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Risk and Outcomes of COVID-19 Patients with Asthma: A Meta-Analysis

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ABSTRACT

Objective: The outbreak of SARS-CoV-2 disease (COVID-19) emerged in 2019, and ultimately spread worldwide, being defined as a pandemic by the World Health Organization on March 11, 2020. The respiratory disease related to COVID-19 can range from being asymptomatic to presenting as devastating ARDS and death. The elderly and individuals with comorbidities and immunocompromised states are at a higher risk. Asthma is an inflammatory spasm of the airways with ACE2 overexpression at the alveolar level. ACE2 and TMPRSS2 expression mediate SARS-CoV-2 infection of host lung cells and hence might increase disease susceptibility in asthmatics.

Materials and Methods: A literature review was done by searching the databases of Pubmed, WHO, clinicaltrials.gov, and Google Scholar, using the keywords of -COVID-19, SARS-CoV-2, coronavirus, asthma, and their combinations, following the timeline of December 2019 to August 10, 2020. We included patients with asthma diagnosed with COVID-19 while excluding non-COVID-19 patients, pregnant patients, and patients with other diseases or comorbidities. Primary outcomes included mortality and ICU admissions of both groups. Based on the available data, we conducted a meta-analysis via RevMan 5.4 using a random-effects model and 95% confidence intervals.

Results: Patients with and without asthma were compared for risk outcomes of mortality. For the 755 COVID-19 patients with asthma and 4969 non-asthmatic COVID-19 patients, we found that the risk of mortality would increase by 9% in the asthmatic group (RR=1.09, CI= 0.58 to 2.03, I2=72%). There was an increased proportion of ICU admissions among the asthmatic group (RR=1.39, CI = 0.80 to 2.42). There was high heterogeneity among the studies (I^2 = 79%). Medications such as corticosteroids improve the mortality and ICU admission rates.

Conclusion: Our results indicate that the number of COVID-19 cases in patients with asthma has been lower than those of the non-asthmatic group. COVID-19 patients with asthma were at increased risk of mortality and ICU admission due to underlying factors or predisposition. Finally, corticosteroids are considered safe and may confer protection against the severity of COVID-19 infection.

Keywords: Covid-19, asthma, corticosteroids, mortality, intensive care.

INTRODUCTION

The novel coronavirus was declared a public health emergency of international concern by the World Health Organization (WHO) on 30 January 2020, and a pandemic on 11 March 2020 (1). As of October 19, 2020, there have been 39.8 million confirmed cases of COVID-19, with 27.4 million recoveries and 1.11 million deaths, reported to the WHO. There are currently no preventative treatments

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or vaccines for COVID-19. Individuals with moderate to severe asthma may have higher risks of contracting the virus, affecting the throat, nose, and lungs, causing an asthmatic attack, and leading to acute respiratory disease and pneumonia (2). SARS-CoV-2 is RNA virus and is believed to mainly affect the respiratory tract. The respiratory disease related to COVID-19 can range from being asymptomatic to presenting as devastating ARDS and ultimately death. Complications related to the cardiovascular, neurological, and dermatological systems other than the respiratory tract have been noted (3). Various clinical trials of remdesivir, convalescent plasma, corticosteroids, and tocilizumab are currently being conducted in the search of treatment.

Asthma is an inflammatory spasm of the airways with ACE2 overexpression at the alveolar level leading to dyspnea, paroxysmal wheezing, and coughing due to airway constriction (4). ACE2 and TMPRSS2 expression mediate SARS-CoV-2 infection of host lung cells and hence might increase disease susceptibility in asthmatics (5). While the research focuses on finding a treatment option and developing a vaccine for the disease, we have yet to understand the natural history of COVID-19 in its entirety. Various gaps lie in the outcomes of COVID-19, particularly in relation to pre-existing chronic conditions like asthma, COPD, diabetes mellitus, and hypertension. About 235 million people suffer from asthma worldwide (6). Various triggers of asthma have been identified, including pollen, dust, sawdust and pet fur. Other viruses have also been shown to have a role in asthma, such as the respiratory syncytial virus (RSV) (7). A study found that the two most common triggers to asthma symptoms were non-adherence to treatment and upper respiratory tract infection (8). While the Centers for Disease Control and Prevention (CDC) states that patients who have moderate-severe asthma may be at a greater risk of severe coronavirus disease, there is limited published data to support this statement at the time (9). Our study aims to determine ICU admission status and mortality afflictions of COVID-19 patients with asthma.

