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META-ANALYSIS

Role of baricitinib in COVID-19 patients: A systematic review and meta-analysis

Manisha Thakur, Akhil Babu, Gopal Lal Khatik, Ashok Kumar Datusalia, Ramchander Khatri, Anoop Kumar

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Abstract

BACKGROUND

Recent studies have indicated the use of baricitinib in coronavirus disease 2019 (COVID-19) patients. However, the use of baricitinib in COVID-19 patients is unclear so far.

AIM

To determine the precise role of baricitinib in the mortality of COVID-19 patients.

METHODS

The relevant studies were searched in PubMed, Google scholar, and Clinical trials registries till July 13, 2021 and sorted out based on inclusion and exclusion criteria. The quality of studies was assessed using Newcastle-Ottawa Scale. A random-effect model was used, and the pooled estimate was calculated as the odds ratio with a 95% confidence interval using Rev Man 5.

RESULTS

A total of 11 studies (4 observational and 7 clinical trials) were found relevant for analysis. The overall estimate measure in terms of odds ratio for observational studies was 0.42 [0.11, 1.67], whereas for clinical trials it was 0.37 [0.09, 1.46], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group.

CONCLUSION

More studies are required to confirm the role of baricitinib in the deaths of COVID-19 patients.

Key Words: Janus kinase inhibitors; Baricitinib; COVID-19; Mortality; Systematic Review; Meta-analysis

Core Tip: Emerging reports have indicated the use of baricitinib in hospitalized coronavirus disease 2019 (COVID-19) patients. However, the use of baricitinib in COVID-19 patients is unclear so far. Current study aimed to find out the exact association of baricitinib in the mortality of COVID-19 patients.

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INTRODUCTION

According to the World Health Organization (WHO), multiple pneumonia episodes of unknown cause were reported in the central Metropolitan area of Wuhan in December 2019 in China. The causal infection was later identified as a novel coronavirus, tentatively termed coronavirus disease 2019 (COVID-19). This virus has been causing havoc on public health across the world since its outbreak in December 2019. More than 2000 incidents of COVID-19 infection were reported as of January 26, 2020, the majority of which were individuals living in or traveling Wuhan. The WHO claimed the COVID-19 pandemic was a Public Health Emergency of International Concern on January 30, 2020[1]. The cases of infection were highly associated with the seafood market in Wuhan[2]. Chinese officials announced 2835 confirmed cases in 2020, with 81 deaths. The causal agent has been identified as a novel coronavirus, COVID-19, a pathogen linked to severe acute respiratory syndrome (SARS), was quickly identified as the cause (SARS-CoV) by Chinese officials[3,4]. Coronaviruses (CoV) belongs to the family "coronaviridae". Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to be spread directly from bats to humans or by a single or several host species[3,5]. The treatment is based on the symptoms of the patients. Various classes of drugs are repurposed and are being used in the management of this infection.

Janus Kinase Inhibitors (JAKi) are also one of the repurposed drugs which are being used in the management of hospitalized COVID-19 patients due to their anti-inflammatory (inhibition of IL-6) and anti-viral effects (inhibit the entry of virus)[6]. Baricitinib is one of the JAKi approved for the treatment of rheumatoid arthritis. It has been observed that most SARS-CoV-2 infected patients were died due to cytokine storms, specifically the excess release of IL-6. Thus, baricitinib might be useful in the reduction of deaths of COVID-19 patients[7,8]. Meta-analysis is one of the quantitative analyses that help in clinical decision-making. The results of the individual studies are pooled and integrated using suitable statistical procedures[9-11]. In the current study, we performed a systematic review of clinical studies to determine the role of baricitinib in the deaths of COVID-19 hospitalised patients.

MATERIALS AND METHODS

The study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Figure 1). The study is registered with the International prospective register of systematic reviews (PROSPERO, Registration number: CRD42021281366).

Search strategy

A search was conducted in PubMed, Google scholar, and Clinical trial registry for observational, randomized, and non-randomized controlled studies, cohort studies, and comparative cross-sectional studies with the following search strategies: "baricitinib", OR "immunosuppressants", OR "anti-rheumatoid", OR "Janus kinase inhibitor" OR "Disease-modifying antirheumatic drug" AND "COVID-19" OR "Coronavirus" OR "Acute respiratory distress syndrome" OR "SARS-CoV-2". The references of included studies were screened to boost the search.

