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Asthma does not influence the severity of COVID-19: a meta-analysis

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ABSTRACT

Objective: Previous studies have reported a correlation between coronavirus disease-2019 (COVID-19) and asthma. However, data on whether asthma constitutes a risk factor for COVID-19 and the prevalence of asthma in COVID-19 cases still remains scant. Here, we interrogated and analyzed the association between COVID-19 and asthma.

Methods: In this study, we systematically searched PubMed, Embase, and Web of Science databases for studies published between January 1, to August 28, 2020. We included studies that reported the epidemiological and clinical features of COVID-19 and its prevalence in asthma patients. We excluded reviews, animal trails, single case reports, small case series and studies evaluating other coronavirus-related illnesses. Raw data from the studies were pooled into a meta-analysis.

Results: We analyzed findings from 18 studies, including asthma patients with COVID-19. The pooled prevalence of asthma in COVID-19 cases was 0.08 (95% CI, 0.06-0.11), with an overall I^2 of 99.07%, $p < 0.005$. The data indicated that asthma did not increase the risk of developing severe COVID-19 (odds ratio [OR] 1.04 (95% CI, 0.75-1.46) $p = 0.28$; $I^2 = 20\%$). In addition, there was no significant difference in the incidence of asthma with analyze age in COVID-19 infections [OR] 0.77(95% CI, 0.59–1.00) $p = 0.24$; $I^2 = 29\%$).

Conclusion: Taken together, our data suggested that asthma is not a significant risk factor for the development of severe COVID-19.

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Asthma; COVID-19; atopic disease; epidemic; meta-analysis

Introduction

The current outbreak of coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has greatly increased the global public health burden and mortality.(1) The common clinical manifestation of COVID-19 includes dry cough and shortness of breath. (2,3) As a chronic inflammatory disorder of the airways, asthma is characterized by a variety of respiratory symptoms,(4) including wheezing, shortness of breath, and cough,(5) which are highly similar to COVID-19. On the other hand, since fever, one of most common COVID19 symptoms, is a clinical symptom presented by any infection which exacerbates asthma, it is not a reliable clinical tool for the diagnosis of COVID-19. Therefore, it is conceivable that milder cases of COVID-19 might be confused with exacerbations of asthma, or the COVID-19 patients may might have comorbidities that may also be associated with asthma. Thus, there is a compelling need to precisely dissect the relationship between COVID-19 and asthma.

There is some clinical data showing a higher prevalence of asthma among the patients with COVID19.(6) In humans, Coronaviruses (CoVs) mainly cause respiratory tract infections,(7) and viral respiratory infections are the most common trigger for severe asthma exacerbations in children and adults. Consequently, the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics (8) and the Centers for Disease Control (CDC) (9) identified asthma as significant risk factor for severe COVID-19 illness. Besides, a clinical study in the UK reported that asthma was a risk factor for COVID19.(10) On the contrary, epidemiologic studies have demonstrated a lower-than-expected prevalence of asthma in patients with COVID-19 (11–13) . Broadhurst, R et al. discounted the idea that asthma is a risk factor for developing severe COVID-19.(14) Besides, in a systematic literature review, only two reports described asthma as a potential risk factors for COVID-19.(15) Therefore, whether asthma constitutes a risk factor for COVID-19 is still unclear.

Identification of risk factors for the development of severe COVID-19 is critical to not only aid in the direct development of new treatments but help in designing infection prevention strategies. Here, we aimed to assess whether asthma, one of most common chronic diseases, is a significant risk factor for developing severe COVID-19 and the prevalence of asthma in patients with COVID-19.

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Methods

Search strategy and inclusion criteria

In this meta-analysis, we searched PubMed, Embase, and Web of Science databases for articles published from Jan 1, 2020 to August 28, 2020. We used the keywords "asthma" OR "wheeze" OR "wheezing" OR "recurrent wheezer" OR "recurrent wheeze" OR "acute wheeze" OR "wheezing episode" OR "asthma episode" OR "Bronchial Asthma" OR "Asthma, Bronchial disease 2019" OR "2019 novel coronavirus disease" OR "coronavirus 2019" OR "2019-nCoV" OR "SARS-CoV-2" OR "COVID 19" OR "coronavirus disease-19". Additional articles were retrieved by screening the reference lists of the included studies. The literature search was restricted to articles published in English. Studies that investigated the epidemiology and clinical characteristics or features of COVID-19 were eligible.

