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REVIEW ARTICLE

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## Consequence of COVID-19 on allergic asthma outcomes: a systematic review and meta-analysis

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Risk

### Abstract

Asthma is a common chronic lung disease, and COVID-19 pandemic as a respiratory viral disease led to lung infection and resulted in millions of deaths. So, the impact of COVID-19 on asthma outcomes and the risk of being infected or hospitalized should be clarified. Systematic review and meta-analysis on the outcomes and risk of asthma for people with COVID-19 was done by searching electronic databases between 1 December 2019 and 31 July 2023. A total of 48 studies from 27 countries spread across all continents were included in the review. The prevalence of asthma among COVID-19 patients was 7.9%, and the analysis demonstrated a 16.5% reduction in the risk ratio for acquiring COVID-19 among subjects with asthma compared to those without asthma. There was no statistically significant difference in hospitalization risk, ICU admission risk, and death risk for COVID-19 patients with no asthma compared to those with asthma. The risk of death from COVID-19 was similar between nonasthmatics and asthmatics. The findings indicated that subjects with asthma may be at a lower risk of having infection with COVID-19 compared to those without asthma, but they have a similar risk of hospitalization and mortality.

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## Introduction

Asthma is the most common chronic adversity of the lungs, and its prevalence was globally estimated to be in up to 350 million people.<sup>1-4</sup> Asthma, which has no complete cure, leads to several fatalities and involves significant expenses for its prevention and control.<sup>2,3</sup> The new coronavirus disease 2019 (COVID-19) pandemic had an impact on one and all, and it spread rapidly across the globe with millions of deaths. Individuals with asthma may be more affected with this virus and were at an increased risk of acquiring the disease or experiencing poor outcomes.<sup>4,5</sup>

The cohort studies and individual case series were reported with conflicting results in subjects with asthma on the vulnerability to and risk of COVID-19 mortality. There are different reports on the vulnerability of asthma patients to COVID-19 based on various national- or local-level case series and analyses, and the conclusions reached were constrained by the inclusion of cases of COVID-19 and their related analyses that confer significant selection bias of asthma.<sup>6,7</sup> The maximum focus was on mortality and not on other important parameters such as admission to an intensive care unit (ICU), risk of being infected, hospitalization, and most importantly ventilator use when admitted.<sup>8-10</sup> A comprehensive understanding of the risk of COVID-19 among subjects with asthma is crucial globally as countries lift lockdown. The relationship between COVID-19 and asthma and also the impact of this virus on symptoms of asthma needs to be analyzed. The risk of SARS-Cov-2 (severe acute respiratory syndrome coronavirus 2) infection affecting people with asthma, hospitalization, ICU admission, and ventilator use should be recognized.<sup>4,5,11,12</sup>

In this study, detailed searches with new analyses were done and therefore, the research question is that are subjects with asthma at a higher risk of being infected or hospitalized or vulnerable to weaker clinical outcomes from COVID-19? And, what is COVID-19's impact on asthma outcomes? Consequently, the objective was to conduct a comprehensive systematic review and meta-analysis of the morbidity and mortality of COVID-19 among subjects with asthma.

## Methods

### Search strategy and also selection criteria

The systematic review and meta-analysis touch upon the risk of asthma in people with COVID-19. Also, it includes publications on the pandemic's early stages, and the protocol used was from published studies, systematic reviews, and meta-analyses; the preferred reporting items were employed in the reporting of this study.<sup>13</sup> A comprehensive search of electronic databases, including the Cochrane Database of Systematic Reviews, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, the World Health Organization COVID-19 Database, Embase, CINAHL, and PEDro, were conducted between 1 December 2019 and 31 July 2023. Also, a hand search of relevant systematic review references was conducted. All studies (primary controlled) reporting on adults with

confirmed COVID-19 were included, with a pre-existing asthma diagnosis that was published in the English language, and the screenings were checked and confirmed by three independent reviewers.

### Data collection

Three reviewers screened abstracts and titles, and excluded irrelevant studies using Rayyan QCRI.<sup>14</sup> Independently, full-text publications were subsequently reviewed and disagreement resolved via consensus and also referral to a fourth reviewer. At the full-text review stage, potential overlaps between studies were identified in order to prevent double counting of individual patients. The data were extracted using a standard electronic form, and the quality of the included studies was rated using the Newcastle-Ottawa Scale.<sup>15</sup>

### Outcomes

The outcomes were: (1) the risk of asthma, expressed as the proportion of confirmed asthmatic patients with a diagnosis of COVID-19; (2) risk of hospitalization from asthma with confirmed COVID-19; (3) risk of ICU admission (confirmed COVID-19 patients with asthma); (4) risk of being ventilated (asthmatic individuals with confirmed COVID-19); and (5) risk of death (asthmatic individuals with confirmed COVID-19).

