fever, cough, shortness of breath, fatigue, sore throat, headache, and sometimes gastrointestinal symptoms [6,7]. Patients with underlying disease, old age, or predisposing risk factors present acute respiratory infectious syndrome, usually associated with widespread systemic inflammation and cytokine storm [8,9]. A mortality rate of 11.7–28.3% was reported among admitted COVID-19 patients [10]. The severity of COVID-19 disease, which is characterized by hyperinflammation and cytokine release storm(CRS), is the result of increased Interleukin 6 (IL-6) expression due to the activation of the Janus Kinase and Signal Transducer and Activator of Transcription (JAK-STAT) pathway [11]. Since inflammation is the most influential factor in COVID-19 pneumonia severity, the JAK/STAT pathway cascade is the path that catches our attention for further investigation. The SARS-CoV -2 infection causes CRS by employing pneumocytes, endothelial cells, macrophages, monocytes, lymphocytes, natural killer cells, and dendritic cells via the JAK/STAT pathway activation. Inflammatory laboratory data measure this hyperinflammation to assess the severity of the disease [12]. Thus, JAK/STAT inhibitors, such as ruxolitinib, baricitinib (Olumiant), and tofacitinib, can decrease the COVID-19 pneumonia severity by reducing extreme inflammation [13].

JAK inhibitor drugs include baricitinib, tofacitinib, perficitinib, filgotinib, upadacatinib, and fostamatinib belonging to targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) [14]. The European Union approved Baricitinib in 2017 to treat rheumatoid arthritis (RA) [15]. Previous studies on baricitinib in RA patients have reported a significant reduction in IL-6 [16]. From the beginning of the pandemic until now, anti-rheumatic drugs have been used in the treatment of COVID-19, and various studies have been performed on their effectiveness [17]. Baricitinib (C16H17N7O2S,

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/17476348.2022.2114899

Article highlights

- Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) causes high morbidity and morbidity in moderate to severe COVID-19 pneumonia through cytokine release syndrome (CRS).
- Baricitinib is an oral reversible selective Janus Kinase-1 (JAK1) and Janus Kinase-2 (JAK2) inhibitor drug, which is used for the treatment of rheumatoid arthritis (RA).
- JAK-inhibitors, especially FDA-approved baricitinib at a dose of 4 mg daily for up to 14 days, reduce mortality, need for mechanical ventilation, and ICU transfer by reducing virus entry and a hyperinflammation reduction in moderate to severe COVID-19 pneumonia.
- Reduced mortality and the need for ICU, faster clinical improvement and discharge, and significantly decreased inflammatory markers in the baricitinib group compared to the control group were obtained from an eight-cohort studies meta-analysis.
- The widespread administration of baricitinib in all countries by adding this drug to the national COVID-19 treatment protocol is recommended.
- Considering the available evidence, evaluating the beneficial effects of baricitinib against its side effects in moderate to severe COVID-19 confirms much more significant benefits of baricitinib in reducing the severity of disease inflammation and mortality and preventing the progression to more severe disease than its side effects; hence, its prescription is recommended according to the indication.

formerly LY3009104) is available as 2 mg oral tablets under the 'Olumiant' brand name, which as an immune-modulatory agent with the mechanism of Janus kinase type 1 and 2 inhibitors, is used to treat moderate to severe RA that has recently been allowed to be used in emergencies (severe COVID-19) in combination with remdesivir [18–21]. It seems that baricitinib has a higher digestive absorption than remdesivir and azithromycin. Baricitinib has a serum half-life (T1/2) of 12.5 hours compared with 0.39 hours in remdesivir [21]. Baricitinib has renal clearance (dose adjustment should be done in low Glomerular Filtration Rate (GFR)) and is dialyzable with 6 L/h Hemodialysis (HD) clearance [22,23]. Baricitinib has peak plasma concentrations, absolute bioavailability, and plasma protein binding equal to 60 min and 79%, respectively [22].

The main gateway for the SARS-CoV-2 to enter the respiratory cells is the angiotensin-converting enzyme 2 (ACE2) receptor, which produces inflammatory storms in patients with a severe and widespread inflammatory response [24,25]. ACE2 receptor binding affinity in baricitinib is far more than in remdesivir and azithromycin [21]. Thus AP2-associated protein kinase 1 (AAK1) disruption by a drug, such as baricitinib, can prevent the entry of SARS-CoV-2 into alveolar epithelial cells and subsequent viremia (dual baricitinib function includes decreased hyperinflammation and prevents virus entrance by inhibiting AAK1 that causes anti-inflammatory and antiviral activity) [21,26–34].

As with other immunomodulatory therapies, baricitinib can control CRS via suppressing the inflammatory storm in patients with severe COVID-19 infection [35,36]. As the severity of COVID-19 and inflammatory storm intensifies due to increased cytokines, the treatment choice to control hyperinflammation will be different, and a drug, such as baricitinib, will be very suitable for this stage [37]. As an oral reversible selective Janus Kinase-1 (JAK1) and Janus Kinase-2 (JAK2) inhibitor drug, baricitinib could bring COVID-19 pneumonia under control by competing with adenosine triphosphate (ATP) and blocking pro-inflammatory signals of cytokines such as Interferon-gamma (IFN-γ), Tumor Necrosis Factor-alpha (TNF-α), granulocyte colony-stimulating factor (G-CSF), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-10 (IL-10), interleukin-17 (IL-17), interleukin-12 (IL-12), and interleukin-23 (IL- 23) in the role of a cytokine-targeted therapy [13,38–41]. Due to impaired interferon-mediated antiviral response with baricitinib, administration of this drug to induce rapid clinical improvement should be considered with caution in severe COVID-19 hospitalized patients [24,42]. Reduction of IFN activity (IFN responses is an innate essential defense barrier against virus entry) by baricitinib decreases the ability of SARS-CoV-2 to enter adjacent cells by intensifying ACE2 downregulation in airway epithelial cells and primary bronchial cells, which causes less entry, less proliferation, and less infection of the host [22,43].

Extracorporeal cytokine removal or therapeutic plasma exchange (TPE) can control cytokine storm in severe COVID-19 by the mechanism of reduction of cytokines similar to cytokine-targeted treatment such as new anti-inflammatory drugs tocilizumab, anakinra, and baricitinib [41]. Common agents with baricitinib are azathioprine, abatacept, adalimumab, anakinra, sarilumab, infliximab, cyclosporine, and probenecid [44]. The anti-cytokine and antiviral nature of baricitinib cause its effective therapeutic effects on COVID-19 [16].

2. Methods

2.1. Protocol and registration

Based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, our systematic review and meta-analysis protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO), systematic review registration number: PROSPERO CRD42021254541 on 18 May 2021.

2.2. Eligibility criteria

Based on a primary search of studies about the effect of baricitinib on COVID-19 pneumonia, the eligibility of the studies for inclusion in our analysis included the following. Any cohort or RCT study on moderate to severe COVID-19 pneumonia with baricitinib in case groups with or without standard antiviral therapies and control groups treated with standard treatments without baricitinib in the other arm, aged patients ≥ 2 years old. Consequently, the participation of both sexes in the study, studies published from December 2019 to May 2022, and without any language restrictions.

2.3. Search strategy

Using our search strategy based on keywords resulting from Medical Subject Headings (MeSH) terms (the supplement file 1), the database of MEDLINE, Excerpta Medica Database (EMBASE), Scopus, Web of Science, Google Scholar, the

Cochrane-controlled trial registry in the Cochrane Library, and the ClinicalTrials.gov website (National Institute of Health) were searched for completed but unpublished studies. All references to selected articles were also read manually to ensure no study was missed. The search was done from early March 2021 to late May 2022.

2.4. Article selection criteria

The Population, Intervention, Comparison, Outcome, Study design (PICOS) index of all eligible published cohort studies was assessed during the last two and a half years. Our search strategy focused on four items: the study type (cohort and CRT studies), participants (hospitalized ≥ 2 years old men and women with moderate to severe COVID-19 pneumonia), intervention (baricitinib vs. other therapies), and outcomes (decreased hospitalized days, decreased need for intubation or ICU transfer, decreased mortality, accelerate recovery, decreased serum inflammatory parameters, and side effect evaluation). In the primary search of databases, 143 duplicated papers were removed out of 694 retrieved articles by EndNote software. Then 423 titles, abstracts, and full- texts of papers published from December 2019 to May 2022 without language restrictions were reviewed by two researchers independently (ST and HS). Excluding 3114 irrelevant papers led to 109 remaining articles, of which eight eligible cohort studies (in the format of the research articles, letters to the editor, or comment articles) and five RCT studies were included in this systematic review and meta-analysis. The studies concerned the evaluation of 'baricitinib' in case groups versus 'standard COVID-19 treatment without baricitinib' in control groups about moderate to severe (oxygen saturation (SaO2) < 94%, fever, cough, myalgia, fatigue, the Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration (PaO_2/FiO_2) ratio of 100–300 mmHg, SARS-CoV-2 nasopharyngeal swab-positive, and evidence of radiological pneumonia) hospitalized COVID-19 patients. When disputes between observations of the two authors were not resolved in cases of eligibility disagreement or discrepancy, the opinion of the third author (MG) was accepted to solve the issue.

2.5. Study screening and data extraction

Authors ST and HS initially screened articles after removing duplicated papers by EndNote software. After reviewing the titles and abstracts of 423 studies, 314 articles were set aside due to irrelevancy. Eight cohort and five RCT studies out of 109 remaining relevant articles were selected to be analyzed according to the inclusion and exclusion criteria.

The primary and highest outcomes assessed in our study were mortality, hospitalized days, need for intubation and ICU transfer, the PaO_2/FiO_2 ratio, and serum levels of C-reactive protein (CRP) and IL-6 in hospitalized ≥ 2 years old patients with moderate to severe COVID-19 pneumonia after treatment with baricitinib in comparison with the standard treatment (hydroxychloroquine, corticosteroids, and antivirals such as lopinavir/ritonavir). On the other hand, the secondary outcomes were discharge rate, time to recovery, fever, lymphocyte count, and Transaminase (ALT) in the baricitinib arm compared with the no-baricitinib arm, and finally, baricitinib safety and side effects.

Due to three missing data, including mean ages and serum levels of IL-6 in a study by Bronte et al., and correct lymphocyte counts in a study by Stebbing et al. in both case and control groups, three emails were sent to the corresponding authors. The completed correct data were entered into the extraction table according to their responses.

The final data of primary and secondary outcomes of the eight included cohorts and five RCT studies were carefully entered into the data extraction table by two authors independently (ST and HS). Our study extraction table was categorized into six headings, including (1) study specifications (title, authors, year, country, study type, and study duration), (2) baseline demographic characteristics of COVID-19 (sample size, gender, mean age, drugs, and dosage, and disease severity), (3) respiratory system parameters at baseline (t0), after 1 week (t7), and after 2 weeks (t14) (PaO_2/FiO_2, time to recovery, discharge rate, hospitalization days, ICU transfer and mechanical ventilation, death), (4) laboratory and immunologic data at baseline (t0), after 1 week (t7), and after 2 weeks (t14) (CRP, lymphocytes, ALT, and IL-6), (5) general system parameters at baseline (t0), after 1 week (t7), and after 2 weeks (t14) (fever), and (6) adverse effects in detail.

It is noteworthy that the meta-analysis of each outcome was performed if data were available in at least two studies due to the insufficient data on some variables among the primary and secondary outcomes in the included cohort and RCT studies.

2.6. Study selection

The initial electronic search yielded 694 citations. After two authors' reviews, 143 duplicated articles and 128 ineligible papers, titles, and abstracts of 423 papers were removed in the initial screening. They independently agreed to exclude 314 records because of irrelevancy. Eventually, eight cohort and five RCT articles of the remaining 109 papers were included in the meta-analysis phase according to the inclusion and exclusion criteria [45–57]. The PRISMA algorithm in Figure 1 illustrates the study selection process.

2.7. Data synthesis, analysis, and exploration of heterogeneity

Heterogeneity between studies was assessed using the I2 index and Q-value statistics. The sample size and means with standard deviations for quantitative variables and the sample size and number of items for qualitative variables were extracted in each group of included articles. The articles reported with InterQuartile Range (IQR) were converted to means and standard deviations using the method introduced by Wan et al. [58]. The mean differences between the two groups for quantitative consequences and the risk ratio were calculated for qualitative consequences. The results of the meta-analysis were integrated using the Random Effect Model. CMA v.3.1 (Comprehensive Meta-Analysis) software was used for statistical analysis. A P-value less than 0.05 was interpreted as a significant level.