Exclusion criteria

Records were managed with EndNote (version X9.0) to exclude duplicates. We excluded study which did not describe asthma and COVID-19, those that did not show the epidemiological relationship between asthma and COVID-19 and those that evaluated only the relationship between COVID-19 and one symptom of asthma (e.g. wheezing). Reviews, non-English language and non-full text articles (e.g. editorials or congress abstracts) were also excluded.

Data extraction

We independently screened titles and abstracts of the potential studies; conflicts were resolved through discussion. We then independently read full-text articles to identify studies meeting the inclusion criteria, and the reference lists from all identified studies as well as reviews were scrutinized for inclusion. We extracted the following variables: author; date; study design; patient demographics; patients type; number of participants in severe and non-severe disease groups.

Data synthesis and statistical analysis

We calculated the pooled prevalence of asthma among the confirmed COVID-19 patients. Odds Ratios (OR) were used to describe the probability of asthma occurrence in patients with severe versus non-severe COVID-19 and the younger versus the older. Due to heterogeneity within and between studies, a random-effects model was used to estimate the Incidence Rate through Stata data analysis tools while fixed-effects model was used to calculate the pooled ORs through Mantel -Haenszel(M-H) method in Review Manager (version 5.3) tools. Both analysis tools provided a more conservative estimate of the 95% CI. Data were presented using forest plots. We examined between-study heterogeneity using the I^2 statistic. We defined COVID-19 severity as those who were admitted to intensive care unit (ICU), needed mechanical ventilation or death.

Results

An initial search generated 690 potentially relevant papers, of which 333 duplications, 9 animal trails and 57 reviews were excluded in first screening of titles and abstracts. Then 28 papers met the inclusion criteria. After more careful full-text review, additional 10 papers were excluded because they did not; provide the relevant data about asthma ($n = 2$), analyze the prognosis of COVID-19 ($n = 2$), count the number of COVID-19 in asthmatic patients ($n = 3$), or were; documented case report ($n = 1$), used the same database ($n = 1$), was a special paper ($n = 1$). None of 1590 COVID-19 had physician-diagnosed asthma in the special paper. (16) We postulated that this could be attributed to the fact that asthma symptoms are similar COVID-19 symptoms (e.g. cough and shortness of breath), therefore, asthma patients were not evaluated. Meanwhile, this article is automatically excluded by using Stata software. Therefore, a total of 18 studies finally met the inclusion criteria and were included in our analysis (Figure 1), and the essential characteristics of the included studies are shown in Table 1.

Prevalence of asthma in confirmed COVID-19 cases

The 18 studies that included 3940 asthma patients reported a total of 41282 COVID-19 cases in their analyses. The pooled prevalence of asthma in the COVID-19 cases was 0.08 (95% CI, 0.06–0.11), with an overall I^2 of 99.07%, $p < 0.005$ (Figure 2).

Disease severity among COVID-19-asthma patients

Only 5 of the 18 articles classified the COVID-19 patients as severe or non-severe. Five studies involving 279 asthma patients reported COVID-19 in their analyses. Approximately 19% (54/279) of the patients experienced severe COVID-19 disease compared to 81% (225/279) exhibited non-severe symptoms. This data demonstrates that asthma patients are not at a higher risk of developing severe COVID-19 [calculated OR, 1.04 (95% CI, 0.75–1.46)]. The overall I^2 was 20%, $p = 0.28$ (Figure 3).