Study selection

Two reviewers (MT and AB) separately screened all the titles and abstracts as per the inclusion and

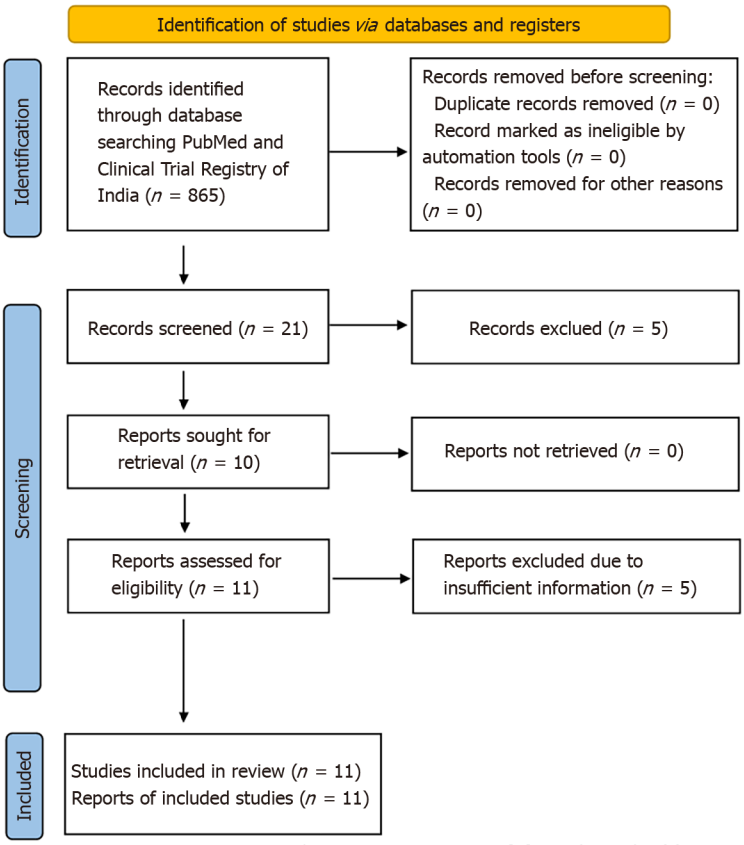

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Figure 1 Selection of studies as per the PRISMA guidelines.

exclusion criteria. The studies were included if participants were on baricitinib therapy, with all age groups, and all sexes. The case reports, case series, narrative review, systematic review, meta-analysis, studies of poor quality as per standard scale were excluded. The reviewers (MT and AB) separately screened the full-text studies for final inclusion. In the case of conflicts over the inclusion, the third reviewer (AK) was consulted.

Quality assessment

The quality assessment of eligible observational studies was done using Newcastle-Ottawa Scale whereas quality assessment of clinical trials was done using NIH quality assessment scale for quality assessment of controlled intervention studies. The assessment was done by two reviewers (MT and AB) separately. The disagreement among authors was resolved after a discussion with four reviewers (GLK, AKD, RK, and AK). The studies were categorized into three categories, *i.e.*, good, fair, and poor quality.

Data extraction

The data was extracted from studies by two reviewers (MT and AB) in an excel sheet. The information includes the name of the first author with publication year, the country where the study has been conducted, gender, study design, the total number of subjects, number of subjects, and deaths in baricitinib, non-baricitinib group.

Sensitivity analysis

The sensitivity analysis was done to check the effect of high or low sample size on the outcome to address the degree of heterogeneity.

Statistical analysis

RevMan 5 was used for all of the analyses. Using a random-effect model, the overall estimate was calculated as an odds ratio with 95% confidence intervals. Cochrane Q and I square statistics were used to calculate study heterogeneity.