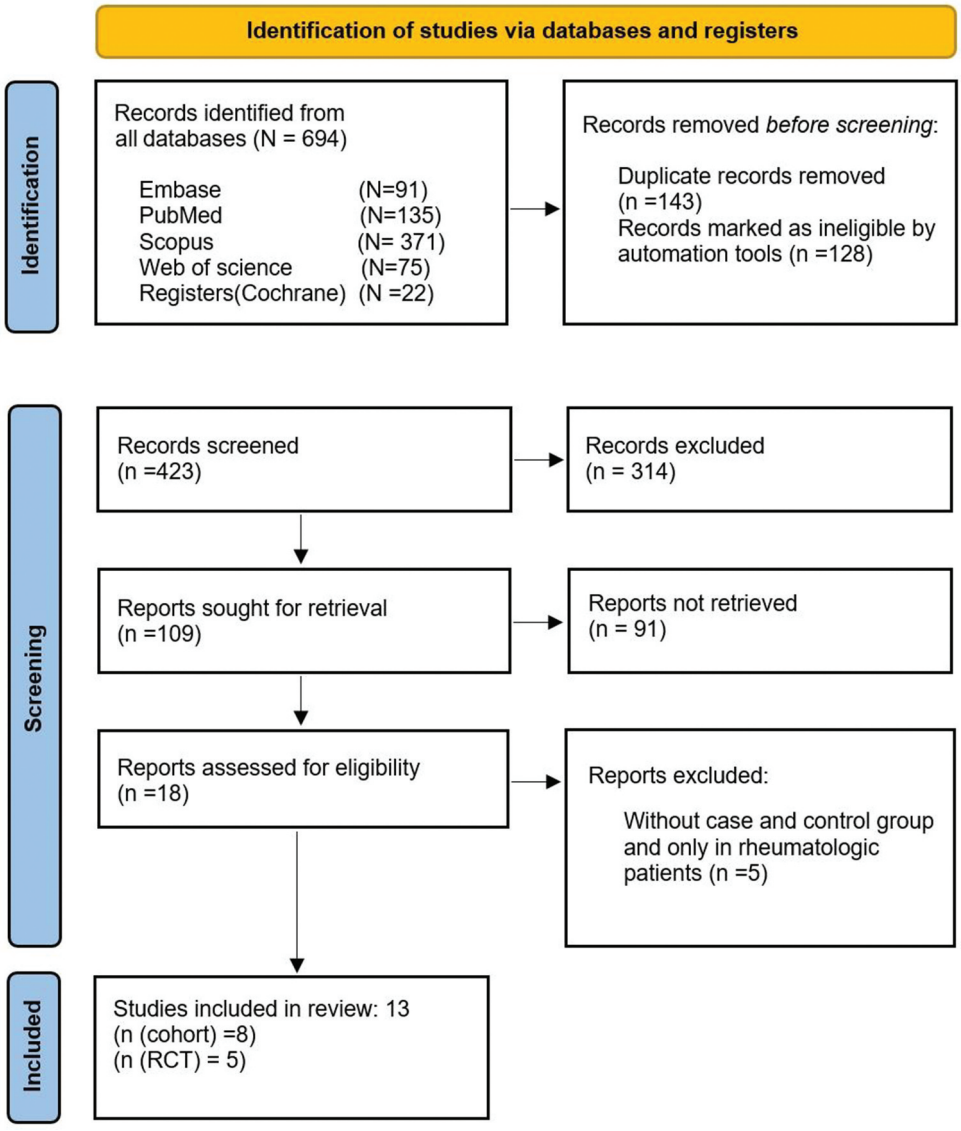

Figure 1. Study flow chart based on PRISMA Flow Diagram.

2.8. Grading the strength of evidence

The overall quality of evidence for each outcome in the involved cohort and RCT studies was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Table of 'Summary of findings' were created using GRADE Profiler (GRADE pro-Guideline Development Tool (GDT)) in this study. Our GRADE assessment was obtained considering five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Table 1 shows the GRADE results for the evidence obtained from the meta-analysis results for each of the studied outcomes. Based on the presented table (Table 1), the obtained evidence strengths were rated from Moderate to High.

3. Results

3.1. Characteristics of the studies included

The included studies were classified into two categories for meta-analysis: cohorts (eight studies) and RCTs (five studies). Among the eight included cohort studies, four surveys were conducted in Italy, four in Spain, respectively (one joint study in Spain and Italy), and a cohort study from Mexico. Most included RCT studies are multicenter and have been conducted in different countries. The demographic characteristics and the clinical, paraclinical, and immunological effects of baricitinib were examined on hospitalized patients with moderate to severe COVID-19 pneumonia in the included cohort and RCT studies. Regarding included eight cohort studies, it should be noted that from a total of 2088 patients (1330 males and 758 females) aged 60–75 years, 687 of whom were treated with baricitinib alone or in combination with antivirals (lopinavir/ritonavir) and corticosteroids (methylprednisolone), and 1401 patients were treated with hydroxychloroquine with antivirals or corticosteroids and standard COVID-19 treatments without baricitinib. About five RCT studies, it is noted that 11,825 patients (7638 males and 4187 females) aged 2–74 years, 5994 of whom were in the baricitinib group, and 5831 patients were in the control group. The basic characteristics of each included study (cohorts and RCTs, separately) are presented in detail in Tables 2 and 3.

Table 1. Evidence quality associated with baricitinib therapeutic effect based on GRADE assessment.

Outcome	Effect size and 95% confidence interval (CI)			Quality of evidence
	Studies Number	Risk Ratio(RR), 95% CI	I-squared	
		Cohort studies		
Deaths	7	0.47 (0.36 to 0.61)	0	High
ICU Transfer	5	1.30 (0.46 to 3.56)	92.83	Moderate
Discharge	2	6.15 (3.51 to 10.78)	0	Moderate
		RCT studies		
Deaths	5	0.84 (0.76–0.93)	49.31	High
Recovery (N)	2	1.07 (1.01–1.41)	0	Moderate
Outcome	Effect size and 95% confidence interval (CI)			Quality of evidence
	Studies Number	Mean Difference, 95% CI	I-squared	
		Cohort studies		
PaO2/FiO2 ratio	3	76.78(50.97 to 102.59)	0	Moderate
Fever	3	−0.64(−1.36 to 0.07)	85.96	Moderate
CRP	3	−47.32(−86.36 to −8.28)	82.03	High
IL-6	2	−13.8(−19.73 to −7.87)	0.000	High
Lymphocyte count	2	0.48(0.35 to 0.61)	0	Moderate
ALT	2	20.17(2.02 to 38.32)	77	High
		RCT studies		
Hospitalization days	5	−0.80 (−0.93 to −0.67)	0	Moderate
Time to Recovery(days)	3	−0.51 (−1.54 to 0.52)	91.84	High

3.2. Meta-analysis results

3.2.1. Cohort studies meta-analysis results

In this section, the main and secondary outcomes of the meta-analysis for the eight included cohort studies (death, ICU transfer, discharge, PaO_2/FiO_2 ratio, fever, CRP, IL-6, lymphocyte count on day 14, and ALT) and their forest plot graphs are explained by interpretation.

3.2.1.1. Death. Based on the report of patients' mortality rates in the baricitinib and control groups in seven included cohort studies, the heterogeneity between the studies was not significant (I-squared = 0.00, P-value = 0.51, df(Q) = 6, Q-value = 5.23). According to the meta-analysis results, the mortality risk in the baricitinib group was 0.47 times that of the control group (Pooled Risk Ratio(RR) = 0.47, 95% Confidence Interval (CI) = 0.36, 0.61, Z-value = −5.69, P-value < 0.001). The Forest Plot graph from the results of the mortality rate meta-analysis is shown in Figure 2.

3.2.1.2. ICU transfer. Based on the report of patients' need for intubation and ICU transfer in the baricitinib and control groups in five included cohort studies, the heterogeneity between the studies was significant (I-squared = 92.83, P-value = 0.00, df(Q) = 4, Q-value = 55.81). According to the meta-analysis results, the ICU transfer risk in the baricitinib group was 1.28 times that of the control group (Pooled RR = 1.28, 95% CI = 0.46, 3.57, Z-value = 0.48, P-value = <0.001). The Forest Plot graph from the results of the ICU transfer rate meta-analysis is shown in Figure 3.

3.2.1.3. Discharge. Based on the report of patients' discharge from the hospital in the baricitinib and control groups in two included cohort studies, the heterogeneity between the studies was not significant (I-squared = 0.00, P-value = 0.891, df(Q) = 1, Q-value = 0.019). According to the meta-analysis results, the discharge rate in the baricitinib group was 6.14 times that of the control group (Pooled RR = 6.14, 95% CI = 3.50, 10.78, Z-value = 6.33, P-value < 0.001). The Forest Plot graph from the results of the discharge rate meta-analysis is shown in Figure 4.

3.2.1.4. PaO_2/FiO_2 ratio. Based on the report of the patients' PaO_2/FiO_2 ratio in the baricitinib and control groups on the first and the seventh days after treatment in three included cohort studies, the heterogeneity between the studies was not significant (I-squared = 0.00, P-value = 0.84, df(Q) = 2, Q-value = 0.357). According to the meta-analysis results, the mean change in the PaO_2/FiO_2 ratio in the baricitinib group was 76.78 mmHg more than the control group (Pooled Mean Difference = 76.78, 95% CI = 50.97, 102.59, Z-value = 5.83, P-value = < 0.001) at the seventh day of treatment during hospitalization compared to the first day. The Forest Plot graph from the results of the PaO_2/FiO_2 ratio meta-analysis is shown in Figure 5.

3.2.1.4. Fever. Based on the report of the patients' fever in the baricitinib and control groups on the first and the seventh days after treatment in three included cohort studies, the heterogeneity between the studies was significant (I-squared = 85.96, P-value = < 0.001, df(Q) = 2, Q-value = 14.24). According to the meta-analysis results, the mean change in the Body Temperature (BT) in the baricitinib group was 0.64°C less than the control group (Pooled Mean Difference = −0.64, 95% CI = −1.36, 0.07, Z-value = −1.76, P-value = 0.08) at the seventh day of treatment during hospitalization compared to the first day. The Forest Plot graph from the results of the fever meta-analysis is shown in Figure 6.

3.2.1.5. CRP. Based on the report of the patients' serum CRP levels in the baricitinib and control groups on the first and the seventh days after treatment in three included cohort studies, the heterogeneity between the studies was significant (I-squared = 82.03, P-value = < 0.001, df(Q) = 2, Q-value = 11.13). According to the meta-analysis results, the mean change in serum CRP levels in the baricitinib group was 47.32 mg/L less than the control group (Pooled Mean Difference = −47.32, 95% CI = −86.36, −8.28, Z-value = −2.38,

Table 2. Basic demographic, respiratory system symptoms and outcomes, laboratory data, and general symptoms characteristics of COVID-19 patients ('baricitinib/control') respectively, in eight included cohort studies in the systematic review.

Author/ date/ Ref.	Bronte et al. (2020 Nov) [45]	Stebbing et al. (2021 Jan) [46]	Cantini et al. (2020 Apr) [47]	Rodriguez-Garsia etal. (2021Jan)[48]	Cantini et al. (2020 Oct) [49]	Masiá et al. (2021 Nov) [50]	Pérez-Alba et al. (2021 Oct) [51]	Abizanda et al. (2021 Oct) [52]	
Location	Italy	Italy/ Spain	Italy	Spain	7 Italian hospital	Spain	Mexico	Spain	
Study Duration	34 weeks	4 weeks	6 weeks	6 weeks	2 weeks	52 weeks	32 weeks	16 weeks	
Type of Study	longitudinal clinical trial (model :cohort) off-lable using drug	cohort observational study	pilot study	prospective observational cohort study	spective,longitudinal multicenter study, off- lable use drug	longitudinal prospective cohort study	retrospective comparative study	propensity score [PS]-matched retrospective cohort study total sample=328	
Sample size(BAR/cont)	76 (20/56)	166 (83/ 83)	24 (12/ 12)	112 (62/ 50)	191 (113/ 78)	994 (110/ 884)	197 (123 / 74)	172 (86/ 86)	156 (78/ 78)
Gender(M/ F)	38/ 38	85/ 81	20/ 4	78/ 34	119/ 72	636/ 358	123/74	129/43	102/54
Mean Age(case/ cont)	68/ 72	74.0/ 74.1	63.5/ 63.0	63/ 64	68/ 63	72/ 65	60.7 / 58.5	58.6/59.2 (< 70)	79.2/79.1 (≥ 70)
Disease Severity	moderate to severe	moderate to severe	mild to moderate	moderate to severe	Moderate	severe	moderate to severe	moderate to severe	
BAR Group (drug and dosage)	daily for 2 days, followed by 4mg/d to 7days (9days)*	+SOC in Italy. 2 or 4 mg/d for 3 -11 d in the Spanish cohort	BAR 4mg/day + L/R (2 weeks)	+ MTP (5 days) ¥	BAR 4mg/day + L/R (2 weeks)	Tocilizumab + BAR	Baricitinib + Dexamethasone	BAR + tocilizumab, anakinra, and corticosteroids	
Control Group (drug and dosage)	therapy (L/R) + (HCQ plus antiviral therapy)**	HCQ + L/R, antibiotics, LMWH and corticosteroids	+ HCQ 400 mg daily (2 weeks)	MTP alone (7-10 days)§	+ L/R tabletes 250 mg/bid	Tocilizumab	Dexamethasone	tocilizumab, anakinra, and corticosteroids	
Deaths, n (%)	1 (5%) / 25 (45%)	14 (16.8%) / 9 (34.9%)	were discharged.	5(4.2%)/ 11(4%)	0 (0) / 7 (8.9%)	28(26%)/46(5%)	25(20.3%)/30 (40.5%)	6(7.0)/13 (15.1)	16(20.5)/ 30 (38.5)
ICU Transfer***			0 / 4		0 / 14	42(38%)/51(6%)	59(47.6%)/26 (35.1%)	41(47.7)/ 21 (24.4)	6(7.7)/2 (2.6)
Discharged N			7 // 1		88 / 10				

(*Continued*)

Table 2. (Continued).