The role of age in the incidence of asthma in COVID-19 patients

Three studies that involving 297 asthma patients reported the presence of COVID-19. A total of 54% of the asthma patients (159/297) reported were aged 50 years or less, while 46% patients (138/297) were more than 50 years. Thus, there was no demonstration of the incidence of asthma with age in COVID-19 [calculated OR, 0.77 (95% CI, 0.59-1.00)]. The overall I^2 was 29%, $p = 0.24$ (Figure 4).

Discussion

Here, for the first time, we conduct a meta-analysis and provide an informed understanding of the relationship between asthma patients and COVID-19. This meta-analysis

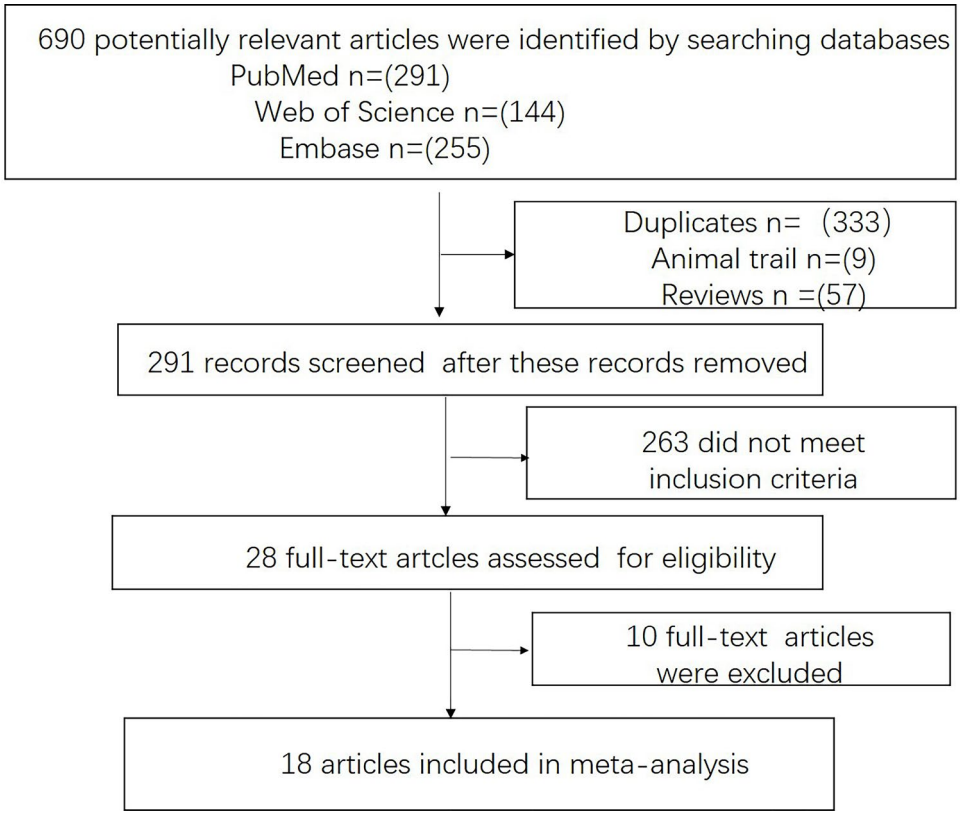

Figure 1. Selection flow diagram of this meta-analysis.

Table 1. characteristic of the included studies.