METHODS

Search Method and Strategy

Six early to mid-level researchers conducted data extraction of studies published from December 2019 through 10th August 2020 by searching the following databases including grey literature sources: PubMed, Science Direct, WHO-COVID-19 database, Clinicaltrials.gov, and Google Scholar. Any disagreements were resolved through active discussion. Boolean logic was employed using the following keywords: COVID-19 and/or SARS-CoV-2 and/or Coronavirus and/or Asthma. There were no language restrictions. We included asthmatic patients of all age groups diagnosed with COVID-19, and observational studies were located. We excluded non-COVID-19 and pregnant patients. The reference lists of included studies were assessed (umbrella method) for retrieved articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used for the review (Figure 1). We tabulated the data using a shared spreadsheet. Duplicates were removed using the software Endnote X9. Our review included studies from countries across LMICs and HICs. The search was rerun on October 1, 2020 before the final analysis.

URL to the Search Strategy

#1 COVID-19 and/or SARS-CoV-2 and/or Coronavirus and/or Asthma
#2 COVID-19 and Asthma
#1 and #2

Data Screening and Eligibility

The final review articles fulfilled the following criteria:

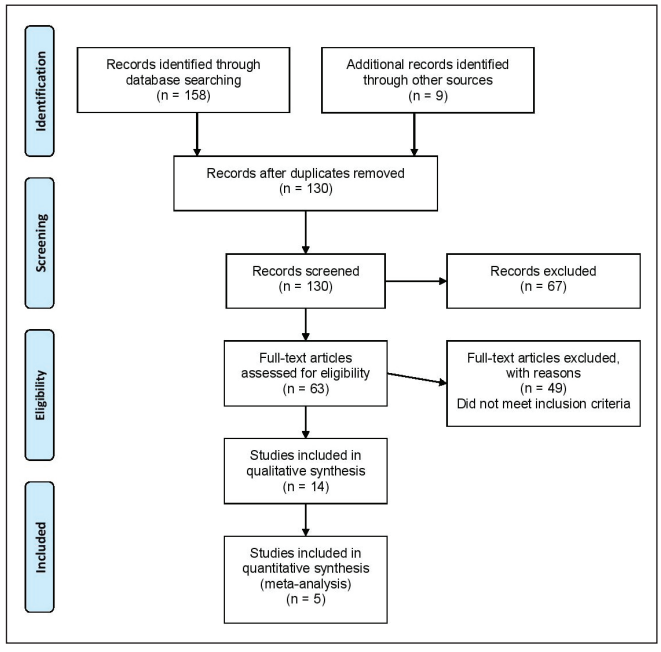

Figure 1. PRISMA flowchart.

1. Reported COVID-19 in patients of asthma.
2. Full text, peer-reviewed articles (case series, cohorts and observational studies)
3. Articles in English.

Articles that did not have patient data, studies limited to pregnant patients, and those limited to specific co-morbidities and organ dysfunctions were excluded to avoid selection bias. In doing so, we had 23 articles for the final review (Table I and Figure 1). Selected articles were independently reviewed by two authors. All disagreements were resolved with a discussion between the two authors, or with input from a third independent reviewer and mutually agreed upon by the authors.

Data Analysis

Statistical analyses were conducted using Review Manager 5.4. Quantitative analysis for dichotomous values was employed by using common measures of effect including Relative Risks (RRs). Confidence intervals (95%) and P-values were also enlisted. To assess the heterogeneity between the studies, the I^2 index was used. Data is visually presented using forest plots. Since less than 10 studies were present for one variable, we did not use funnel plots to assess for publication bias.

Risk of Bias Assessment

The risk of bias assessments was performed at the outcome measurement level during data collection. Assessment of all included Cohort studies was done using the Newcastle Ottawa scale. A tool published by the Duke University and McMaster Evidence-based Practice Workshops and Guide to the Medical Literature was used for systematic reviews and Meta-analysis.