Author/ date/ Ref.	Bronte et al. (2020 Nov) [45]	Stebbing et al. (2021 Jan) [46]	Cantini et al. (2020 Apr) [47]	Rodriguez-Garsia etal. (2021Jan)[48]	Cantini et al. (2020 Oct) [49]	Masiá et al. (2021 Nov) [50]	Pérez-Alba et al. (2021 Oct) [51]	Abizanda et al. (2021 Oct) [52]
hospitalization days (median)	12 // 11			14 / 13		19 / 6	8//6	
PaO2/FiO2, median (IQR) (t0, t7)	241: 331 / 220: 225		290:410/268:302		265:336/267:293			
Fever (°C),median (IQR) (t0, t7)	36.9: 36.4/ 37.2: 36		38:36.1/38.1:37.7		38:36.1/38:37.5			
CRP (t0, t7)	53.15: 9.7/64.5: 38		82: 22.6 / 30: 17		82: 9.6/ 63: 54			
IL-6 (pg/ml)(t0, t7)	24.5:7.5/18.8:14.2				29.4: 5/32.6:29.3			
Lymphocytes (cells/µL) (t0,t14)	992:1372/ 954:1011		700:1300/ 890:900		930:1300/880:900			
ALT(U/L)median (IQR) (t0, t14)			24.8: 78 / 44: 44.5		29: 45 / 34: 54.8			

* A low dose of 2 mg twice daily for 2 days followed by 2 mg per day was maintained for patients older than 75 years. A dose reduction was also considered in instances of renal insufficiency (glomerular filtration rate [GFR] <30 mL/ min/1.73 m^2), hepatotoxicity, or myelotoxicity.

** Supportive therapy, such as antibiotic prophylaxis and anticoagulant, is at the clinicians' discretion.

*** ICU admission needs invasive mechanical ventilation during hospitalization.

¥ 7–10 days of lopinavir/ritonavir 200/50 mg, two tablets/12 h + hydroxychloroquine 200 mg, a loading dose of two tablets/12 h for the first day followed by one tablet/12 h + 6 methylprednisolone 80,125 or 250 mg/day for 3 days and then prednisone, combined with baricitinib for 5–10 days. Baricitinib was administered under two schemes: a loading dose of 4 mg the first day and then 2 mg daily (low-dose baricitinib, n = 40) or 4 mg daily each day (high-dose baricitinib, n = 22). Patients older than 75 years received low-dose baricitinib.

§ 7–10 days of lopinavir/ritonavir 200/50 mg, two tablets/12 h + HCQ 200 mg, a loading dose of two tablets/12 h for the first day followed by one tablet/12 h + patients received three consecutive days of pulse corticosteroid therapy (corticosteroids pulses) followed by prednisone at a starting dose of 30 mg/day. Therapy was discontinued by tapering after 7–10 days of treatment. Methylprednisolone, total dose, median (IQR), mg: 500 (375–750) (both groups).

Abbreviations. BAR: baricitinib, HCQ: hydroxychloroquine, L/R: lopinavir/ritonavir, MTP: methylprednisolone, SOC: standard of care

Table 3. Five included RCT studies in the systematic review, basic demographic, laboratory data, hospitalization, recovery, and mortality of COVID-19 patients ('baricitinib/control').

	RCT Name	ACCT-2	COV-BARRIER		RECOVERY	ACTT-4
	RCT Number	NCT04401579	NCT04421027		NCT04381936	NCT04640168
	Authors/date/ref. number	Kalil et al.(4 March 2021) [53]	Marconi et al.(1 December 2021) [54]	Ely et al.(1 April 2022) [55]	Horby et al.(1 January 2022) [56]	Wolfe et al.(23 May 2022) [57]
	Type of Study	Multicentre, double-blind, randomized, placebo-controlled trial	Multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial	Multicentre, randomized, double-blind, placebo-controlled, parallel-group trial	An investigator-initiated, individual randomized, controlled, open-label, platform trial	Multicentre, randomized, double-blind, double placebo-controlled trial
CRTs Characteristics	Randomization	Randomly assigned in a 1:1 ratio. The trial team was unaware of the trial-group assignments until after all data queries were resolved, and the database was locked.	Randomly assigned (1:1) to receive BAR or matched placebo for up to 14 days. Computer-generated random sequence randomization to allocate participants 1:1 to the BAR group or the placebo group.	Randomly assigned (1:1) to BAR or placebo in combination with SOC (baseline systemic corticosteroid). Participants, study staff, and investigators were masked to study group assignment.	Randomly allocated (1:1) to either usual SOC or SOC plus BAR using web-based simple randomization with allocation concealed until after randomization.	Randomly assigned (1:1) to receive either BAR, RDV, and placebo, or DEX, RDV, and placebo using a permuted block design. The treatment allocation table was generated using SAS version 9.4.
	Location (country)	67 trial sites in 8 countries: US(55), Singapore (4), South Korea (2), Mexico (2), Japan (1), Spain (1), UK (1) & Denmark (1)	101 centers across 12 countries in Asia, Europe, North America, and South America	Multinational across 18 centers in four countries (Argentina, Brazil, Mexico, and the USA).	At 177 hospital organizations in the United Kingdom	67 trial sites in the USA (60 sites), South Korea (two sites), Mexico (two sites), Singapore (two sites), and Japan (one site).
	Race – no. (%)	Asian: 49 (9.5%)/52 (10.0%) Black: 77 (15.0%) /79 (15.3%)White: 251 (48.7%) /245 (47.3%) Other or unknown: 138 (26.8%)/142 (27.4%)	American Indian or Alaskan Native: 148(20%) /168 (23%)Asian:80 (11%) /94(13%)Black or African American: 39(5%)/36(5%)Native Hawaiian or other Pacific Islander: 3 (<1%) /2 (<1%)White: 480 (64%) /440(59%)	American Indian or Alaska Native: 15 (29%) /17 (34%)Asian: 0/ 1 (2%)Black or African American: 1 (2%) /1 (2%)Multiple: 2 (4%)/ 0White: 32 (63%)/ 30 (60%)Missing 1 (2%) /1 (2%)	White:3192(77%) /3104 (77%)Black, Asian, and minority ethnic: 457(11%)/455 (11%)Unknown:499 (12%) /449 (11%)	American Indian or Alaska Native: 8 (2%)/10 (2%)Asian: 35 (7%) /35 (7%)Native Hawaiian: 1 (<1%) /4 (1%)Black or African American: 94 (18%) /94 (19%)White: 307(59%)/281 (57%)
	Duration	8 May 2020, to 1 July 2020 (7 weeks)	11 June 2020, to 15 January 2021 (28 weeks)	23 December 2020, to 10 April 2021 (15 weeks)	2 February 2021, to 29 December 2021 (44 weeks)	1 December 2020, to 13 April 2021 (18 weeks)
	Intervention/ Control	RDV(≤10 days) + BAR (≤14 days) /RDV (≤10 days) + placebo	BAR + SOC / placebo + SOC (up to 14 days or until discharge from hospital, whichever occurred first.)	BAR + SOC(baseline systemic corticosteroid)/ placebo + SOC (baseline systemic corticosteroid) (for up to 14 days)	SOC + BAR 4 mg once daily by mouth/SOC alone for 10 days or until discharge if sooner	BAR + RDV + placebo (14 day)/ DEX + RDV+ placebo (10 days)
	Detail of included participants	Hospitalized patients with moderate and severe covid-19 pneumonia	At least 18 years of age hospitalized patients with laboratory-confirmed sars-cov-2 infection, evidence of pneumonia or active symptomatic covid-19, and at least one elevated inflammatory marker (c-reactive protein, d-dimer, lactate dehydrogenase, or ferritin).	Patients ≥18 yrs, who had been hospitalized with laboratory-confirmed SARS CoV-2 infection, with IMV or ECMO at study entry & randomization, progression risk indicator with at least one high inflammatory marker > ULN based on the CRP, D-dimer, LDH, or ferritin.	Patients ≥2 years admitted to hospital with clinically suspected or laboratory-confirmed SARS-CoV -2 infection and no medical history that might, in the clinicians opinion, put the patient at significant risk if they were to participate in the trial.	Hospitalized adults male or non-pregnant female ≥18 years old with laboratory-confirmed SARS-CoV-2 infection) who required supplemental O_2 administered by low-flow (≤15 L/min), high-flow (>15 L/min), or NIV modalities

(*Continued*)

Table 3. (Continued).

	RCT Name	ACCT-2	COV-BARRIER		RECOVERY	ACTT-4
Methods	Detail of Excluded participants		Participants required IMV were receiving IS, ALT, or AST concentration > five times the ULN, or an eGFR<30 mL/min/ 1 · 73 m^2	Patients received high-dose corticosteroid (>20 mg/day for≥14 consecutive days in the month before the study unless indicated SOC for concurrent disease. Immunosuppressed patients who had suspected serious active bacterial, fungal, or untreated TB.	Patients aged <2 years, eGFR<15 mL/min/1.73 m^2 or on dialysis or hemofiltration, ANC <0.5 x 10^9 /L, evidence of active TB infection, or were pregnant or breastfeeding.	
	Sample size (BAR/ control)	1033 (515/518)	1525 (764/761)	101 (51/50)	8156 (4148/4008)	1010 (516/494)
	Mean Age (BAR/ control)	55.0 ± 15.4/55.8 ± 16	57 · 8 ± 14.3/57 · 5 ± 13 · 8	58 · 4 ± 12.4/58 · 8 ± 15 · 2	58.5 ± 15.4/57.7 ± 15.5	58 · 2 ± 14 · 3 /58 · 5 ± 13 · 7
	Gender(M/ F), no. (%)	652(63.1)/381(36.9)	963 (63.1)/562 (36.8)	55 (54.4)/46 (45.5)	5378(65.9)/2778(34)	590 (58.4)/ 420 (41.6)
	BMI (BAR/ control)	32.2 ± 8.2 /32.3 ± 8.4	30 · 4 ± 6 · 4/30 · 6 ± 6 · 6	34 · 3 ± 7 · 8/ 32 · 1 ± 6 · 3		32 · 9 ± 8 · 6/33 · 6 ± 9 · 0
	Disease Severityordinal scale score	Moderate to severeordinal scale score 4-7	Ordinal scale score:4–6	Ordinal scale score:4–6	Severe	Severe
	BAR Group (drug and dose)	4-mg daily dose (either orally for 14 days or until hospital discharge. Patients with an estimated GFR < 60 ml/ min/1 · 73 m^2 received BAR at a dose of 2 mg once daily.	BAR at a dose of 4 mg/day for up to 14 days or until discharge from the hospital, whichever occurred first; however, 2 mg/day was given if the patient had baseline GFR: 30 to<60 mL/min/1 · 73 m^2	Baricitinib 4 mg once daily for up to 14 days or until discharge from hospital, whichever occurred first. Participants assigned to BAR with baseline eGFR of 30 to < 60 mL/ min/1 · 73 m^2 received BAR 2 mg or matched placebo.	BAR 4 mg daily for 10 days (or until discharge if sooner). The dose was to be reduced for patients with eGFR <60 mL/min/1.73 m^2 or receiving probenecid and for children<9 yrs.	RDV, IV 200-mg loading dose and 100-mg daily for up to 10 days or until hospital discharge or death. A 4-mg daily dose of BAR (or placebo) orally for up to 14 days or until hospital discharge or death; reduced with eGFR<60 mL/min/1 · 73 m^2 + placebo
	Control Group (drug and dose)	RDV IV as a 200-mg loading dose on day 1, followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death.	Interventions were packaged in identical bottles containing tablets of either 2 mg BAR or a matching placebo, given daily for up to 14 days or until discharge from the hospital, whichever occurred first.	Matched placebo was crushed for NGT delivery (or given orally when feasible) and given once daily for up to 14 days or until discharge from the hospital, whichever occurred first.	Corticosteroid ± RDV and casirivimab + imdevimab, although the use of tocilizumab	A 6-mg daily dose of DEX (or placebo) IV for up to 10 days or until hospital discharge or death +RDV, IV 200-mg loading dose, and 100-mg daily for up to 10 days or until hospital discharge Or death +placebo

(*Continued*)

Table 3. (Continued).