Author	Date (Y-M)	Area	Study Type	Sex (M/F)	Age	Patient Type	Score of Quality Evaluation Scale
Arentz et al. (17)	20-03	Evergreen Hospital	Cross-Sectional	11/10	70(43–92)	Inpatients	6 (11)
Argenziano et al. (18)	20-05	NYP/CUIMC electronic health record	Case-Control	596/404	63(50–75)	Inpatients and Outpatients	7 (9)
Avdeev et al. (19)	20-04	Clinic of pulmonology, Sechenov First Moscow State Medical	Cross-Sectional	–	62(34–83)	Inpatients	6 (11)
Beurnier et al. (20)	2020	Bicêtre Hospital, France	Cohort	–	63(49–70)	Inpatients	5 (9)
Bhatraju et al. (21)	20-03	9 Seattle-area hospital	Cross-Sectional	15/9	64(23–97)	Inpatients	9 (11)
Borobia et al. (22)	20-03	La Paz University Hospital	Case-Control	1074/1152	61(46–78)	Inpatients	7 (9)
Cummings et al. (23)	20-05	2 New York-presbyterian hospitals	Cohort	171/86	–	Inpatients	8 (9)
Docherty et al. (24)	20-03	hospitals in England, Scotland, and Wales	Cohort	12068/8065	73(58–82)	Inpatients	8 (9)
Duanmu et al. (25)	20-01	a medical center in Santa Clara Country	Case-Control	56/44	45(32–65)	Inpatients and outpatients	5 (9)
Garg et al. (26)	20-04	14 states in the USA	Cross-Sectional	–	>18	Inpatients	8 (11)
Gold et al. (27)	20-05	the Georgia Department of Public Health, and eight Georgia hospitals	Case-Control	151/154	60(23–95)	Inpatients	7 (9)
Goyal et al (28)	20-04	2 hospitals in New York City	Case-Control	238/155	62.2(48.6–73.7)	Inpatients	5 (9)
Li et al. (13)	20-04	Tongji Hospital	Cohort	279/269	60(48–69)	Inpatients	7 (9)
Lieberman-Cribbin et al. (29)	2020	Mount Sinai Health System	Case-Control	–	–	Inpatients and Outpatients	5 (9)
Mahdavinia et al. (30)	20-04	Rush University Medical Center	Cross-Sectional	407/528	>18	Inpatients and Outpatients	9 (11)
Richardson et al. (31)	20-04	hospitals in Northwell Health	Cohort	3437/2263	63(52–75)	Inpatients	7 (9)
Song et al. (32)	2020	Tongji Hospital	Case-Control	500/461	62(51–72)	Inpatients	5 (9)
Zhang et al. (33)	2020	Department of Allergology, Zhongnan Hospital of Wuhan University	Case-Control	155/135	57(22–88)	Inpatients	5 (9)

demonstrated a pooled prevalence of asthma in COVID-19 patients and suggested that asthma patients are not predisposed to severe COVID-19 infections.

In compliance with our findings, CoVs, which are relatively harmful respiratory pathogen, have not been correlated with asthma which is a chronic inflammatory disorder of the airways where many cells (34) and cellular elements play a role and feature variable airway obstruction and bronchial hyperresponsiveness. (35) Our pooled estimate of the prevalence of asthma in COVID-19 was 0.08 (95% CI, 0.06–0.11), which was almost similar to asthma in respiratory CoV from a previous study that reported a mean prevalence of 0.084 (95% CI, 0.051, 0.136). (36) In terms of clinical manifestations, clinical symptoms of