### Data analysis

In [Table 1](#), descriptive statistics were utilized to summarize the details of the included studies. It was mentioned that the Newcastle-Ottawa Scale was applied to assess the quality of methodology of the included studies based on the relevant study designs, case-control or cohort. The main sets (two) of meta-analyses were performed. To estimate the prevalence of asthma among individuals with COVID-19, a binomial distribution was employed to model within-study variability. The Wilson score was used to calculate 95% confidence intervals for all the binary outcomes, and a Sidik-Jonkman random-effects meta-analysis was conducted. The degree of quantitative heterogeneity was evaluated through the implementation of a formal test of homogeneity and the estimation of the proportion of variability attributable to heterogeneity. In addition, prespecified subgroup analyses were conducted on the studies' quality and content, and univariate meta-regression using proportions of current smokers, age, and former smokers as covariates were performed. All pooled results were presented in the results section, and statistical analyses were performed using Stata 16.

## Results

The searches resulted in 41,392 citations. After removing of duplications, 17,831 abstracts and titles were screened, and 17,027 publications were excluded. From the remaining 804 manuscripts, 756 were excluded after reviewing

Table 1 Detailed summary of the studies.

	Refer- ence	Country	Setting	Design	COVID-19 positive		Age (years)	Male	Current smokers	COPD	NOS Score
					Asthma	Overall					
1	26	Argentina	Mixed	Retrospective cohort study	12,580	207, 079	41	1,03,487	4,074	4,405	9
2	27	Australia	Mixed	Case series	10	99	54	51	-----	2	8
3	28	Australia	Hospital	Case series	22	197	45	94	-----	4	7
4	29	Belgium	Hospital	Retrospective cohort study	57	596	58.75	294	-----	-----	9
5	30	Brazil	Hospital	Retrospective cohort study	7	114	32.4	0	-----	-----	7
6	31	China	Hospital	Retrospective cohort study	244	39,420	55.7	1,9655	-----	-----	9
7	32	China	Hospital	Retrospective cohort study	68	562	47	265	-----	-----	8
8	33	China	Hospital	Retrospective cohort study	1	290	57	155	10	6	8
9	34	Denmark	Mixed	Retrospective cohort study	354	5,104	54.6	2,399	-----	432	9
10	35	France	Mixed	Retrospective cohort study	814	7,320	43	2,301	790	87	7
11	36	France	Hospital	Retrospective cohort study	37	112	60	49	-----	-----	9
12	37	Ghana	Hospital	Retrospective cohort study	24	307	37.9	174	-----	-----	7
13	38	Italy	Hospital	Retrospective cohort study	20	1,043	52.5	704	-----	-----	9
14	39	Kuwait	Hospital	Retrospective cohort study	235	3,995	40.4	2,814	140	17	9
15	40	Kuwait	Hospital	Retrospective cohort study	43	1,096	41	888	44	5	9
16	41	Mexico	Hospital	Retrospective cohort study	4,942	1,78,306	44.1	88,083	-----	-----	8
17	42	Mexico	Mixed	Retrospective cohort study	1,188	38,324	46.9	2,2362	3,277	889	9
18	43	Mexico	Hospital	Retrospective cohort study	1,448	66,123	52.4	40,124	-----	2,619	9
19	44	Norway	Mixed	Retrospective cohort study	515	7,632	33.22	-----	-----	161	7
20	45	Spain	Hospital	Retrospective cohort study	113	2,539	62.66	1,275	154	89	9
21	46	Spain	Hospital	Retrospective cohort study	577	6,310	59	2,983	873	-----	9
22	47	Spain	Mixed	Retrospective cohort study	288	10,454	58	4,172	258	180	9
23	48	Spain	Mixed	Retrospective cohort study	2,330	35,387	38.8	17,172	6,119	1,404	9
24	49	Spain	Community	Retrospective cohort study	10	376	54	192	-----	-----	8
25	50	South Korea	Community	Retrospective cohort study	725	7,340	47.1	2,970	-----	350	9
26	51	South Korea	Community	Retrospective cohort study	686	7,272	45.3	2,927	-----	-----	9
27	52	South Korea	Hospital	Case-control study	66	2,200	56.71	785	92	30	9
28	53	South Korea	Mixed	Retrospective cohort study	218	7,372	44.5	3,000	-----	-----	9
29	54	Sweden	Mixed	Case-control study	133	1,981	61	14,65	-----	75	9
30	55	Sweden	Mixed	Case-control study	4,493	68,575	46	26,808	-----	2,168	9
31	56	Turkey	Hospital	Retrospective cohort study	58	767	51.99	374	80	43	8
32	57	UK	Hospital	Retrospective cohort study	1,557	17,606	67	10,560	231	-----	9
33	18	UK	Mixed	Retrospective cohort study	29,792	1,98,420	37.7	93,765	22,134	1,873	9
34	58	UK	Hospital	Retrospective cohort study	102	617	65	-----	-----	-----	9
35	59	UK	Hospital	Retrospective cohort study	12	52	54.82	29	-----	-----	8
36	60	USA	Hospital	Retrospective cohort study	105	727	49.46	-----	-----	-----	8
37	61	USA	Hospital	Retrospective cohort study	18	242	-----	123	-----	30	8
38	62	USA	Hospital	Retrospective cohort study	41	113	50	53	2	57	9
39	63	USA	Hospital	Retrospective cohort study	272	6,245	-----	3,060	-----	-----	8
40	64	USA	Mixed	Prospective cohort study	163	1,298	52	762	55	-----	9
41	65	USA	Hospital	Case-control study	562	3,248	-----	911	131	-----	8
42	66	USA	Hospital	Retrospective cohort study	4	33	63	22	0	1	8
43	67	USA	Hospital	Retrospective cohort study	30	529	70	286	39	36	7
44	22	USA	Hospital	Retrospective cohort study	468	10,523	58.35	5,707	-----	286	9
45	68	USA	Hospital	Case-control study	88	1,045	64.6	352	-----	18	8
46	69	USA	Hospital	Retrospective cohort study	951	4,558	60.5	-----	-----	-----	9
47	70	USA	Hospital	Retrospective cohort study	598	5,596	38.4	2,635	123	88	9
48	71	USA	Hospital	Retrospective cohort study	220	1,526	53.3	654	43	-----	9