Ethical Approval and Funding

This study did not require ethical approval as data was obtained from already available databases, and patients were not directly involved. No funding was obtained for this review.

RESULTS

Title and abstract search led to the retrieval of 167 studies. Post-duplicate removal, a total of 130 studies were screened, with 63 full-text articles assessed for eligibility. Overall, 14 studies were included in the qualitative analysis and 5 studies were added to the quantitative analysis. The characteristics of the included studies are listed in Table I. We did not assess for publication biases, because less than 10 studies were present in the meta-analyses.

ICU Admission Status for Asthmatic and Non-Asthmatic Groups

Patients with and without asthma were compared for risk outcomes of mortality. For the 463 COVID-19 patients with asthma and 3207 non-asthmatic COVID-19 patients, we found that the ICU admission would increase by 39% in the asthmatic group (RR=1.39, CI = 0.80 to 2.42) (Figure 2). There was high heterogeneity among the studies (I^2 = 79%).

Mortality Among Asthmatic and Non-Asthmatic Groups

Mortality data was reported by 5 studies. A meta-analysis from 755 asthmatic patients and 4969 patients was conducted. We found an increased effect size of mortality among the asthmatic group (RR=1.09, CI= 0.58 to 2.03, I2=72%) (Figure 3). While our results are limited due to the lack of conclusive studies assessing mortality

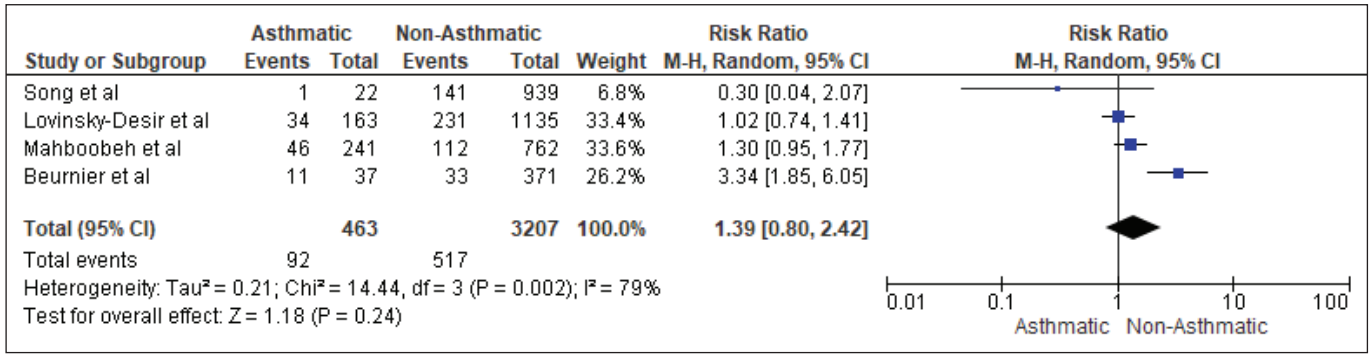

Figure 2. Forrest Plot of the ICU admission in the asthmatic group versus the non-asthmatic group.

Table I. Characteristics of the studies included in the qualitative analysis.