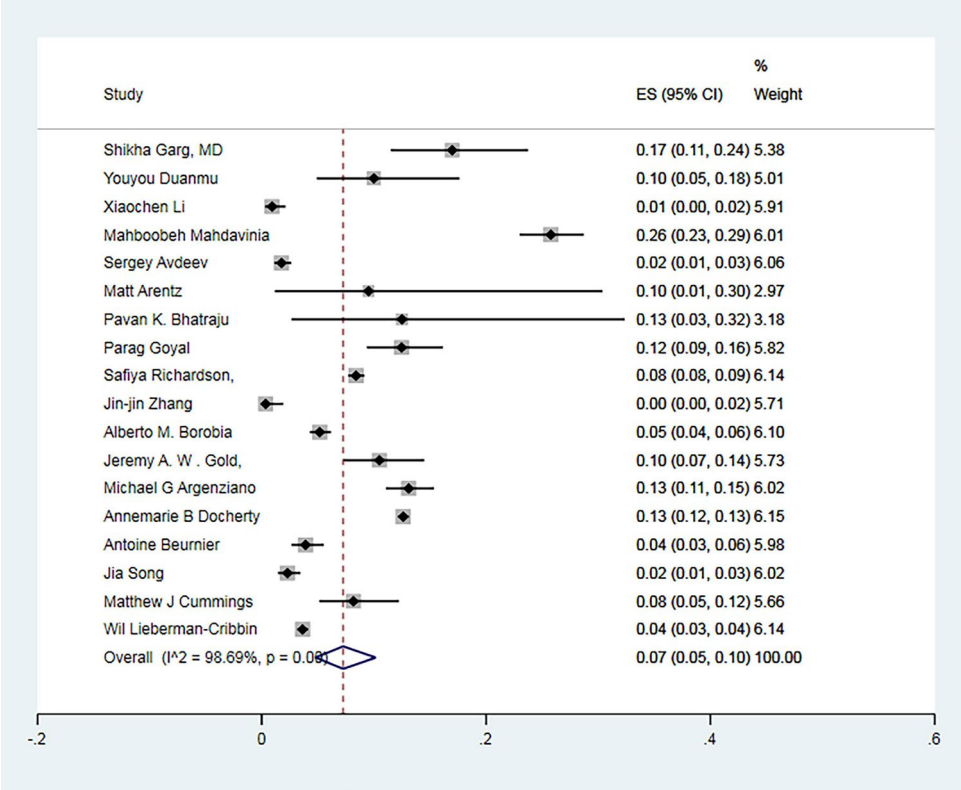

Figure 2. The forest plot of meta-analysis of asthma in COVID-19 cases.

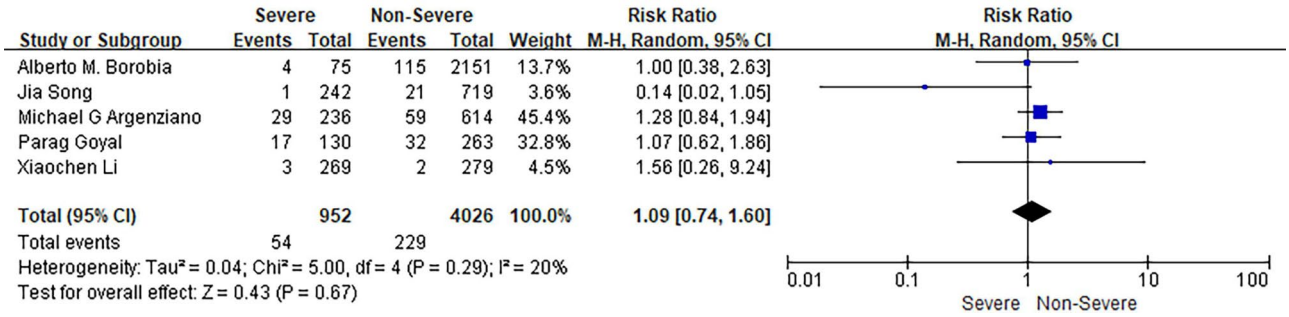

Figure 3. The forest plot of meta-analysis of asthma in severe and non-severe COVID-19 cases.

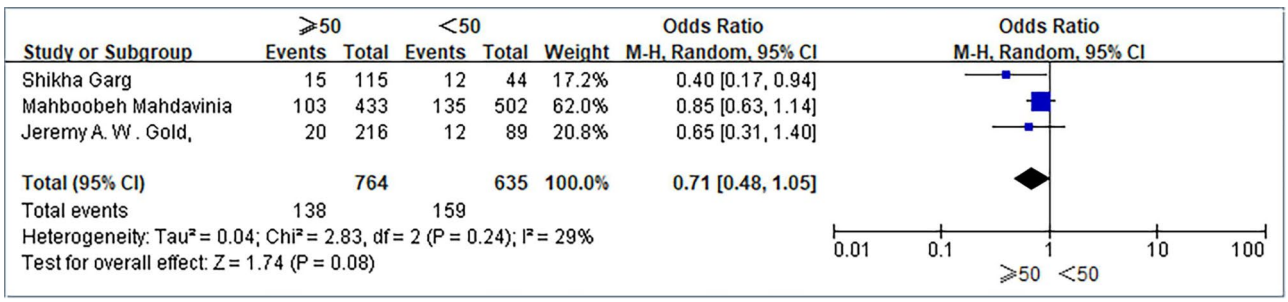

Figure 4. The forest plot of meta-analysis of asthma with COVID-19 cases in different age group.