the full text and a total of 48 studies were included in the review (Figure 1). Studies involving overlapping patient populations were excluded from the analysis if they reported identical outcomes.

### Descriptive characteristics

This review is based on a pooled sample of patients diagnosed with COVID-19 who reported information related to asthma. Most of these hospital-based studies were from 27 countries spread across Europe, South America, Asia, North America, Africa, and Australia (Table 1).

The mean  $\pm$  SD age of COVID-19 patients was  $49.2 \pm 13.6$  years; 43.9% were male and 56.1% were female; and 6.6% were current smokers and 7.9% were former smokers. The asthma prevalence among those infected with the novel coronavirus (COVID-19) was 7.9%, and 2.8% also had COPD.

### Risk of results' bias

According to the Newcastle-Ottawa scores, all of the studies had scores of more than 7 and were of high quality.

### Meta-analysis of the risk of acquiring COVID-19

The pooled analysis of studies demonstrated a 16.5% reduction in the risk ratio for acquiring COVID-19 among

individuals with asthma compared to those without asthma. There was considerable heterogeneity across the studies and meta-regression by age revealed that the older ages was associated with enhanced risk of COVID-19 in individuals with asthma. However, the current smoker group did not demonstrate a statistically significant association.

### Meta-analysis of the risk of hospitalization

There was no statistically significant difference with regard to the risk of hospitalization for COVID-19 individuals with and without asthma, and there was considerable heterogeneity observed across the studies. A meta-regression by age and current smoking status revealed no significant association between asthma and the risk of hospitalization due to COVID-19.

### Meta-analysis of the risk of ICU admission

There was a no statistically significant difference in the ICU admission risk for subjects with asthma compared to those without asthma in a pooled analysis, and substantial heterogeneity was observed across the studies. A meta-regression analysis, with age and current smoking status as moderators, did not yield statistically significant results.