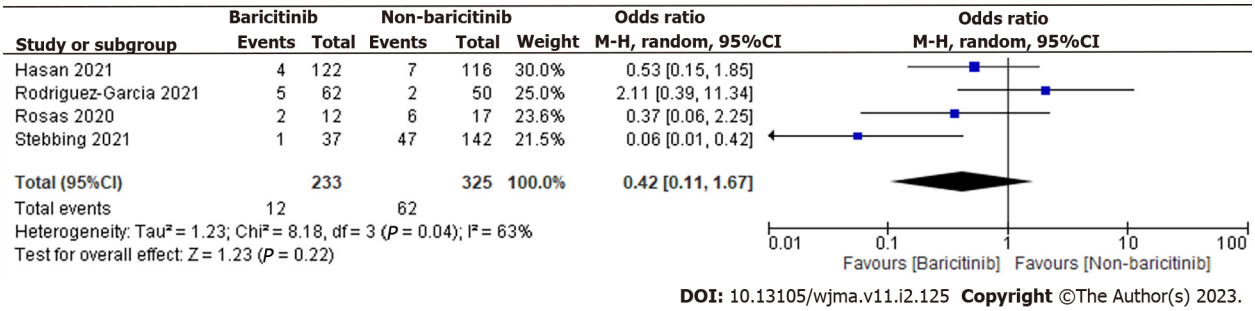

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Figure 2 Forest Plot showing overall estimate measure of observational studies as odds ratio using random-effect model.

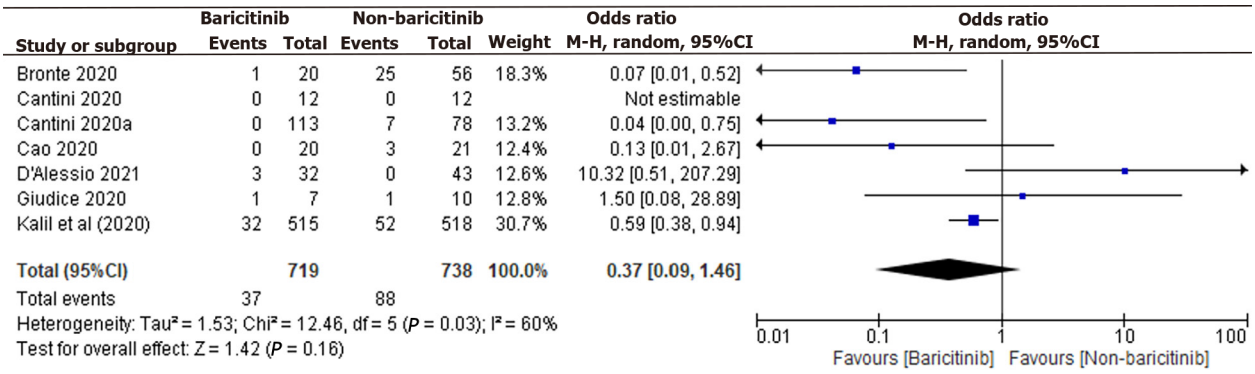

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Figure 3 Forest Plot showing overall estimate measure of clinical trials as odds ratio using random-effect model.

RESULTS

Search results and study characteristics

We found 865 articles after the initial search. After primarily screening of titles, 21 relevant articles were found. Further, based on the screening of abstracts, 16 were retrieved, out of which 05 articles were excluded due to insufficient information. Finally, 11 articles[11-22] were included for qualitative and quantitative analysis. Figure 1 depicts the selection of articles. The full-text or secondary screening with bibliography searches yielded no additional articles for inclusion. Out of the 11 studies, 4 were observational studies whereas the remaining 7 studies were clinical trials. The four studies were conducted in Italy, two in Spain, one in Italy and Spain, and one each at, Omaha, Bangladesh, Germany, Wuhan. The characteristics of included observational studies were compiled in Table 1 whereas the characteristics of included clinical trials were compiled in Table 2.

Quality assessment

All observational studies on the Newcastle-Ottawa Scale were found to be of good to fair quality based on their scores in the selection, comparability, and outcome subscales. Three of the four studies were of high quality, while the fourth was of fair quality (Table 3). According to the NIH quality assessment scale, 5 studies were of good quality, while the remaining two were of fair quality (Table 4).