	RCT Name	ACCT-2	COV-BARRIER		RECOVERY	ACTT-4
	Comorbid conditions no. (%)	None:64(12.9%)/ 91(18.3%) One: 148(29.8%)/ 122 (24.5%)≥2: 28(57.3%) / 285(57.2%)	Obesity: 250 (33%)/253 (33%)Diabetes (types 1 and 2): 224 (29%)/233 (31%)Chronic respiratory disease: 34(4%) /36(5%)HTN:365(48%)/366 (48%)	Obesity:28(55%)/29(58%)Diabetes (type 1 and type 2): 20 (39%) /16 (32%)Chronic respiratory disease:1 (2%) /2 (4%) HTN:31(61%)/24(48%)	DM: 961(23%)/941(23%)Heart disease: 782(19%)/706 (18%)Chronic lung disease: 882(21%)/783 (20%)TB: 0 (0%) /0 (0%)HIV:13(<1%)/9 (<1%)Severe liver disease: 33 (<1%) /33 (<1%)Severe kidney disease: 101 (2%)/ 79 (2%)	No comorbidities: 44 (9%)/52 (11%)One comorbidity: 107 (21%) /92 (19%)≥2 comorbidities:353(70%)/334 (70%)Chronic respiratory disease:45(9%) 44(9%)HTN:298 (59%)/480(59% Obese307(61%)/302(63%CKD: 49 (10%) /43(9%)
	Concomitant comedication	All the patients received standard supportive care at the trial site hospital	SOC included systemic corticosteroids, such as DEXA, and antivirals, including RDV or both.	SOC(baselinesystemic corticosteroid)	Corticosteroid RDV tocilizumab	All patients received standard supportive care from the trial site hospital.
	Drugs were prohibited	Glucocorticoids, which were permitted only for standard indications such as AI, asthma exacerbation, laryngeal edema, septic shock, and ARDS	Higher corticosteroid doses (DEXA >20 mg per day [or prednisone equivalent] administered for >14 consecutive days in the month before the study entry) were not permitted unless indicated per SOC for a concurrent condition, such as asthma, COPD, or AI.			Concomitant use of experimental treatment or off-label use of marketed medications intended as a treatment for COVID-19 were prohibited unless specified in the local hospital policy or National Institutes of Health COVID-19 treatment guidelines. More than one dose of 6-mg of dexamethasone (or an equivalent steroid) given before enrolment was prohibited.
Precipitants Characteristics	VTE prophylaxis	VTE prophylaxis was recommended for all the patients without a major contraindication	Prophylaxis for VTE events were required for all participants unless a major contraindication, such as an active bleeding event or history of HIT.	VTE prophylaxis per local practice was required for all participants unless contraindicated.		VTE prophylaxis was recommended unless there was a contraindication.
	Systemic corticosteroid use at baseline	223(21.58%)	57(9%)/82(14%)	43 (84%)/44 (88%)	3962(96%)/3809(95%)	383 (74%)/361 (73%)
	Duration of symptoms before enrollment	8 (5–10)/8 (5–11)	<7 d:137(18%)/116(15%)≥7 d:625 (82%)/640(85%)	<7 d: 2 (4%)/4 (8%)≥7 d: 49(96%)/ 44(88%)	9 (6–12)/9 (6–11)	8 · 3 (4 · 3)/7 · 9 (4 · 1)
	CRP			124 · 9/109 · 5	84(42–146)/87(44–143)	123 · 4(121 · 3)/120(97 · 8)

(*Continued*)

Table 3. (Continued).

	RCT Name	ACCT-2	COV-BARRIER		RECOVERY	ACTT-4
Mortality over 28 days	Deaths by d. 28(n)	24 /37	62 (8%)/100 (13%)	20 (39%) /29 (58%)	513 (12%)/546 (14%)	27 (5.2%)/30(6%)
	Kaplan–Meiers estimate of mortality by d. 28 % (95% CI)	5.1 (3.5–7.6) / 7.8 (5.7–10.6)		40 · 6% (25 · 8–59 · 7) / 59 · 0% (41 · 1–77 · 7)		5 · 5% (3 · 8–7 · 9) / 6 · 4% (4 · 5–9 · 0)
	Hazard ratio (95% CI)	0.65 (0.39–1.09)	0 · 57 (0 · 41–0 · 78)	0 · 54 (0 · 31–0 · 96)	RR (95% CI): 0.87 (0.77–0.98)	1 · 21 (0 · 72–2 · 04)
	p-value		0 · 0018	0.03	0.026	
	The median duration of hospitalization (IQR) – days	8(5–15)/ 8 (5–20) Rate Ratio (95% CI): 0.0 (–1.1 to 1.1)	12 · 9 (0 · 40) /13 · 7 (0 · 40)LSMD: – 0 · 76 (–1 · 6 to 0 · 0), p-value: 0 · 063	23 · 7 (7 · 1)/ 26 · 1 (3 · 9) LSMD:– 2 · 30(–4 · 59–0 · 0) p-value:0 · 050	8 (5–17)/8 (5–20)	7(4–12)/6(4–11)–1 · 0(–1 · 8 to – 0 · 2)
Recovery	Participants recovered (n)	433(84%)/406(78%)		19 (37%) /13 (26%), RR:1 · 57 (0 · 77 to 3 · 19) P-value:0 · 16		
	Median Time to recovery, (95% CI) – days	7(6–8)/8(7–9)	10(9–11)/11 (10–12)	NA(28-NA)/NA(NA-NA)		6(5 · 0–6 · 0)/5(5 · 0–6 · 0)
	Rate ratio(95% CI)	1.16 (1.01–1.32)	1 · 11 (0 · 99–1 · 24)	_		1 · 04 (0 · 91–1 · 19) Median days and 95% CI calculated by Kaplan-Meier methodology
	p-value	0.03	0 · 15	_		

Abbreviations. ACCT-2: Adaptive COVID-19 Treatment Trial 2, RECOVERY: Randomised Evaluation of 14 COVID-19 Therapy, ACTT-4: Adaptive COVID-19 Treatment Trial 4, BAR:baricitinib, BMI: Body Mass Index, VTE: Venous thromboembolism, CI: Confidence Interval, IQR: Interquartile range, US: United State, UK: United Kingdom, RDV: remdesivir, ARDS: Acute respiratory distress syndrome, SOC: standard of care, HIT: heparin-induced thrombocytopenia, DEX: dexamethasone, COPD: chronic respiratory, pulmonary disease, AI: adrenal insufficiency, IS: immunosuppression, ALT: alanine transaminase, AST: aspartate aminotransferase, ULN: upper limit normal, LSMD: least squares mean difference, ECMO: Extracorporeal membrane oxygenation, LDH: lactate dehydrogenase, TB: tuberculosis, GFR: glomerular filtration rate, NGT: nasogastric tube, ANC: absolute neutrophil count, DM: Diabetes mellitus, NIV: non-invasive ventilation, HTN: hypertension, CKD: chronic kidney disease, IMV: invasive mechanical ventilation.

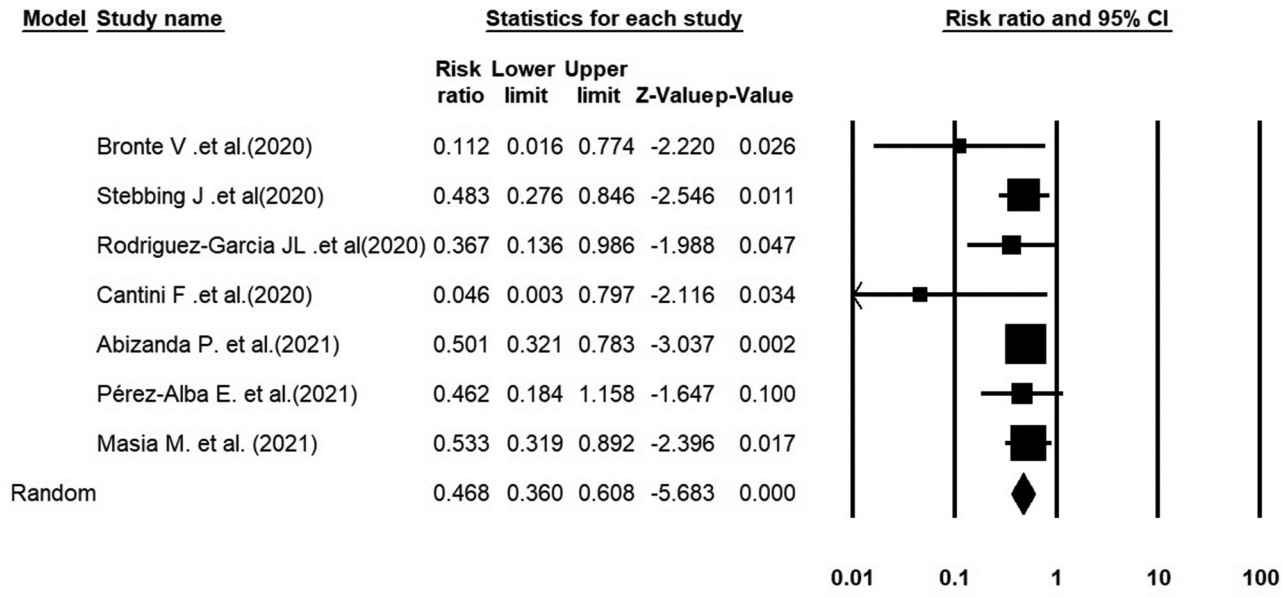

Figure 2. The pooled direct comparison effect of baricitinib therapy versus standard treatment on the mortality rate of COVID-19 pneumonia related to cohort studies.

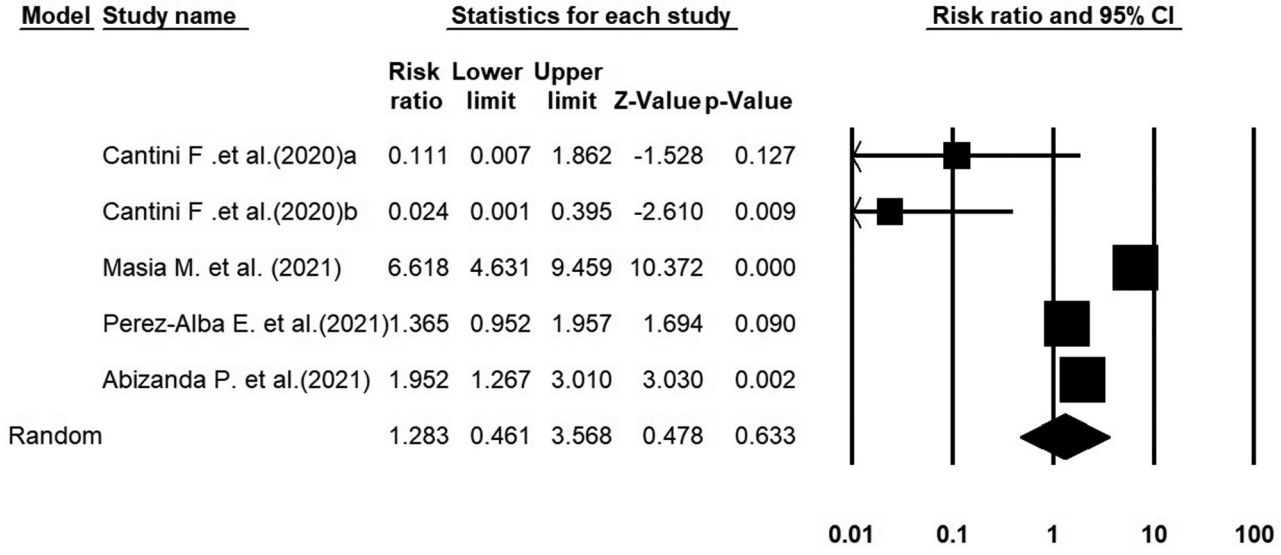

Figure 3. The pooled direct comparison effect of baricitinib therapy versus standard treatment on the need for mechanical ventilation and ICU transfer of the patients with COVID-19 pneumonia related to cohort studies.