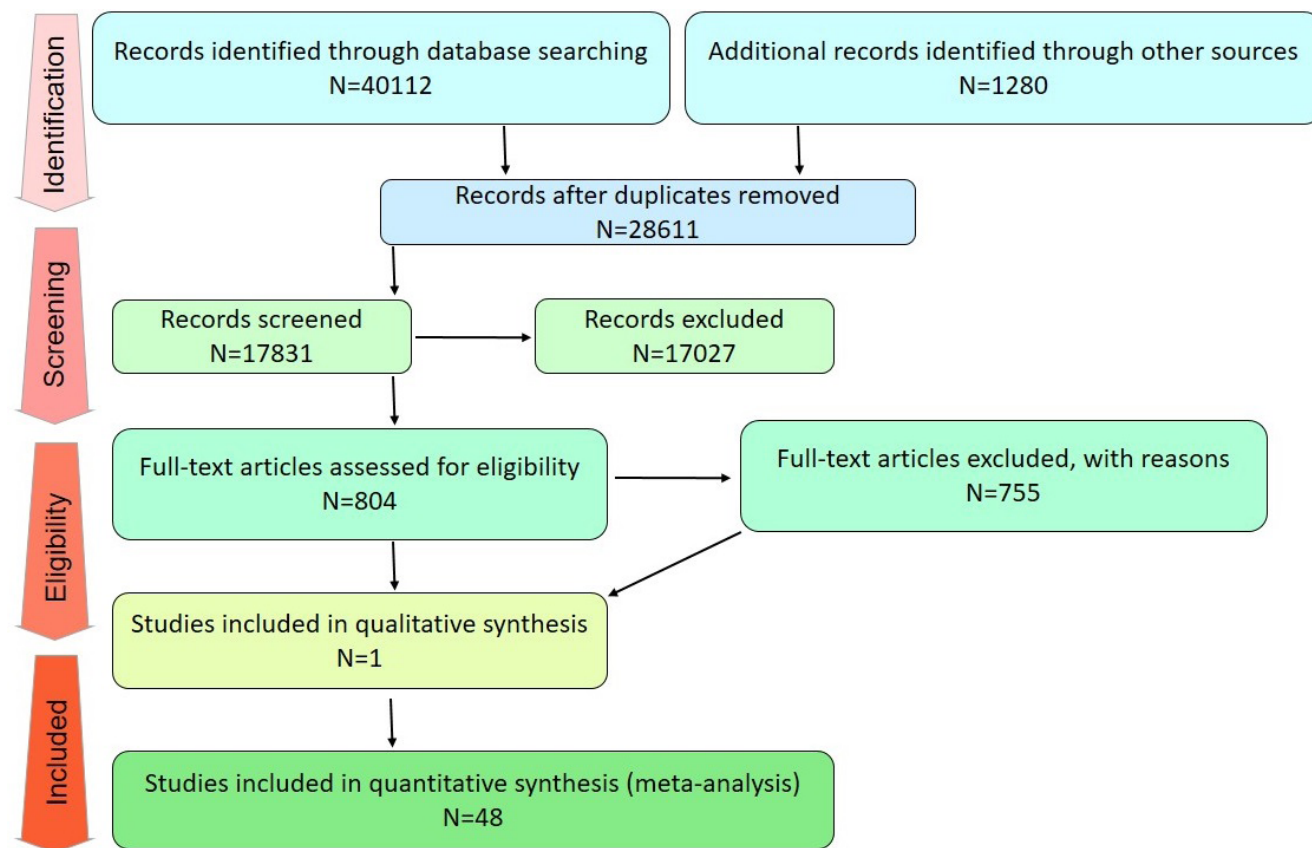


Figure 1 Summary of the results of the screening and evaluation of the publications and citations searched.

## Meta-analysis of the risk of ventilator use when admitted in the ICU

In relation to the probability of mechanical ventilation, a statistically significant difference was not observed in the likelihood of being treated with a ventilator once admitted to the ICU for asthma compared to those with no asthma. Considerable heterogeneity was observed across the studies and a meta-regression analysis was conducted to determine the relationship between age and current smoking status. However, the results were not statistically significant.

## Meta-analysis of the risk of death

The analysis revealed no statistically significant difference in the risk of death from COVID-19 between individuals with and without asthma, and considerable heterogeneity was observed across the studies. Including age as a moderator in the meta-regression analysis yielded no significant reduction in the risk of death, nor did it reveal any significant association with the current smoking status.

## Analyses of the subgroup

Subgroup analyses by continent revealed substantial differences in the risk of acquisition of COVID-19 between the continents. The lowest risk was observed in Asia, while no major differences in hospitalization were found between continents. Nevertheless, significant discrepancies were observed in ICU admission rates across continents, and the maximum risk was found to be in Asia and the lowest in South America. In addition, the risk of ventilator use had significant differences across the continents, and the maximum risk was found in Europe. Similarly, the risk of death was found to vary considerably across the continents. The maximum risk was observed in Asia.