Analysis of observational studies

A total of 558 patients were found in selected 4 observational studies. 233 of the 558 coronavirus disease 2019 (COVID-19) cases were taking baricitinib, while the remaining 325 were not. The overall estimate was 0.42 [0.11, 1.67], indicating that the baricitinib group had a non-significant reduction in COVID-19 patient deaths compared to the non-baricitinib group (Figure 2).

Analysis of clinical trials

In total, 1457 patients were found in 7 clinical trials. 719 of the 1457 COVID-19 cases were taking baricitinib, while the remaining 738 were not. The overall estimate was 0.37 [0.09, 1.46], indicating that the baricitinib group had a non-significant reduction in COVID-19 patient deaths compared to the non-baricitinib group (Figure 3).

Table 1 Characteristics of included observational studies

Ref.	Country	Study design	Sample size	Sex		Baricitinib group		Non-baricitinib group	
				Male	Female	Number of patients	Death	Number of patients	Death
Hasan *et al*[14], 2021	Bangladesh	Cohort study	238	159	79	122	4	116	7
Stebbing *et al*[15], 2021	Italy, Spain	Observational	790	438	352	37	1	142	47
Rodriguez-Garcia *et al*[16], 2020	Spain	Cohort study	112	78	34	62	5	50	2
Rosas *et al*[19], 2020	Spain	Case control study	29	20	9	12	2	17	6

Table 2 Characteristics of included clinical trials

Ref.	Country	Study design	Sample size	Sex		Baricitinib group		Non-baricitinib group	
				Male	Female	Number of patients	Death	Number of patients	Death
Bronte *et al*[13], 2020	Italy	Clinical trial	76	38	38	20	1	56	25
Kalil *et al*[12], 2020	Omaha	Clinical trial	1033	652	381	515	32	518	52
Cantini *et al*[17], 2020	Germany	Clinical trial	24	20	4	12	0	12	0
Cantini *et al*[18], 2020	Italy	Clinical trial	191	119	72	113	0	78	7
Cao *et al*[20],2020	Wuhan	Clinical trial	41	24	17	20	0	21	3
D'Alessio *et al*[21],2021	Italy	Clinical trial	75	52	23	32	3	43	0
Giudice *et al*[22], 2020	Italy	Clinical trial	17	13	4	7	1	10	1

Table 3 Quality assessment of observational studies using new castle Ottawa scale

Ref.	Selection	Comparability	Exposure	Total score	Quality of the study
Hasan *et al*[14], 2021	****	**	***	9	Good
Stebbing *et al*[15], 2021	***	*	***	7	Good
Rodriguez-Garcia *et al*[16], 2020	****	*	***	8	Good
Rosas *et al*[19], 2020	**	**	***	7	Fair

*For each numbered item within the selection and outcome categories.

Heterogeneity

The I^2 (90%) and chi^2 statics have shown high heterogeneity among studies.

Sensitivity analysis

We have analyzed the forest plots of both observational and clinical trials and found that there is a study with high and low sample sizes, particularly in clinical trials. Therefore, analysis was also done again to check the effect of these studies on the outcome. The studies with a high and low sample sizes *i.e.*, Kalil *et al*[12] and Giudice *et al*[22], were excluded, and analysis was done again. The overall estimate was 0.23 [0.02, 2.37], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group (Figure 4). Overall, results were not affected by the studies with high and low sample sizes.

DISCUSSION

The current analysis was done to find out the role of baricitinib in the reduction of deaths of COVID-19 hospitalized patients. To the best of our knowledge, very few meta-analyses have been done so far on the use of baricitinib in COVID-19 treatment. Recently, Chen *et al*[23], have performed a meta-analysis

Table 4 Quality assessment of clinical trials using NIH scale

No.	Ref.	Type of study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality of the study
1	Bronte *et al*[13], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
2	Kalil *et al*[12], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Good
3	Cantini *et al*[17], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
4	Cantini *et al*[18], 2020	Clinical trial	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	Fair
5	Cao *et al*[20], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
6	D'Alessio *et al*[21], 2021	Clinical trial	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
7	Giudice *et al*[22], 2020	Clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	NO	Yes	NR	Good