COVID-19 (such as, fever, cough, shortness of breath et al.) on admission are also common in severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) patients. What's more, SARS-CoV and MERS-CoV, belonging to respiratory CoV, did not appear to increase the risk of asthma exacerbations.(36,37) To further investigate whether asthma is a risk factor for severe COVID-19, we performed subgroup analyses to establish the difference in the prevalence of asthma between patients with severe and non-severe COVID-19. The data showed no significant difference existed.

Whereas there is lack of concrete explanation, clinical manifestations of coronaviruses could be associated with the distribution of the angiotensin converting enzyme 2 (ACE2) in the respiratory airway epithelium. SARS-CoV-2 binds to the ACE2, a transmembrane endopeptidase that cleaves both angiotensin 1 and 2. ACE2 acted as a receptor for SARS-CoV. The downregulation of ACE2 during SARS-CoV infection is believed to contribute to the pathological changes in lungs.(38) Furthermore, transmembrane peptidase serine 2 (TMPRSS2) and protease furin have been shown to be cofactors facilitating SARS-CoV-2 infectivity. (39) It has been reported (40) that there were no differences in the expression levels of ACE2, TMPRSS2, or furin gene expression between healthy volunteers and people with mild to moderate and severe asthma. On the other hand, Jackson, D J et al.(41) documented that respiratory allergy and controlled allergen exposures are associated with significant downregulation of ACE2, and the expression of ACE2 was lowest in those with both high levels of allergic sensitization and asthma. Meanwhile, IL-13, a type 2 cytokine, which is strongly related to allergic asthma, significantly reduced ACE2 expression.(41) Chang YJ et al.(42) proved the importance of the IL-13 in influenza-induced acute asthma exacerbations. In another study, Jia Song et al.(32) showed that the number of ACE2 positive cells in bronchial and alveolar epithelial cells were increased in Chronic Obstructive Pulmonary Disease (COPD) patients, but reduced in asthmatic patients. In contrast to asthma, COPD increases the risks for severe COVID-19 among hospitalized patients.(43) Besides, after normalizing for age, expression of the ACE2 has no significant differences in disease severity. (41) Thus, age did not affect the incidence of asthma in COVID-19 patients.

In addition, inflammatory cytokine storm has recently been shown to contribute to the severe clinical manifestations and worse COVID-19 outcomes.(13) Lymphocytopenia has been observed for COVID-19 patients with severe disease, while neutrophil-lymphocyte ratio was proved to be an independent risk factor for increased mortality in COVID-19 patients with COPD.(44) Compared to asthmatics, COVID-19 patients with COPD, especially those in severe condition, had higher levels of neutrophil percentage, C-reactive protein (CRP), and various inflammatory cytokines. However, asthmatic patients are mainly eosinophilia. In a mouse model study, the increased eosinophil levels in asthmatic airways may be one of the protective mechanisms from virus infection.(45) Coupled with the above observations, our data demonstrated that asthma is not a significant risk factor for the development of severe COVID-19.

Conclusion

Taken together, asthma is not a significant risk factor for the development of severe COVID-19. Nevertheless, due to the novelty of COVID-19, We have to acknowledge our findings may be limited by insufficient study sample sizes. We suggest that future studies focused on respiratory allergy, asthma and, perhaps, other allergic disorders should provide insights into the impact of underlying allergies on COVID-19 susceptibility and disease severity.

Author's contributions

YS, YM and YL conceived the study. YS, YM, TW, PY and YL created the study protocol. TW, PY, JW, ZL, JQ and LC reviewed the studies and extracted data. TW and PY drafted the first manuscript. All authors reviewed and approved the final manuscript. YS and YM are the guarantors for the overall contents of this manuscript.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The intent of this policy is not to prevent authors with these relationships from publishing work, but rather to adopt transparency such that readers can make objective judgments on conclusions drawn.

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