

*Review article*

## **Asthma as a Risk Factor for the Progression of COVID-19**

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### **SUMMARY**

**Background:** Asthma is one of the most common chronic respiratory diseases in the world, standing for the most frequent cause for hospitalization and emergency cases. Respiratory viruses are the most triggering cause.

**Aim:** To assess the role of viral infections, especially COVID-19, in the pathogenesis of asthma initiation and exacerbations.

**Method:** Electronic search was done for the manuscripts focusing on asthma as a risk factor for complications after COVID-19 infection. The outcomes were titles, materials, methods and classified studies related or not related to the review study. Three hundred publications were identified and only ten studies were selected for analysis. Seven studies were review, one retrospective, one longitudinal cohort study and one letter to the editor.

**Results:** The included literature sources have highlighted different effect of asthma on COVID-19 progression. Asthma can be triggered by this virus and asthmatic patients with COVID-19 should not stop their treatment. Others suggest that asthma does not appear to be a significant risk factor for developing severe COVID-19 requiring hospitalization or intubation.

**Conclusions:** Asthma is considered as comorbidity factor leading to complications and mortality in subjects infected with COVID-19.

**Keywords:** COVID-19, asthma, immunity

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## INTRODUCTION

Asthma can be defined as a chronic long-term inflammatory disease of the airways of the lungs associated with increased contractibility of the surrounding smooth muscles of the bronchi and bronchioles (1). It affects about 8 - 9% of children and adults in Europe and 7.8% in the United States (2). Patients usually complain about episodes of recurrent wheezing, chronic cough, tightness in the chest, and shortness of breath that occur many times per day or week during night or exercise (3).

The cause of asthma is a complex dysfunctional interaction between genetic factor, environmental factor and immune imbalance, with airway inflammation due to environmental exposures to non-harmful allergen like flour dust, house dust, mite, foods, tobacco, rubber-derived proteins, animal dander and insect bites, and fish or seafood derived allergens (4, 5). Dysregulated immune response has an important role in the development of asthma that leads to elevated serum immunoglobulin E (IgE) levels, excess release of primary allergic mediators from mast cells, such as histamin, infiltration of eosinophils into the lungs, and inflammation of the airways, with a shift from T helper 1 (Th1) to Th2 responses, which leads to type I hypersensitivity reaction (6). Prostaglandin D2 (PGD2) regulates the T-helper2 (TH2) and type-2 innate lymphoid cells (ILC2), and may act as diagnostic marker and therapeutic target for asthma (7). Measuring the value of serum PGD2 in asthmatics is crucial to predict disease susceptibility, severity and disease control. Additional potential trigger factors comprise drugs like aspirin and beta blockers, respiratory viral infections like rhinovirus (RV), the common cold virus which is the most common trigger factor of exacerbations, and *Chlamydia pneumoniae* (8, 9). Reduction of chronic inflammation in the airways of the lungs is an important part of treatment and long-term control of asthma. This should be achieved by corticosteroids as inhaler and short acting beta-2 adrenoceptor agonist such as Salbutamol (10). Another important thing is the coexistence of asthma with other viruses like HIV (11, 12). There are other risk factors associated with this new, pandemic disease, like diabetes mellitus and obesity (13).

The aim of this study was to review the role of viral infections, especially COVID-19, in the pathogenesis of asthma initiation and exacerbations, but

also to discuss interrelated protective and risk factors of asthma as well as treatment options.

## METHODS

### Search plan

Electronic databases using "Pubmed", "Iraq Virtual Science Library", "Index medicus for the eastern Mediterranean region" and "MedLine", were searched and a combination of the following search words was used: "coronavirus" or "COVID-19 virus" or "SARS-CoV2 virus" or "2019-nCov virus", and "asthma" or "shortness of breath" or "wheezy chest" or "type I hypersensitivity" or "cough" or "chest pain" or "dyspnoea" or "difficulty breathing". No limitation was applied during the search. A reference list of relevant studies was searched as well. Some authors and researchers were also communicated through email for their papers and articles.