P-value = 0.02) on the seventh day of treatment during hospitalization compared to the first day. The Forest Plot graph from the serum CRP levels meta-analysis is shown in Figure 7.

3.2.1.6. IL-6. Based on the report of the patients' serum IL-6 levels in the baricitinib and control groups on the first and the seventh days after treatment in two included cohort studies, the heterogeneity between the studies was not significant (I-squared = 0.00, P-value = 0.39, df(Q) = 1, Q-value = 0.74). According to the meta-analysis results, the mean change in serum IL-6 levels in the baricitinib group was 13.80 pg/mL less than the control group (Pooled Mean Difference = −13.80, 95% CI = −19.73, −7.87, Z-value = −4.6, P-value < 0.001). The Forest Plot graph from the meta-analysis of serum IL-6 levels is shown in Figure 8.

3.2.1.7. Lymphocyte count. Based on the report of the patients' lymphocyte count in the baricitinib and control groups at the first and the fourteenth days after treatment in two included cohort studies, the heterogeneity between the studies was not significant (I-squared = 0.00, P-value = 0.87, df(Q) = 1, Q-value = 0.028). According to the meta-analysis results, the mean change in lymphocyte count in the baricitinib group was 0.48 × 10^9/L more than the control group (Pooled Mean Difference = 0.48, 95% CI = 0.35, 0.61, Z-value = 7.15, P-value < 0.001) on the fourteenth day of treatment during hospitalization compared to the first day. The Forest Plot graph from the results of the lymphocyte count of the day 14 meta-analysis is shown in Figure 9.

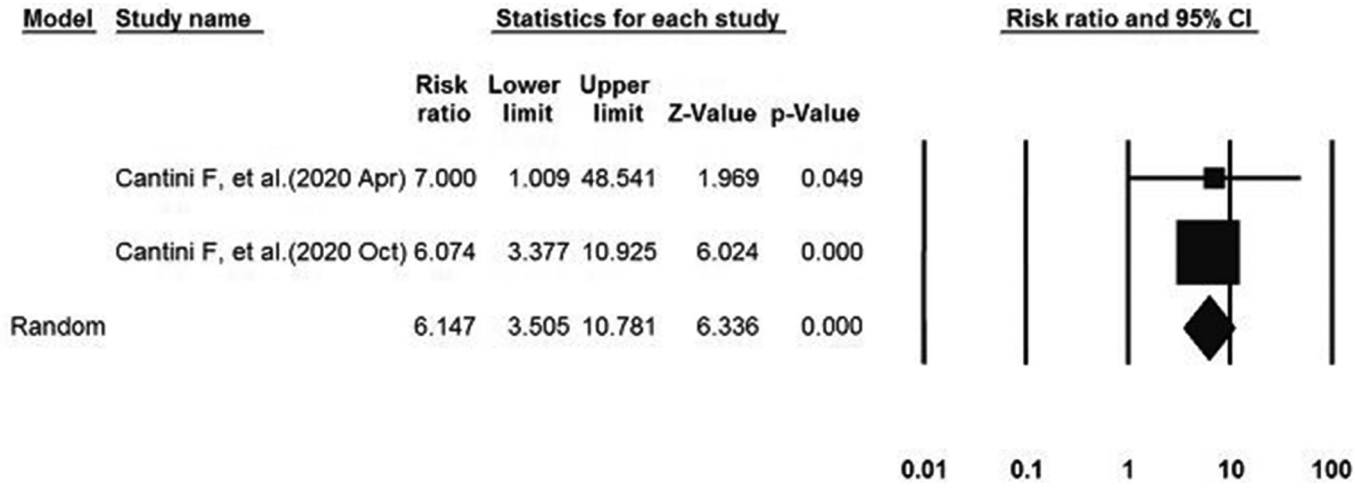

Figure 4. The pooled direct comparison effect of baricitinib therapy versus standard treatment on the discharge rate of the patients with COVID-19 pneumonia related to cohort studies.

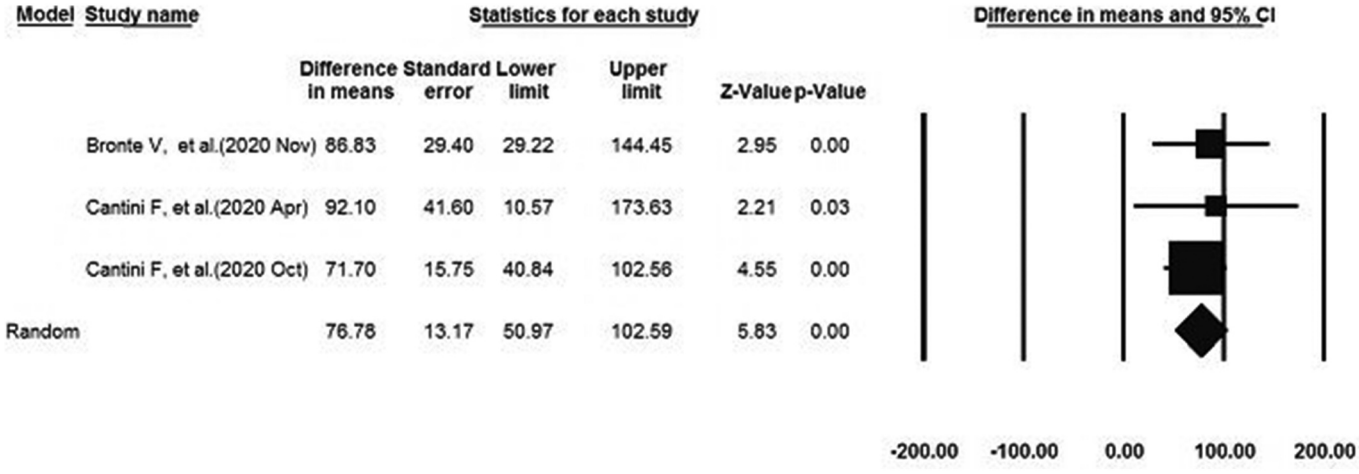

Figure 5. The pooled direct comparison effect of baricitinib therapy versus standard treatment on PaO_2/FiO_2 Ratio of the patients with COVID-19 pneumonia related to cohort studies.

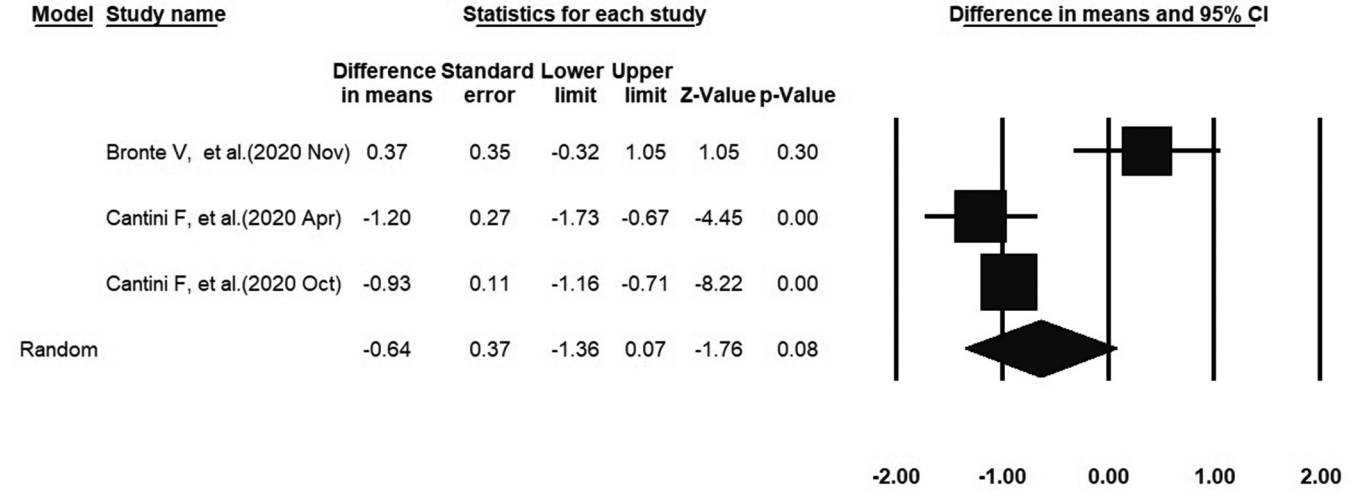

Figure 6. The pooled direct comparison effect of baricitinib therapy versus standard treatment on the fever of the patients with COVID-19 pneumonia related to cohort studies.

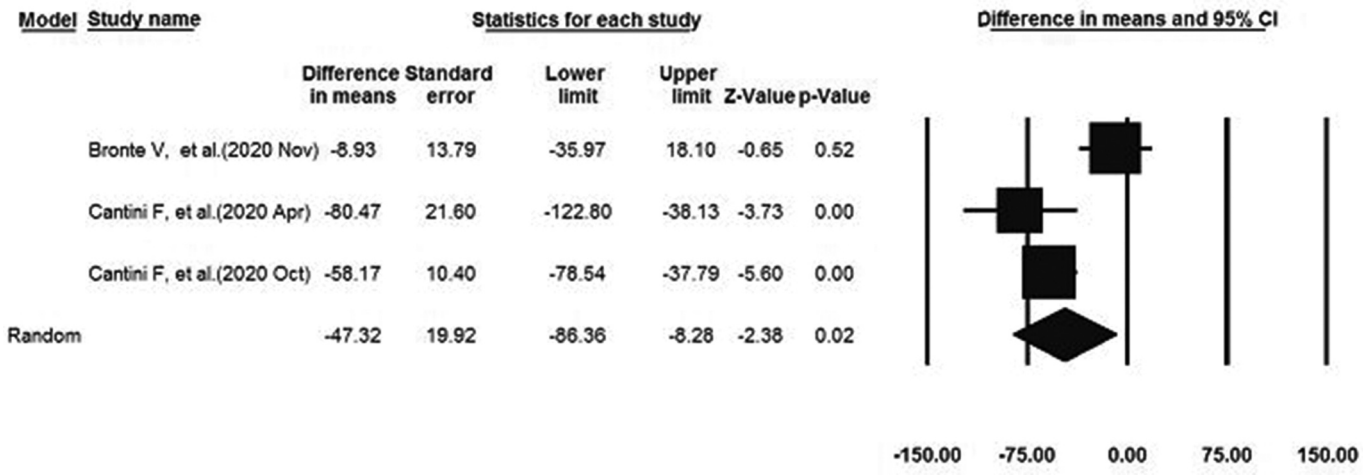

Figure 7. The pooled direct comparison effect of baricitinib therapy versus standard treatment on CRP of the patients with COVID-19 pneumonia related to cohort studies.

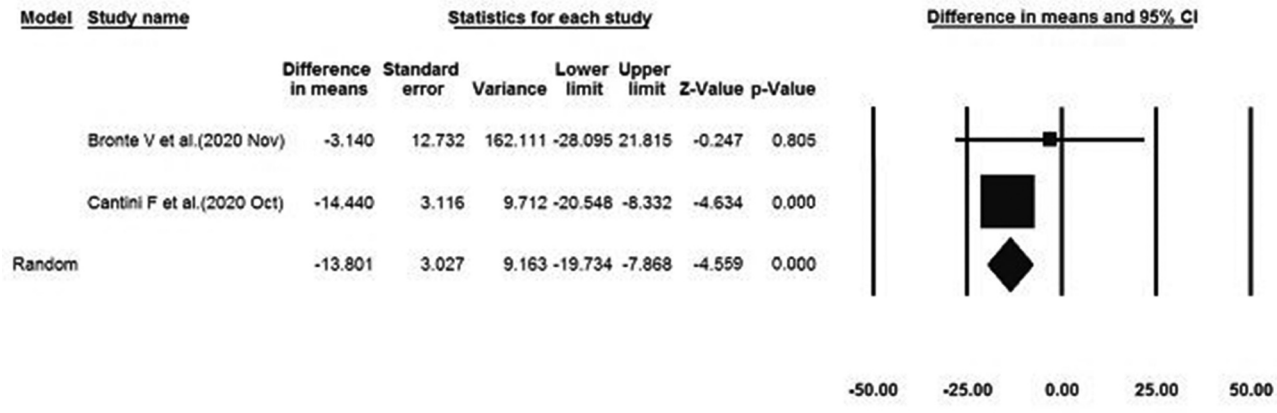

Figure 8. The pooled direct comparison effect of baricitinib therapy versus standard treatment on IL-6 in the patients with COVID-19 pneumonia related to cohort studies.