No	First author	Title of Study	DOI	Study Design	Patient Population	Age	Treatment	Comment	NOS Scale
1	Lee (20)	Epidemiological and Clinical Characteristics of Coronavirus Disease 2019 in Daegu, South Korea	10.1016/j.ijid.2020.07.017	Cohort	Adults and Children	Range: 19 months to 98 years, with the age group of ≥ 60 years being the most affected	Standard-of-Care Treatment.	The mortality was low in Daegu, which may be due to the mass screening efforts to treat and hospitalize severe cases, along with quarantine measures for asymptomatic patients.	Good Quality
2	Chhiba (18)	Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19	10.1016/j.jaci.2020.06.010	Cohort	Adults	The 40-69 years age group made up 55.3% of the sample size, followed by the >70 years group with 17.6% and the <40 years group with 27.1%.	Inhaled corticosteroids, combination ICS plus long-acting β-agonists (ICS/LABA), and/or systemic corticosteroids.	A potential protective role was found for ICS in COVID 19.	Fair quality
3	Wang (21)	Risk factors for hospitalization, intensive care and mortality among patients with asthma and COVID-19	10.1016/j.jaci.2020.07.018	Case Series	Adults	Median age was 54 years (interquartile range, 37-66 years).	Inhaled corticosteroids, LABA, SABA, controllers, anticholinergics, and leukotriene modifiers were administered.	Mortality was similar for asthma and non-asthma COVID-19 patients in the MGB outpatient 134 and inpatient setting.	Good quality
4	Mahdavinia (11)	Asthma prolongs intubation in COVID-19	10.1016/j.jaip.2020.05.006	Cohort	Adult and Children	Mean/SD: Asthmatic group 33.59/9.24; Non-asthmatic 31.63/7.5.	All intubated COVID-19 patients were on nebulized albuterol and most were treated with systemic steroids.	Asthma was significantly associated with female sex and higher BMI. Asthma was significantly associated with longer intubation time. Asthma was not associated with a higher rate of death. Peripheral eosinophilia was associated with asthma.	Good quality
5	Grandbastien (22)	SARS-CoV-2 Pneumonia in Hospitalized Asthmatic Patients Did Not Induce Severe Exacerbation	10.1016/j.jaip.2020.06.032	Cohort	Adults	The mean age of the participants was 59 years.	Patients were administered systemic corticosteroids and inhaled β2 agonists	Patients with asthma appeared not to be at risk for severe SARS-CoV-2 pneumonia. Moreover, SARS-CoV-2 pneumonia did not induce severe asthma exacerbation.	Fair Quality
6	Nepogodiev (23)	Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study	10.1016/S0140-6736(20)31182-X	Cohort	Adults	Of the total, 214 patients (19%) were younger than 50 years, 353 patients (31.3%) were in the 50–69 years age group, and 558 patients (49.5%) were aged 70 years or older. Age was missing for three patients.	Standard-of-Care Treatment	Postoperative pulmonary complications occurred in half of the patients with perioperative SARS-CoV-2 infection and were associated with high mortality. Pulmonary complications occurred in 52% of the asthmatics, whereas the 30-day mortality in asthmatics was 26.9%.	Good quality
7	Nepogodiev (23)	Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study	10.1016/S0140-6736(20)31182-X	Cohort	Adults	214 (19%) were younger than 50 years, 353 (31.3%) were aged 50–69 years, and 558 (49.5%) were aged 70 years or older.	Standard-of-Care Treatment	Postoperative pulmonary complications occurred in 50% of the patients with perioperative SARS-CoV-2 infection and were associated with high mortality outcomes.	Good quality
8	Baqui (24)	Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study	10.1016/S2214-109X(20)30285-0	Observational, cross sectional	Adults	The mean age was 49.5 years for survivors and 66.2 years for non-survivors.	Standard-of-Care Treatment	The regional effect is driven by an increasing comorbidity burden in regions with lower levels of socioeconomic development. The ethnicity effect may be related to differences in susceptibility to COVID-19 and access to health care (including intensive care) across ethnicities.	Good quality

Table I. Cont.