### Inclusion and exclusion criteria

The articles were screened about this subject and labeled as related studies. Articles were considered appropriate if the study aimed to emphasize and discuss the different aspects including asthma, dyspnoea, and shortness of breath, cough and wheezy chest that were associated with COVID-19. Only studies written in English and published between 1 December 2019 and 30 December 2020 were included in this study. Excluded studies were conference or meeting proceeding, dissertation, workshops, case study, case series, studies with abstract only and studies discussing medical treatment of coronavirus, diagnosis, respiratory failure and recovery of COVID-19 patients.

### Data extraction

Data extracted from studies included in the review were as follows: title, type of the study, study information, findings and conclusions.

### Study selection

A total of 10 articles met the selected criteria and were included in the review. A flowchart given in Figure 1 showed the source of these studies and their selection process (14).

## RESULTS

This study literature sources discuss the role

and effect of asthma as a risk factor for the clinical course of COVID-19 infection and demonstrate how COVID-19 exacerbates and triggers asthma. There

**Table 1.** Characteristics of studies included in this review

| No | Authors, Year                                                                                                                                                                                                                                                                                                                                                                                                             | Title of the article                                                                                       | Study type of the article | Conclusions and findings of the article                                                                                                                                                                                                                                                                                                                              |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. | Johnston SL.2020 (15)                                                                                                                                                                                                                                                                                                                                                                                                     | Asthma and COVID-19: Is Asthma a Risk Factor for Severe Outcomes?                                          | Review                    | COVID-19 has spread very rapidly in China, invading other countries in Europe and America. This necessitates the identification of risk factors for the outcome of COVID-19 like asthma.                                                                                                                                                                             |
| 2. | Chiba KD, Patel GB, Vu THT, Chen MM, Guo A, Kudlaty E, Mai Q, Yeh C, Muhammad LN, Harris KE, Bochner BS, Grammer LC, Greenberger PA, Kalhan R, Kuang FL, Saltoun CA, Schleimer RP, Stevens WW, Peters AT. 2020 (16)                                                                                                                                                                                                       | Prevalence and Characterization of Asthma in Hospitalized and Non- hospitalized Patients with COVID-19     | Retrospective             | Asthma was not related to an increased risk of hospitalization whether the patients used systemic corticosteroid or inhaler corticosteroids                                                                                                                                                                                                                          |
| 3. | Morais-Almeida M, Aguiar R, Martin B, Ansotegui IJ, Ebisawa M, Arruda LK, Caminati M, Canonica GW, Carr T, Chupp G, Corren J, Dávila I, Park HS, Hanania NA, Rosenwasser L, Sánchez-Borges M, Virchow JC, Yáñez A, Bernstein JA, Caraballo L, Chang YS, Chikhladze M, Fiocchi A, González-Díaz SN, Tanno LK, Levin M, Ortega-Martell JA, Passalacqua G, Peden DB, Rouadi PW, Sublett JL, Wong GWK, Bleecker ER. 2020 (17) | COVID-19, Asthma, and Biological Therapies: What We Need to Know                                           | Review                    | Asthmatic patient with COVID-19 should not stop their biologic treatment. Their immune response did not change after treatment. Stopping this therapy leads to asthma exacerbation and emergency hospitalization.                                                                                                                                                    |
| 4. | Morais-Almeida M, Pité H, Aguiar R, Ansotegui I, Bousquet J. Morais-Almeida M, Pité H, Aguiar R, Ansotegui I, Bousquet J. 2020 (18)                                                                                                                                                                                                                                                                                       | Asthma and the Coron avirus Disease 2019 Pandemic: A Literature Review                                     | Review                    | Asthma is usually triggered by viruses and it is uncertain whether patients with asthma are at a higher risk of developing COVID-19 and becoming severely ill, which requires hospitalization. Reports from the USA and the UK found that asthma is much more common in adults with mild to severe COVID-19 than has previously been reported in Asia and in Europe. |
| 5. | Abrams EM, Jong GWG and Yang CL. CMAJ 2020 (19)                                                                                                                                                                                                                                                                                                                                                                           | Practice Five Things to Know about Asthma and COVID-19                                                     | Review                    | There is an increase in the number of asthmatic patients who were admitted to hospital because COVID-19 triggers asthma exacerbations, as other viruses do. Therefore, asthma is listed as a risk factor for COVID-19 morbidity and mortality                                                                                                                        |
| 6. | Wang JY, Pawankar R, Tsai HJ, Wu LS, Kuo WS.2020 (20)                                                                                                                                                                                                                                                                                                                                                                     | COVID-19 and Asthma, the Good or the Bad?                                                                  | Review                    | COVID-19 had a distressing effect on the host immunity via the inhibition of interferon secretion, leading to aberrant innate immune response, macrophage stimulation and inflammation that leads to cytokine storm and exhaustion of the cellular immunity of T lymphocytes                                                                                         |
| 7. | Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, Woodruff PG, Mauger DT, Erzurum SC, Johansson MW, Denlinger LC, Jarjour NN, Castro M, Hastie AT, Moore W, Ortega VE, Bleecker ER, Wenzel SE, Israel E, Levy BD, Seibold MA, Fahy JV.2020. (21)                                                                                                                                                     | COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids | longitudinal cohort study | Higher gene expression of ACE2 (angiotensin converting enzyme 2) and TMPRSS2 (transmembrane protease serine 2) mediates viral infection of host cells in the sputum of patients with asthma, which leads to poor COVID-19 outcomes.                                                                                                                                  |