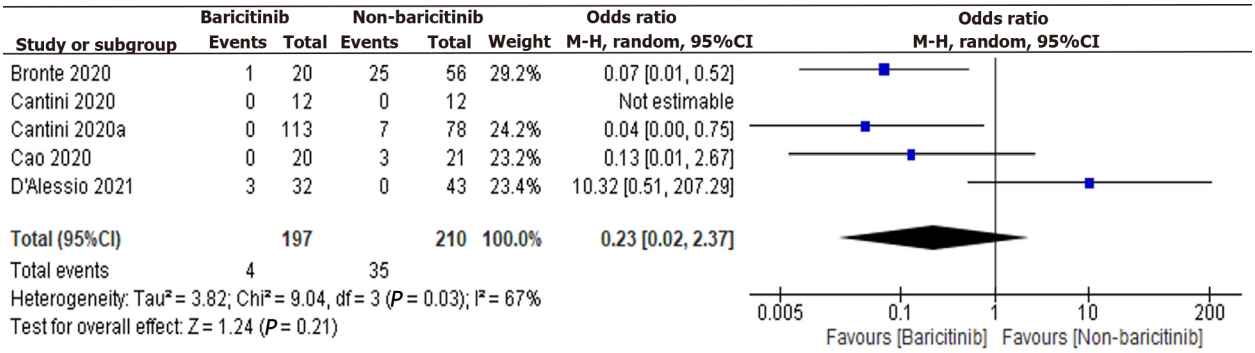

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Figure 4 Forest Plot showing overall estimate measure of clinical trials as odds ratio after exclusion of studies with high (Kalil *et al*[12], 2020) and low sample size (Giudice *et al*[22], 2020) using random-effect model.

of 11 studies and reported the safety and efficacy of JAK-inhibitors including baricitinib in COVID-19 patients. Another JAK inhibitor *i.e.*, ruxolitinib is also used in hospitalized patients. The meta-analysis results of Wijaya *et al*[24], have demonstrated a significant clinical improvement and decrease in the risk of mortality of COVID-19 patients. The potential of baricitinib in the reduction of deaths of hospitalized COVID 19 patients is also indicated by a meta-analysis conducted by Walz *et al*[25]. Recently, Putman *et al*[26], have also performed a meta-analysis to find out the efficacy of anti-rheumatoid therapy, including baricitinib and steroids for the treatment of COVID-19. However, number of available studies regarding the use of baricitinib in COVID-19 patients at that time was very less. The already published meta-analysis have also analyzed different design of studies together which make less valid conclusion. In the current meta-analysis, we have analyzed observational and clinical trials separately. However, the results of both observational and clinical trials have shown the non-significant deaths of COVID-19 hospitalized patients in the baricitinib group as compared to non-baricitinib group. Further, the sensitivity analysis results have also shown no effect of outliers on the outcome.

CONCLUSION

In conclusion, more research is needed to draw a valid conclusion about the use of baricitinib in the reduction of COVID-19 patient deaths.

ARTICLE HIGHLIGHTS

Research background

More research is needed to draw a valid conclusion about the use of baricitinib in the reduction of coronavirus disease 2019 (COVID-19) patient deaths.

Research motivation
More research is needed to confirm the role of baricitinib in COVID-19 patient deaths.

Research objectives
A total of 11 studies (4 observational and 7 clinical trials) were found relevant for analysis. The overall estimate measure in terms of odds ratio for observational studies was 0.42 [0.11, 1.67], whereas for clinical trials it was 0.37 [0.09, 1.46], indicating a non-significant reduction in COVID-19 patient deaths in the baricitinib group versus the non-baricitinib group. The degree of heterogeneity among studies was also discovered to be high.

Research methods
The study was conducted as per the PRISMA guideline using RevMan 5 software.

Research results
To investigate the role of baricitininb in the reduction of COVID-19 patient deaths.

Research conclusions
Can baricitinib reduce the deaths of COVID-19 patients?

Research perspectives
Emerging reports have indicated the use of baricitinib in hospitalized COVID-19 patients. However, the use of baricitinib in COVID-19 patients is unclear so far.

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FOOTNOTES

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