9	Mao (25)	Assessing risk factors for SARS-CoV-2 infection in patients presenting with symptoms in Shanghai, China: a multicentre, observational cohort study	10.1016/S2589-7500(20)30109-6	Cohort	Adults	The median, IQR of the participants was 46, 20-69.	Standard-of-Care Treatment	Exposure history, white blood cell count less than 4 × 109 per L, lymphocyte count less than 0.8 × 109 per L, ground glass opacity, and having both lungs affected were independent risk factors for confirmed COVID-19 infection.	Good quality
10	Ruano (26)	Impact of the COVID-19 pandemic in children with allergic asthma	10.1016%2Fj.jaip.2020.07.019	Cohort	Children	The median, IQR of the participants was 10, 7-11.	The symptomatic treatment included paracetamol (86%), β2-agonist rescue inhaler (34%), or increased long-term asthma-control medications (14%).	Children with asthma did not develop severe COVID-19 infection. The symptoms were mild, with the most frequent being fever; the cases required significantly more rescue and asthma-control treatment as compared to pediatric patients without COVID-19.	Fair quality
11	Avdeev (27)	Low prevalence of bronchial asthma and chronic obstructive lung disease among intensive care unit patients with COVID-19	10.1111/all.14420	Cohort	Adults	The median, IQR of asthmatic patients was 62, 34-83.	Standard-of-Care Treatment	Patients with bronchial asthma were not at an increased risk of SARS-CoV-2 induced ARDS.	Fair quality
12	Song (28)	Distinct effects of asthma and COPD comorbidity on disease expression and outcome in patients with COVID-19	10.1111/all.14517	Cohort	Adults	The median, IQR of the participants was 63, 49-70.	Treatments administered were oxygen therapy, mechanical ventilation, antibiotics, antifungals, antivirals (kaletra, arbidol hydrochloride, ribavirin, chloroquine), interferon atomization, glucocorticoid therapy, and intravenous immunoglobulin therapy	COVID-19 patients with COPD had a higher risk of developing ARDS than patients with asthma (OR, 19.762; 95% CI 1.461-267.369; P = 0.025) and a 5.8% higher risk of developing acute kidney injury. Frequency of receiving mechanical ventilation in COVID-19 patients with COPD vs. asthma was 47.6% vs. 4.6% (OR 12.2, 95% CI 1.03-144.6, P = 0.048).	Good quality
13	Beurnier (16)	Characteristics and outcomes of asthmatic patients with COVID-19 pneumonia who require hospitalisation	10.1183/13993003.01875-2020	Cohort	Adults	The median and IQR of the participants was 54, 42–67.	Treatments included antibiotics, Azithromycin IV or oral corticosteroids for asthma exacerbation during hospitalisation, in addition to SABA prescription pressurised metered-dose inhalers and spacer chamber dry powder inhaler. Two patients were treated with anti-immunoglobulin E monoclonal antibody (omalizumab) for severe allergic asthma.	Worst outcomes were observed mainly in patients with major comorbidities, of which 84% had a BMI ≥25 kg/m2; the most common comorbidities were obesity (36%), hypertension (27%), and diabetes (19%).	Good quality
14	Lovinsky-Desir (17)	Asthma Among Hospitalized Patients with COVID-19 and Related Outcomes	10.1016%2Fj.jaci.2020.07.026	Cohort	Adults and Children	The median (IQR) for all participants with asthma was 51 (27).	Medications administered were azithromycin, systemic corticosteroids, hydroxychloroquine, tocilizumab, and remdesivir.	Although more patients with asthma may be hospitalized for COVID-19 compared to the prevalence of asthma in their region, a history of asthma is not associated with worse COVID-19 outcomes among hospitalized patients with severe disease.	Good quality

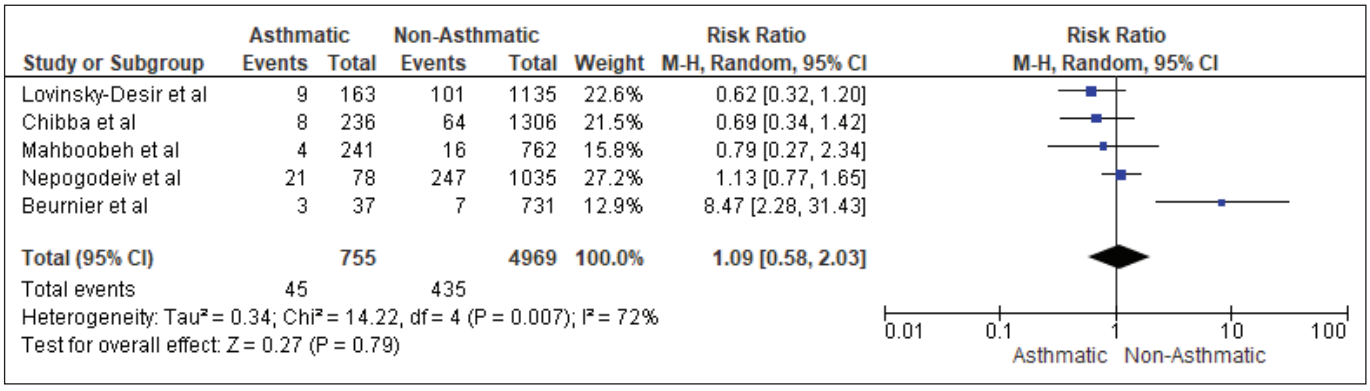

Figure 3. Forrest Plot of mortality rates in the asthmatic group versus the non-asthmatic group.

outcomes in asthmatic patients, we found that there was a 9% higher risk of death in the group. Medications such as corticosteroids may reduce mortality and ICU admission rates.