|     |                                                                                                                               |                                                                                |                      |                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8.  | Liu S, Zhi Y, Ying S. 2020. (22)                                                                                              | COVID-19 and Asthma: Reflection During the Pandemic                            | Review               | Asthmatic patients should have increased susceptibility for SARS-CoV-2 infection due to a deficient antiviral immune response and the tendency for exacerbation elicited by common respiratory viruses. Conventional therapeutics for asthma, including inhaled corticosteroids, allergen immunotherapy (AIT), and anti-IgE monoclonal antibody might also reduce the risks of infection through enhancing antiviral defense. |
| 9.  | Hartmann-Boyce J, Gunnell J, Drake J, Otunla A, Suklan J, Schofield E, Kinton J, Inada-Kim M, Hobbs FDR, Dennison. 2020. (23) | Asthma and COVID-19: Review of Evidence on Risks and Management considerations | Review               | The burdens of asthma and of COVID-19 are not equally distributed across the population.                                                                                                                                                                                                                                                                                                                                      |
| 10. | Broadhurst R, Peterson R, Wisnivesky JP, Federman A, Zimmer SM, Sharma S, Wechsler M, Holguin F. 2020. (24)                   | Asthma in COVID-19 Hospitalizations: An Overestimated Risk Factor?             | Letter to the Editor | It is suggested that asthma does not appear to be a significant risk factor for developing severe COVID-19 requiring hospitalization or intubation.                                                                                                                                                                                                                                                                           |

were seven reviews (15, 17 - 20), one retrospective study (16), one longitudinal cohort study (21 - 23) and one letter to the editor (24).

The included literary sources have highlighted different effects of asthma on COVID-19 progression. Asthma may be triggered by this virus and asthmatic patient with COVID-19 should not stop their therapy as immunity boosters against infection. Others suggest that asthma does not appear to be a significant risk factor for developing severe COVID-19 requiring hospitalization or intubation. The characteristics of the included studies along with chief findings are explained in Table 1.