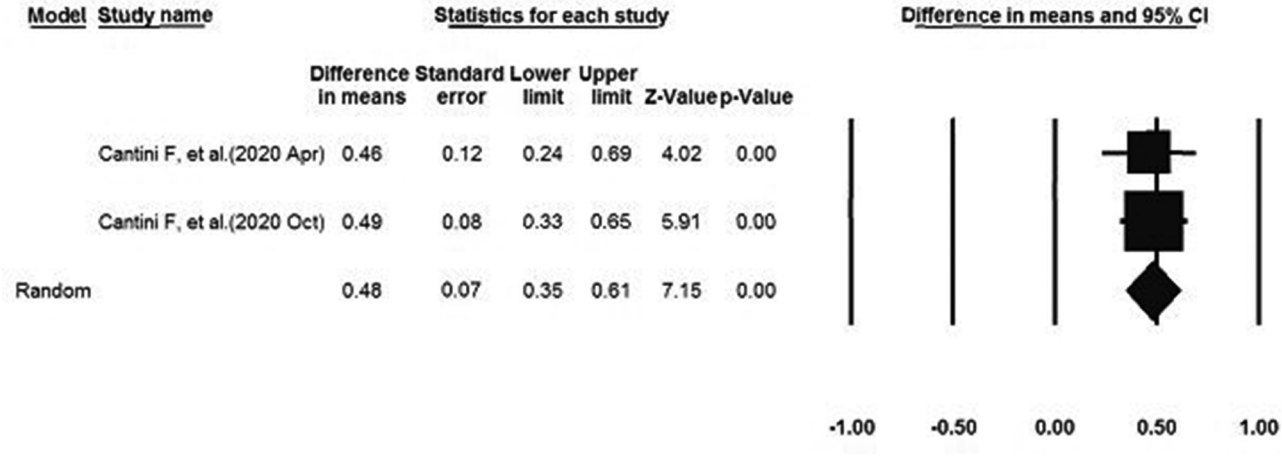

Figure 9. The pooled direct comparison effect of baricitinib therapy versus standard treatment on lymphocyte count in the patients with COVID-19 pneumonia related to cohort studies.

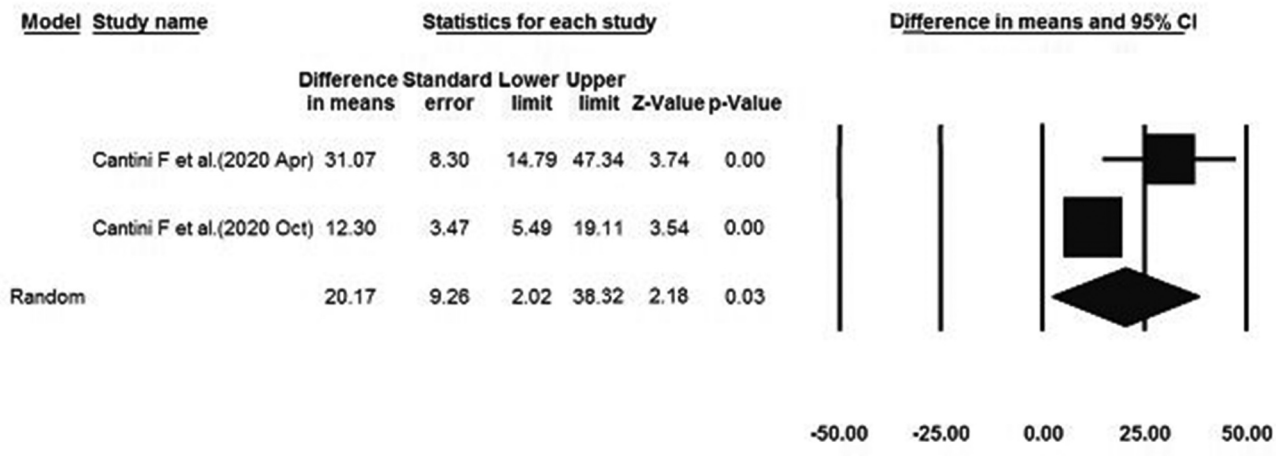

Figure 10. The pooled direct comparison effect of baricitinib therapy versus standard treatment on ALT in the patients with COVID-19 pneumonia related to cohort studies.

3.2.1.8. ALT. Based on the report of the patients' ALT in the baricitinib and control groups on the first day and the fourteenth day after treatment in two included cohort studies, the heterogeneity between the studies was significant (I-squared = 77.0, P-value = 0.04, df(Q) = 1, Q-value = 4.35). According to the meta-analysis results, the mean change in ALT in the baricitinib group was 20.17 U/L more than the control group (Pooled Mean Difference = 20.17, 95% CI = 2.02, 38.32, Z-value = 2.18, P-value = 0.03) at the fourteenth day of treatment during hospitalization compared to the first day. The Forest Plot graph from the ALT meta-analysis is shown in Figure 10.

3.2.2. RCT studies meta-analysis results

3.2.2.1. Death. Based on the report of patients' mortality rates over 28 days in the baricitinib and control groups in five included RCT studies, the heterogeneity between the studies was insignificant (I-squared = 49.31, P-value = 0.09, df(Q) = 4, Q-value = 7.90). According to the meta-analysis results, the mortality risk in the baricitinib group was 0.84 times that of the control group (Pooled Risk Ratio(RR) = 0.84, 95% Confidence Interval (CI) = 0.76, 0.93, Z-value = −3.37, P-value = 0.001). The Forest Plot graph from the results of the mortality rate meta-analysis is shown in Figure 11.

3.2.2.2. Hospitalisation days. Based on the report of the patients' hospitalized days in the baricitinib and control groups in five included RCT studies, the heterogeneity between the studies was not significant (I-squared = 0.00, P-value = 0.69, df(Q) = 4, Q-value = 2.24). According to the meta-analysis results, the mean hospitalization days in the baricitinib group was 0.80 days less than the control group (Pooled Mean Difference = −0.80, 95% CI = −0.93, −0.67, Z-value = −12.51, P-value < 0.001). The Forest Plot graph from the results of the meta-analysis of hospitalization days is shown in Figure 12.

3.2.2.3. Recovery. Based on the report of patients recovery in the baricitinib and control groups in two included RCT studies, the heterogeneity between the studies was not significant (I-squared = 0.00, P-value = 0.337, df(Q) = 1, Q-value = 0.923). According to the meta-analysis results, the recovery rate in the baricitinib group was 1.07 times that of the control group (Pooled RR = 1.07, 95% CI = 1.01, 1.41, Z-value = 2.44, P-value = 0.014). The Forest Plot graph from

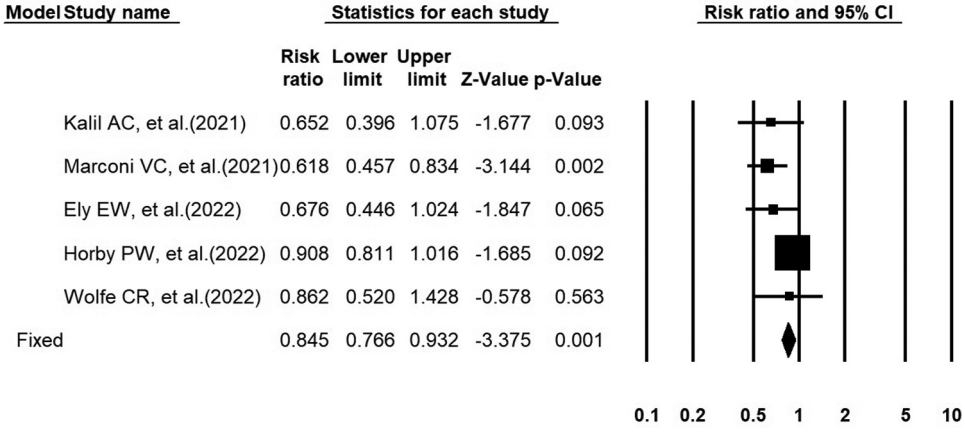

Figure 11. The pooled direct comparison effect of baricitinib therapy versus standard treatment on the mortality rate of COVID-19 pneumonia related to RCT studies.

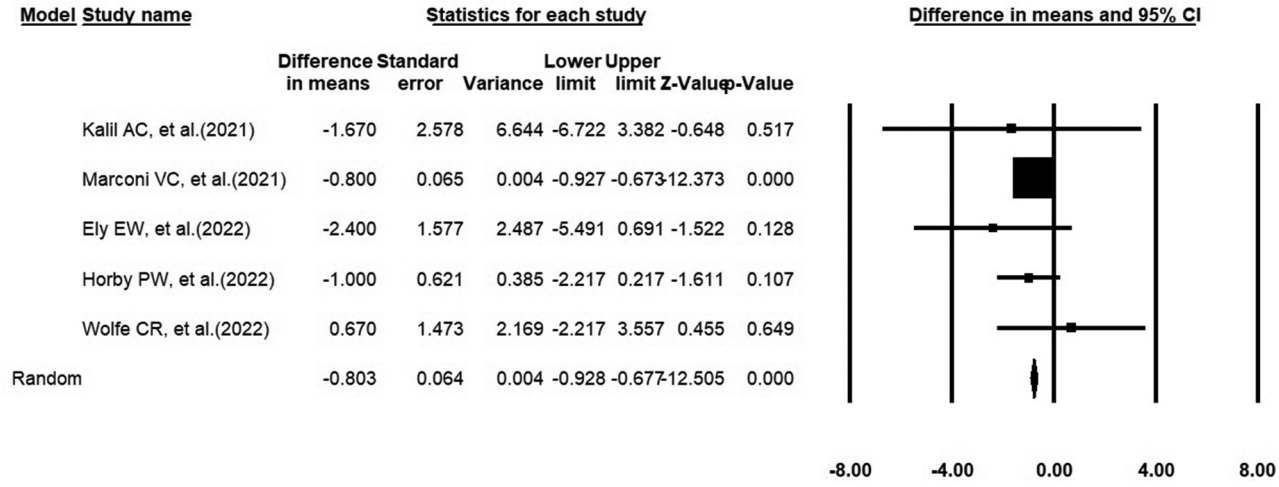

Figure 12. The pooled direct comparison effect of baricitinib therapy versus standard treatment on hospitalized days of the patients with COVID-19 pneumonia related to RCT studies.

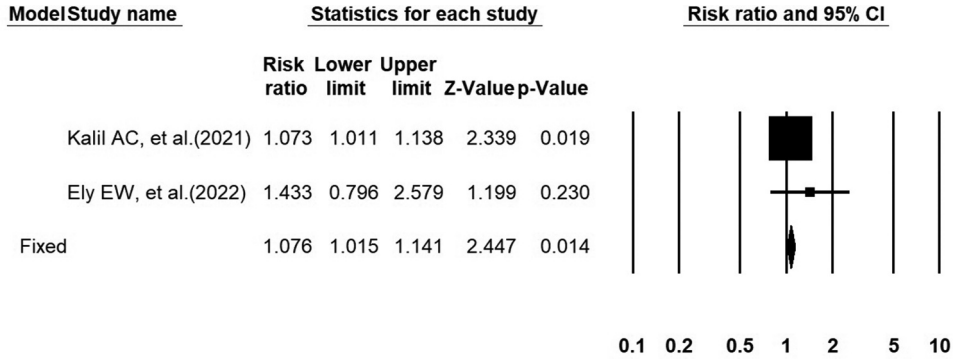

Figure 13. The pooled direct comparison effect of baricitinib therapy versus standard treatment on the Recovery Rate of the patients with COVID-19 pneumonia related to RCT studies.

the results of the recovery rate meta-analysis is shown in Figure 13.

3.2.2.4. Time to recovery. Based on the report of the patients' time to recovery(days) in the baricitinib and control groups in three included RCT studies, the heterogeneity between the studies was significant (I-squared = 91.84, P-value = 0.00, df(Q) = 2, Q-value = 24.50). According to the meta-analysis results, the mean days about time to recovery in the baricitinib group was 0.51 days less than the control group (Pooled Mean Difference = −0.51, 95% CI = −1.54, 0.52, Z-value = −0.96, P-value = 0.33). The Forest Plot graph from the meta-analysis of Time to recovery is shown in Figure 14.

3.3. Risk of bias assessment

Risk assessment was performed using risk assessment tools. We also assessed the risk of bias across included cohort and RCT studies. If more than 50% of the information was at low risk of bias, the domain was judged to be at low risk of bias. Similarly, if most information in the included studies had an unclear/high risk of bias, the domain was considered to be at an unclear/high risk of bias. Overall, the quality of the selected articles was reported as 'medium' based on the authors' consensus in scoring the eight included cohort and five RCT studies.

3.4. Publication bias

The Eggers Regression test results showed no evidence of diffusion bias between cohort studies included in the meta-analysis (t-value = 1.38, df = 7, p-value = 0.38).

4. Baricitinib adverse effects: a literature review

Common short-term side effects of baricitinib are headache, upper respiratory tract infection, and nasopharyngitis [22,59–62]. Baricitinib can mildly increase Aspartate Aminotransferase (AST) and ALT (17%) and cause transient reversible elevation of liver enzymes without the need for discontinuation or dose adjustment. Therefore, initial Liver function tests (LFT) controls and subsequent monitoring are suggested in some studies [13,58–60]. No cases of hepatotoxicity have been reported so far [18].