## Discussion

The objective of this meta-analysis was to assess the vulnerability of patients with asthma who are infected with COVID-19. This discrepancy can be attributed to the more rigorous inclusion criteria employed, which excluded case series and single-arm cohort studies. The focus was on including only studies published by the nonasthma control group. Moreover, the prevalence rate was found to be lower than the global prevalence of self-reported symptoms of asthma. In this meta-analysis, the proportion estimated was less than in the recent UK studies which reported prevalence in those who were infected with the variant of B.1.1.7; lower prevalence rates were reported in other studies in Turkey and in Italy.<sup>16-18</sup> The current study found a significant decrease in the risk of acquiring COVID-19.

The study reported lower rates of positivity for COVID-19 test in asthma patients compared to those without asthma.<sup>19</sup> Moreover, a community study demonstrated a lower prevalence of asthma in individuals who tested positive for the COVID-19 test compared to those who had

negative COVID-19 test results.<sup>20,21</sup> Several mechanisms may contribute to the lower risk of acquiring COVID-19 in subjects with asthma compared to individuals with no asthma. A retrospective study demonstrated that asthma is associated with poor outcomes and lower risk, and that both in those with and without asthma, the presence of eosinophilia is associated with reduced risk of mortality. Although not statistically significant, a greater proportion of individuals with asthma exhibited eosinophilia compared to those without asthma.<sup>22</sup> Subgroup analyses by continent revealed statistically significant differences in the risk of contracting the novel coronavirus (COVID-19) between the continents. The lowest risk was observed in Asia, followed by America and Europe. In addition, it was observed that there was consistent risk reduction in three out of the four regions, and all countries with a large testing regime may account for this variance between regions. Furthermore, it is crucial to acknowledge that the outcome may not be representative of other countries where testing protocols have been less comprehensive.

Furthermore, the lower risk of acquiring COVID-19 may be attributed to the angiotensin-converting enzyme 2 receptor expression that is significantly lower in asthmatic patients compared to healthy controls,<sup>23</sup> which supports the result of the current study analysis. The data demonstrated a clear correlation between increasing age and elevated risk of contracting the novel coronavirus. In a final directive, health authorities advised asthmatic patients to practice social distancing and to take particular care to avoid contracting the novel coronavirus. Furthermore, the pooled point estimate indicates a potential enhanced risk of hospitalization for COVID-19 for subjects with asthma, with a considerable degree of uncertainty. Similarly, the pooled point estimate indicates a potential increased risk of ICU admission due to COVID-19 for subjects with asthma, although this is not statistically significant.

It was reported that inhaled budesonide administration in early stage reduced the likelihood of urgent medical care and also time to recovery from COVID-19. The study demonstrated that the budesonide group exhibited a more rapid recovery compared to the usual care group.<sup>24,25</sup> A main finding of the current study was the similar risk of death between nonasthmatics and asthmatics from COVID-19. The information provided was limited on smoking that limits our ability to assess the impact of smoking.

Furthermore, reported were details of both nonasthma and asthma patients wherein COVID-19 infection status was used, and there was no access to information to determine if individuals with asthma were disproportionately represented among cases of mild or asymptomatic illness that did not undergo testing. This would suggest that there may be a need for further investigation into the potential underdiagnosis of asthma in this population. The findings from this analysis indicated that individuals with allergic asthma may be at a lower risk of COVID-19 infection compared to those without asthma but have a similar risk of ICU admission, ventilator use, hospitalization, and mortality. In light of the rapid evolution of the COVID-19 virus and the emergence of variants globally, it is imperative to exercise caution for individuals with asthma. Moreover, further research is necessary to ascertain the precise risk profile.

## Ethics Approval and Consent to Participate

Not Applicable.

## Consent for Publication

Not Applicable.

## Availability of Data and Materials

Not Applicable.

## Conflict of Interest

There is no conflict of interest.

## Funding

Not Applicable.

## Authors' contributions

X.L., D.S., K.C., and Q.W. searched the literature, screened the inclusion/exclusion reviews, extracted data, did quality assessment, and contributed to writing the review. All of them performed the statistical analysis and oversaw the study from inception to completion. X.L. and D.S. are co-first authors, and they contributed equally to this work. QW is the corresponding author.

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