Quality Assessment

The assessment of the included studies in the qualitative and quantitative analyses was conducted using the Newcastle Ottawa scale (10). In doing so, 10 (71.4%) studies were found to be of good quality, and 4 (28.6%) studies were found to be of fair quality.

DISCUSSION

While any respiratory virus may cause an asthmatic attack, the outcomes of COVID-19 infection in asthmatic patients are unclear due to underreported data. Current literature suggests that asthma may not be a strong risk factor for acquiring coronavirus disease 2019, but poorly controlled asthma may lead to a complicated disease course for patients with COVID-19 (11,12). Expert groups ideate that every effort ought to be made to avoid exposure to the SARS-CoV-2 virus using personal protective equipment, and regular medications including oral glucocorticoids, inhaled glucocorticoids, and biological agents such as mepolizumab and omalizumab that are necessary to control asthmatic symptoms should be continued (13,14). CDC identify that persons with asthma, particularly those aged 65 or above, are an at-risk group for severe COVID-19 illness necessitating good asthma control to minimize the risk of exacerbation. Asthmatic patients taking long-term oral glucocorticoids must continue the medication to avoid life-threatening complications. For patients with COVID-19 infection across all age groups, inhaled asthma medications must be given via inhalers as opposed to nebulizers whenever possible to avoid aerosolizing the virus and enhancing the spread of the disease. The current and long-term effects of COVID-19 in asthmatic patients are likely to be have high priority in future research (15).

Our study finds that the risk of mortality was increased by 9% in asthmatic patients with COVID-19 as compared to non-asthmatic patients with COVID-19. In their study, Buenier et al. found that negative outcomes were linked to patients with underlying comorbidities, namely obesity (36%), hypertension (27%), and diabetes (19%) (16). Additionally, Lovinsky-Desir et al. reported limited deaths among asthmatic patients younger than 40 years, further suggesting that patients aged 65 are at risk of more severe disease (17). Chhiba et al. reported that COVID-19 related inflammatory markers such as C-reactive protein (CRP), Lactate dehydrogenase (LDH) and Ferritin were lower in patients with asthma as compared to patients without asthma (18). The study suggested that the decreased inflammatory burden seen in asthmatic patients with COVID-19 may be due to the immunomodulation related to asthma or the dampening effects of asthma treatment using inhaled corticosteroids on the inflammation in COVID-19 patients (18). Our study reported a 39% higher likelihood of ICU admission among asthmatic patients with COVID-19 as compared to non-asthmatic patients. On the contrary, Antonicelli et al. did not find an increased rate of ICU admission in asthmatic patients with COVID-19. Asthmatic patients with COVID-19 may present with prolonged intubation time, warranting further assessment of risk outcomes (19).

Our review has limitations due to the limited sources of data reporting outcomes in asthmatic versus non-asthmatic patients. The number of patients with asthma is fewer

than those without asthma in our quantitative analysis. While the gold standard for meta-analyses is randomized controlled trials, the data for our review is sourced from cohort studies only. There is a confounding variable of pre-existing medications including corticosteroids which may influence the outcomes post-treatment for COVID-19 infections. While not all studies reported pre-admission prescriptions of patients, our review quantitatively analyzed mortality data and ICU admissions and performed a descriptive qualitative analysis.

In conclusion, our results indicate that the number of COVID-19 cases in patients with asthma has been lower than those of the non-asthmatic group. COVID-19 patients with asthma were at increased risk of mortality and ICU admission due to underlying factors or predisposition. Corticosteroids were considered safe and may confer protection against the severity of COVID-19 infection. A high prevalence of comorbidities is associated with severe COVID-19 infections, whereas asthma was associated with an increased risk of COVID-19 ICU admission. Healthcare communities ought to prioritize at-risk groups including the elderly, patients with comorbidities (asthma, COPD, diabetes mellitus, and hypertension), and under-represented ethnic-racial groups as they are at a greater risk of contracting disease. Large multicenter studies are required to understand the association of asthma with COVID-19 and the long term outcomes.

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