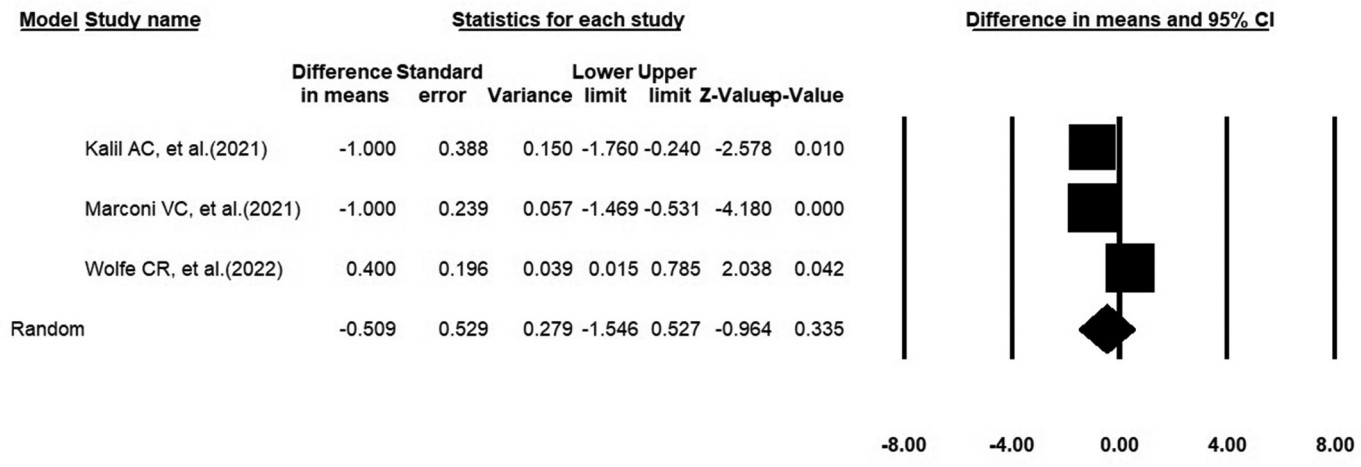

Figure 14. The pooled direct comparison effect of baricitinib therapy versus standard treatment on time to recovery of the patients with COVID-19 pneumonia related to RCT studies.

It has also been suggested that baricitinib may increase the incidence of lymphopenia and anemia in patients with COVID-19 [63,64]. Baricitinib, especially during the first month, can reduce neutrophil counts but not below 1000 [65]. Cases in which baricitinib should not be started or stopped include absolute lymphocyte count < 0.5×10^9 /L, absolute neutrophil count < 1×10^9 /L, and Hemoglobin < 8 g/ml [17,66]. The only contraindication to baricitinib is creatinine clearance < 30 ml/min [22]. Recommended laboratory parameters in patients treated with baricitinib include serum creatinine, absolute lymphocyte count, absolute neutrophil count, hemoglobin, platelets, ALT, AST, bilirubin, and Creatine phosphokinase (CPK), Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL) in prolonged use [22].

There is a possibility of reactivation of previous latent infections, including Epstein Barr Virus (EBV), Tuberculosis (TB), Herpes simplex virus (HSV), Herpes Zoster Virus (HZV), and Hepatitis B with Baricitinib [64]. There is no report on baricitinib-induced mortality [67]. Due to the possibility of reactivation of hepatitis B during treatment with baricitinib, the serum levels of Hepatitis B surface Antigen (HBsAg) and antibody to Hepatitis B core Antigen (anti-HBc) should be controlled before starting treatment. Moreover, close monitoring should be done in patients with a history of hepatitis B to quickly diagnose hepatitis reactivation and start the antiviral drug against HBV (tenofovir or entecavir) as soon as possible [18]. However, experience has shown that short-term use of baricitinib (7–14 days) will not activate latent infections [67]. Some infectious side effects, such as HZV, are dose-dependent (occur at a dose of 4 mg/day vs. 2 mg/day) [68]. No side effects have been reported with short-term use of baricitinib up to 8 mg daily [69]. IFN-γ blockade by baricitinib is the cause of HSV reactivation [22]. Risk of developing bacterial and fungal superinfection increases in COVID-19 treatment with JAK inhibitors (e.g. baricitinib) and IL-6 inhibitors (e.g. tocilizumab) [70].

Usual dosage of Baricitinib is 4 mg once/day, 2 mg once/day in estimated Glomerular Filtration Rate (eGFR) 30–60 mL/min/1.73 m^2, 1 mg once/day in eGFR 15–30 mL/min/1.73 m^2 and not recommended in eGFR <15 mL/min/1.73 m^2 [67]. There is no evidence that baricitinib crosses the placenta [22].

In drug safety, no specific side effects have been reported with baricitinib in combination with methylprednisolone compared with methylprednisolone alone [48,61]. Among JAK inhibitors, the complication of increasing the number of platelets (approximately 50×10^9/L, immediately after the start and reaching the peak within 2 weeks) is unique to baricitinib [22]. It may be suggested that increased susceptibility to thrombotic events by baricitinib in the context of the hypercoagulopathy state of COVID-19 can have a double effect on the occurrence of thromboembolic events. On the other hand, the results of immune, inflammatory, and coagulation system function in patients with COVID-19 indicate a tendency towards thromboembolic events [68,70]. Increasing serious infections and dose-dependent arterial and venous thromboembolic risk are late complications [22,68,71]. In Adaptive COVID-19 Treatment Trial 2 (ACTT-2), cases of Pulmonary Thromboembolism (PTE) and venous thromboembolism with no statistically significant difference were observed compared with the control group [53].

In a study by Lenz et al., one case of pulmonary thromboembolism and one case of methicillin-resistant *Staphylococcus aureus* (MRSA) infection were reported as a result of treatment with baricitinib and hydroxychloroquine in 15 patients with moderate to critical COVID-19 pneumonia. However, determining whether these complications were due to baricitinib adverse effect or the COVID-19 complication requires further clinical trials with larger sample sizes [72]. In a comprehensive global study about the adverse effects of baricitinib in 1598 patients, infections (herpes zoster, oral herpes, and herpes virus infection) and thromboembolic events were still rare, and death and life-threatening events were found in 9.76% of patients [73]. Due to the immunosuppressive effects of both corticosteroids and baricitinib, co-administration of both drugs is not recommended because of the increased risk of infections [74]. Concurrent use of immunosuppressant drugs makes patients more susceptible to infections [75].

Table 4. Reported adverse effects of baricitinib in COVID-19 treatment in thirteen included studies.

	Authors/date/ reference number	PTE	DVT	Transaminitis ≥ 2XULN	Transaminitis ≥ 3XULN	Treatment-emergentadverse event	Treatmentemergent infection	Major adverse cardiovascular event	Other rareadverse effects
Cohort Studies	Bronte et al. (2020 Nov) [45]	During the hospitalization, the patients enrolled in the baricitinib group did not experience any type of infections and DVT or PTE							
	Stebbing J, et al. (2021 Jan) [46]			8 (17%)in Spanishcohort4.5 % in Albacete7 (19%)in Pisa	4 (9%) in Spanish cohort		Spanish:oral candidiasis: 2(4.3%) bacteremia for Enterococcus faecium:1(0.09%)bacterial pneumonia with negative cultures: 1 (0.09%)Albacete:UTI:17 (4.5%) HZV reactivation: 1(2.6%)		new AF(all had previous heart disease):3(3.6%) hypertensive episode:1(1.2%)episode of HF in the presence of known heart disease:1(1.2%) urinary obstruction:1(1.2%)episode of diarrhea:1 (1.2%)GIB in an individual with gastric malignancy:1(1.2%)
	Cantini et al.(2020 Apr) [47]				1(8%)				
	Rodriguez-Garsia et al. (2021Jan)[48]						oral candidiasis: 2 (3.2%)		hyperglycaemic decompensation in non-diabetic subjects:5(8%)ketoacidotic decompensation in a diabetic patient:1(1.6%) delirium treated with neuroleptics:2(3.2%) third degree AVB that required apermanent pacemaker:1(1.6%)
	Cantini et al.(2020 Oct) [49]			4 (3.5%)			oral candidiasis: 1 (0.8%)urinary infection: 1 (0.8%)		
	Masiá et al.(2021 Nov) [50]						total: 17 (17.9%)Bacterial respiratory coinfection:6(6.3%)Bacteremia:5 (5.2%)Invasive fungal infection:4 (4.2%)		
	Pérez-Alba et al. (2021 Oct) [51]			3 (2.4%)			Bacterial pneumonia:17(13.7%) UTI :6 (4.8%)Catheter-related bloodstream infection:12 (9.7%)		
	Abizanda et al.(2021 Oct) [52]	no serious adverse events were obsereved that were directly attributed to baricitinib							
CRT Studies	Kalil et al. (4 March 2021) [53]	5 (1.0%)	11 (2.2%)	6 (1.2%)			Septic shock: 4 (0.8%)Pneumonia: 2 (0.4%)Sepsis:1 (0.2%) Pneumonia bacterial: 3 (0.6%) UTI:5 (1.0%) Bacteraemia: 2 (0.4%)	Cardiac arrest: 2 (0.4)	Multiple organ dysfunction syndrome: 1 (0.2%) AKI:5(1.0%)Pneumothorax: 1 (0.2%)Anaemia:24 (4.7%)Lymphopenia: 11 (2.2%)AF:1 (0.2%) pyrexia: 10 (2.0%) Hyperglycaemiae: 25 (4.9%)HTN: 11 (2.2%)
	Marconi et al. (1 December 2021) [54]	13(2%)	4(1%)			total,n (%) : 334 (45%) Mild:133(18%) Moderate:90(12%) Severe:111(15%)	119 (16%)Serious infections:64 (9%) HSV: 1 (<1%) HZV: 1 (<1%) TB :1 (<1%) Opportunistic infections: 6 (1%) Candida infection: 1 (<1%) Fungal retinitis: 1 (<1%)	8 (1%)CV death:1 (<1%)MI: 4 (1%) Stroke :4 (1%)	
	Ely et al.(1 April 2022) [55]	2(4%)	1(2%)			total,n (%) : 44 (88%)Mild:3 (6%) Moderate:17(34%) Severe:24(48%)	35 (70%)Serious infections :22 (44%) HSV:1 (2%)	CV death 1 (2%) Stroke 1 (2%)	
	Horby et al. (1 January 2022) [56]	156(3.8%)	14(0.3%)		1(0.02%)	total,n (%): 13(0.3%)Non-CoV-2 infection:5(0.1%) Bowel perforation:3 (0.07%)PTE :2(0.04%) Ischaemic colitis:1 (0.02%)Seizure:1(0.02%)	Pneumonia: 235 (5.7%) UTI: 66 (1.6%)Biliary tract infection: 1 (<0.1%) Other intra-abdominal infection: 12 (0.3%)Blood stream infection: 68(1.6%)	CV death 7 (0.2%) Stroke 0 (0.0%) AF or AFL:71(1.7%) SVT:83(2.0%) Ischaemic stroke:7 (0.2%) MI:7 (0.2%)	
	Wolfe et al.(23 May 2022) [57]	12 (2%)	9(2%)			21(4%)	Septic shock:6 (1%)Sepsis: 3 (1%) Bacterial pneumonia:3 (1%)UTI: 4 (1%)	Cardiac arrest: 2 (<1%)	

Abbreviations. PTE: pulmonary thromboembolism, DVT: deep vein thrombosis, ULN: upper limit normal, UTI: urinary tract infection, TB: tuberculosis, HSV: herpes simplex virus, HZV: herpes zoster virus, CV: cardiovascular, MI: myocardial infarction, AF: atrial fibrillation, SVT: supraventricular tachycardia, HTN: hypertension, AVB: Atrioventricular Block, HF: heart failure, GIB: gastrointestinal bleeding, AKI: acute kidney injury

The most important side effects of short-term baricitinib administration up to 14 days on COVID-19 pneumonia are thromboembolic events (Deep Vein Thrombosis (DVT), PTE), hepatic transaminitis, urinary infection, and, in the next minor degrees, oral candidiasis, bacteremia, GI disorders, HSV or HZV reactivation, and severe lymphopenia. Because of the importance of baricitinib safety and its adverse effects on COVID-19 pneumonia, the reported side effects attributed to baricitinib in the thirteen included studies are categorized in Table 4. Based on these findings, compared to the effective benefits of baricitinib, there is no major concern about this side effect in hospitalized with moderate to severe COVID-19 patients.