## DISCUSSION

It has been confirmed that viral infection like COVID-19 triggers and exacerbates acute asthma attacks and episodes. The possible mechanisms include virus-induced cellular factors regulating the host immune response, inflammation of respiratory airways, repair and remodeling of the bronchi, and increase in proinflammatory cytokines and chemokines production (25, 26). Other possible explanation may be due to an increase in epithelial production of IL-25 and IL-33 that promote Th2 type of inflammation (27 - 29). On the other hand, viral infection can be an early marker for impairment in viral immune response through diminished interferon production and abnormal host immune response by induced expression of IgE receptors (30). Patients with asthma and or chronic obstructive pulmonary

diseases are more liable to be infected with severe form of COVID-19 virus infection; therefore, particular care must be taken to protect those patients throughout this epidemic (31). Those patients had lower counts of lymphocytes Th (CD4+), Tc (CD8+) cells, and B cells and higher levels of cytokines receptors (TNF- $\alpha$ , IL-2 receptor), cytokines IL-10, IL-8, IL-6 and decreased ACE2 protein expression in the lower respiratory airways. This is due to IL-4 and IL-13 downregulated ACE2 expression, while TNF- $\alpha$ , IL-12, and IL-17A upregulate ACE2 expression (32).

On the contrary, other descriptive studies have shown no significant difference in the period of hospitalization and the risk of intensive respiratory care unit (RCU) admission between asthmatic and non-asthmatic patients. These studies suggest that asthma as other comorbidity factors like diabetes mellitus, hypertension, obesity and cardiovascular diseases may not increase the mortality rate of COVID-19 or extend the duration of hospitalization and requirement for RCU admission (33). Asthma and its medications (short-acting  $\beta_2$ -agonists) were not an independent risk factor for the clinical outcomes of COVID-19 and did not affect the clinical outcomes of COVID-19 course (34). Green I. et al. (35) reported that susceptibility to COVID-19 infection was lower in patients with pre-existing asthma due to significant reduction in the expression of ACE-2 receptor which is the portal entry of the virus. Expression of ACE2 in respiratory airway epithelial cells in COVID-19 is affected by inflammatory cytokines profile. Allergic asthma may have a protective

effect against SARS-COV-2 infection. However, the association between asthma and SARS-COV-2 is not fully established (36).

These differences among studies may be due to design of the study, type of the patients, sample size, type of asthma, racial differences of the patients, and presence of other obstructive pulmonary disease.

Thus, further studies with a larger sample size, more specific characteristics of patients selection, and from other countries are required to establish strong evidence.

## CONCLUSION

Asthma is considered as a comorbidity factor that leads to severe complications and high mortality in subjects infected with COVID-19.

## Acknowledgements

Not applicable. This study was reviewed and approved by the Ethics and Scientific Committee of Al-Kindy college of Medicine (N0. 1855 – 21/4/2022)

## Conflict of interest

None

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## Astma kao faktor rizika za napredovanje kovida 19

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### SAŽETAK

**Uvod.** Astma je jedna od najčešćih hroničnih respiratornih bolesti u svetu i najčešći je uzrok hospitalizacije i urgentnih stanja. Respiratorni virusi su najčešći uzrok.

**Cilj.** Cilj rada bio je procena uloge virusnih infekcija, naročito kovida 19, u patogenezi početka i egzacerbacije astme.

**Metode.** Urađeno je elektronsko pretraživanje radova koji se opisuju astmu, kao faktor rizika, za nastanak komplikacija nakon kovida 19. Rezultati pretrage bili su naslovi, materijali, metode i klasifikovane studije, koje su se odnosile na ovu preglednu studiju ili nisu bile povezane sa njom. Identifikovano je trista publikacija, a samo deset studija odabrano je za analizu. Sedam studija bili su pregledni radovi, jedna retrospektivna studija, jedna longitudinalna kohortna studija i jedno pismo uredniku.

**Rezultati.** Uključeni izvori literature istakli su različite efekte astme na napredovanje kovida 19. Ovaj virus može biti okidač za pojavu asme. Bolesnici sa astmom i kovidom 19 ne bi trebalo da prestanu sa terapijom. Drugi autori smatraju da astma nije značajan faktor rizika za razvoj teškog oblika kovida 19, koji zahteva hospitalizaciju ili intubaciju.

**Zaključci.** Astma se smatra faktorom komorbiditeta koji dovodi do komplikacija i mortaliteta kod osoba sa kovidom 19.

*Ključne reči: kovid 19, astma, imunitet*