5. Discussion

Since the JAK inhibitors are used in moderate to severe COVID-19 pneumonia, the dual function of baricitinib as its superior feature includes decreasing hyperinflammation (cytokine outbreak) and preventing SARS-CoV-2 entry into the cells (viral endocytosis); it is considered more effective than other JAK-inhibitors such as ruxolitinib [39,74,76]. Although several JAK inhibitors, such as baricitinib, ruxolitinib, and fedratinib, have recently been studied for their effects on COVID-19. Moreover, only baricitinib was approved by the United States (US) FDA and the European Medical Association as the only JAK inhibitor in COVID-19 therapy because of the high affinity to AAK 1 and the need to take it orally only once a day based on the results of cohort and RCT studies [4,75,77,78]. Baricitinib has been approved as the only JAK inhibitor in COVID-19 therapy. The approved doses of baricitinib are 2 mg/day by FDA, 2 mg/day by Health Canada, and 4 mg/day in some European and Asian countries [22]. As recommended by FDA, the duration of treatment with baricitinib in COVID-19 is 14 days or until discharge from the hospital (whichever is earlier) [79]. Currently, Rodriguez-Garcia et al., who presented further clinical improvements and less need for supplementary oxygen at the time of discharge and a month later [48], have published the results of an observational cohort study about the effect of corticosteroids with and without baricitinib on COVID-19. In response to a case report by Christopher Cerda-Contreras et al., who attributed pancreatitis to baricitinib in a 72-year-old COVID-19 patient, end-organ damage and pancreatitis resulting from severe immune deficiency due to concomitant administration of baricitinib and dexamethasone in the absence of antiviral therapy were raised by Titanji et al. [80,81]. Baricitinib, as Cingolani et al. reported, is the rescue treatment in a patient with COVID-19-induced severe respiratory failure who was unresponsiveness to antivirals and IL-6 antagonist therapy [82]. The flipside of the coin about baricitinib is the inhibition of the IFN activity, which is the main part of the innate immune in response to viral infections via preventing viral replication [26]. Gonzalez et al. raised rheumatologists' challenges with COVID-19: on the one hand, the incidence, mortality rate, and disease severity of patients treated with an immunosuppressive agent compared to the general population and, on the other hand, the effectiveness of targeted therapies as a COVID-19 treatment [83]. Because of the cumulative immunosuppressive effect and the increased risk of infections, concomitant prescription of baricitinib with other immunosuppressive drugs and virus vaccines is not recommended [44]. Baricitinibs low affinity for binding to plasma proteins and the least interference with (Cytochrome P450) CYP enzymes and drug transporters have led to its appropriate ability to co-administration with antiviral drugs such as remdesivir and other drugs (lopinavir/ritonavir) [84,85]. Marinho et al. investigated the possibility of concomitant use of inhibitory drugs in COVID-19 due to their similar binding to an enzyme site which is often domain III of the SARS-CoV-2 primary protease. Their results showed that this disease was indorsed by co-administration of baricitinib, quinacrine, and azithromycin [86]. A comprehensive investigation of baricitinib-induced thromboembolic events is very important in COVID-19 patients because it is difficult to diagnose baricitinib-induced pulmonary thromboembolism from COVID-19 pulmonary involvement even with the use of imaging. Concomitant initiation of prophylactic anticoagulants with baricitinib in the COVID-19 setting is controversial [22]. Due to the reported thrombotic events of baricitinib, based on the reported cases of PTE and DVT in patients receiving baricitinib for RA, the Summary of Product Characteristics (SmPC) in FDA (2017) advised caution in prescribing this drug in patients at high risk of thromboembolic events including obesity, older age, history of thromboembolic event, recent surgery, and sedentary behavior [65,87]. To reduce the dose-dependent thromboembolic side effects of baricitinib, FDA approved a dose of 2 mg daily instead of 4 mg in April 2018 [87]. Despite the thromboembolic events reported for baricitinib in previous studies, Gudu et al. claimed that the immunosuppressive effects of baricitinib and, consequently, the reduction of prothrombotic signals in COVID-19 significantly reduced this side effect [88]. For the first time, Richardson et al. used an artificial intelligence platform, BenevolentAI. They suggested the potential role of baricitinib in treating severe COVID-19 patients in inhibiting JAK1 and 2 and AAK1, leading to a reduction in systemic inflammation [31,89]. Within the scope of Emergency Use Authorization (EUA)s licensed by the FDA, it is recommended to administer baricitinib in combination with remdesivir in hospitalized adult patients with suspected or definitive COVID-19 and children over 2 years of age who need oxygen, Intermittent mandatory ventilation (IMV), and Extracorporeal Membrane Oxygenation (ECMO) [90,91]. No studies have been performed on baricitinib in pregnant or lactating women [15,90]. A study by Sanchez-Piedra et al. on patients with rheumatic and musculoskeletal diseases (RMDs), such as RA, spondyloarthropathies (SpA), or systemic lupus erythematosus, treated with immunomodulatory therapies with COVID-19, revealed no significant difference in mortality rates (7.3% vs. 12%) and hospitalization (68.3% vs. 53.6%) compared to the general population [92]. In November 2020, FDA granted emergency use authorization for baricitinib in treating severe/critically ill COVID-19 patients [93]. With the rise of the global COVID-19 pandemic and the resulting high mortality, the lack of effective antiviral treatment against the SARS-CoV-2 and the lack of vaccines led physicians and scientists to use drugs for other diseases in these patients in the hope of reducing efficacy and mortality [94–97]. According to Spinelli et al., comparing the incidence

and severity of COVID-19 disease in patients with RA treated with baricitinib versus other biologic DMARDs will greatly help determine the effective role of baricitinib in prevention, mild postoperative symptoms, and preventing patients from becoming critical [98]. The main reason for the effectiveness of baricitinib in treating severely ill hospitalized patients is its JAK inhibitor and AAK1 inhibitor, causing its anti-inflammatory and anti-viral properties, respectively [99]. Due to the inhibitory and reducing effect of cytokines in the control of cytokine storm, the role of baricitinib in the treatment of moderate and severe COVID-19 is much more prominent than in mild cases. Therefore, baricitinib is not recommended in patients with mild or asymptomatic COVID-19 [15,34]. In the theoretical analysis of the JAK/STAT pathway previously infected with SARS-CoV-2, Banerjee et al. obtained the maximum reduction in the size of the JAK/STAT system among immunosuppressive drugs for baricitinib alone and, therefore, it was proposed as an effective drug in severe COVID-19 pneumonia treatment [100]. Among the effective drugs in COVID-19, remdesivir (antiviral), dexamethasone (antiinflammatory), and baricitinib (Janus kinase inhibitor) have so far been considered the best treatments [101]. In an *in-vitro* study using a whole-blood platform to evaluate baricitinib on SARS-CoV-2-specific-response in 39 COVID-19 patients, Petrone et al. showed significantly decreased IFN-γ response [102].

P-values of death, ICU transfer, discharge, PaO_2/FiO_2 ratio, CRP, IL-6, lymphocyte count on day 14, and ALT in the baricitinib group vs. control group in cohort studies meta-analysis, and p-value of death, hospitalization, and recovery in RCT studies meta-analysis were statistically significant (p-value < 0.05). In addition to the eight included cohort and five RCT studies about therapeutic effects of baricitinib on COVID-19 pneumonia with two case and control arms in this meta-analysis, two retrospective case-control studies, an interventional study in rhesus macaques, and two case series were conducted up to 2022. According to the https://www.clinicaltrials.gov/ database, there are currently several recruiting clinical trials on the effect of baricitinib on COVID-19 pneumonia. In a randomized interventional study of eight rhesus macaques by Hoang et al., a reduction in inflammation, lung infiltration by inflammatory cells, Neutrophil Extracellular Trap-osis (NETosis) activity, and limited pulmonary pathology were observed in necropsies of four animals treated with baricitinib compared with four animals that received no treatment. The faster and stronger decrease in pulmonary macrophages secreting cytokines responsible for inflammation and subsequent recall of neutrophils in baricitinib-receiving animals confirm the important immunologically anti-inflammatory role of baricitinib in SARS-CoV-2 pneumonia-induced hyperinflammation [40]. Pavez et al. studied the incidence of COVID-19 in rheumatological patients treated with biologics or JAK inhibitors in Spain for 59.8 months with 355 sample size and reported extremely low COVID-19 incidence than those in the general population, despite the pre-study impression [103]. A study by Salvarani et al. in a geographic area (Emilia Romagna) in Italy concerning the high diffusion of COVID-19 showed that the susceptibility or severity of developing COVID-19 was not significantly different between rheumatic patients treated with biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) compared to the general population [104]. In a retrospective nonrandomized uncontrolled cohort study by Titanji et al. in the United States of America (USA), Atlanta Veterans Affairs Medical Center (VAMC), 15 patients with moderate to severe COVID-19 were evaluated for the therapeutic effect of concomitant treatment with baricitinib and hydroxychloroquine. Reported outcomes were decreased fever and serum IL-6 levels in 86.7% of patients, reduced oxygen demand, improved cough, shortness of breath, diarrhea, confusion, and recovery in 80% of patients, and three deaths (two underlying diseases including dementia and lymphoma, and 1 case due to cardiogenic shock) [105]. In a retrospective observational study of 60 patients with interstitial pneumonia caused by COVID-19 in Spain, Rosas et al. concluded that concomitant treatment with tocilizumab and baricitinib was without serious side effects [106]. In a retrospective case-control study by Hassan et al. in Bangladesh, an 8 mg loading dose of barcitinib was evaluated in 37 patients with moderate to severe COVID-19 (20 cases and 17 controls). They reported a significant reduction in oxygen requirement, the number of days to achieve oxygen above 95%, normal respiratory status, the need for transfer to the ICU, mechanical ventilation, and the number of hospitalized days [107–110]. Lo, et al. reported a positive effect of baricitinib in the treatment of COVID-19 in an 87-year-old woman with RA who was treated formerly with baricitinib for one year. Oxygen, hydroxychloroquine, and lopinavir/ritonavir were administered in addition to baricitinib. The woman was discharged without needing oxygen with significant progress, while her spouse and son died without receiving baricitinib with the above drugs [28]. In a case series conducted by Stebbing et al. on four patients with moderate to severe bilateral COVID-19 pneumonia treated with baricitinib, clinical improvements of all signs and symptoms alongside decreased serum levels of IL-6, CRP, ferritin, D-Dimer, and reduction of nasopharyngeal SARS-CoV-2 RNA viral load detected by Reverse transcription polymerase chain reaction (RT-PCR) confirms the strong anti-inflammatory effects of baricitinib in severe cases of COVID-19 pneumonia [16].

5.1. Limitations of the study

The first limitation was that data related to all clinical and laboratory variables were not present in all eight-cohort studies. Thus, the parameters were assessed in at least two studies were meta-analyzed in this review. The second limitation was the small number of samples in some studies. The third limitation was the similarity between the authors of the two cohort studies (Cantini et al.) [47,49], which may have led to bias. The first was performed on 24 hospitalized patients with mild to moderate COVID-19 pneumonia in a hospital in Italy in the last 2 weeks of March 2020; the results were published in April 2020 [47]. Subsequently, the second study by the same authors was performed on 191 patients in seven Italian hospitals in May 2020, and the results were published in October 2020 [49]. The fourth limitation was related to the countries of the included cohort studies, which were often

done in Italy and Spain. Fifth, the random effect model was utilized due to the limited numbers and conditions of studies.

6. Conclusion

Baricitinib is FDA-approved for administration in COVID-19. The results of the ACTT-2 study and our systematic review and meta-analysis of eight included cohort studies and five RCT studies confirm the effective role of baricitinib in controlling cytokine storm and hyperinflammation, decreasing mortality, reducing the need for mechanical ventilation and transfer to ICUs. In addition, more and faster discharge, reduced inflammatory and cytokine laboratory markers using the oral form of the drug, and no serious side effects. Accordingly, short-term prescription of baricitinib tablets at a dose of 4 mg every 12 h for 7–14 days in combination with antiviral drugs with and without corticosteroids and prophylactic anticoagulants is strongly recommended in hospitalized patients with moderate to severe COVID-19 pneumonia. Certainly, the widespread administration of baricitinib in all countries by adding this drug to the national COVID-19 treatment protocol will be a great step in the pandemic control, mortality reduction, and treatment of this disease until the vaccination of the whole world or the discovery of an antiviral drug.

Acknowledgments

We would like to thank the Research Development & Coordination Center (RDCC) for helping us with the data's meta-analysis. In addition, we would appreciate the cooperation of the Clinical Research Development Unit, Imam Reza General Hospital, Tabriz, Iran, in conducting this research.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Ethical approval and consent to participate

Ethical approval was not required in this systematic review and meta-analysis. The code of ethics is IR.TBZMED.REC.1399.1192.

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