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Comparative Study of Various Case Studies to investigate the Impact of Covid-19 on Asthmatic Persons at the Different Geographical Location

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ABSTRACT

Asthma is an inflammatory, highly ubiquitous, chronic, and uncontagious respiratory disease of lung pathways. SARS-CoV-2 is primarily a novel severe acute respiratory coronavirus that causes COVID-19. Asthma patients are apprehensive that they are at higher threat of acquiring COVID-19 compare to other populations. The comparative case study from different datasets across the world reveals that asthma as comorbidity is not a premorbid condition for the development and may not increase the mortality of COVID-19. Meta-analysis of the database illustrates that inhaled-corticosteroid effective to control the exacerbation in case of Asthmatic COVID-19 patients.

Keywords
COVID-19; lung inflammation; prevalence; premorbid; comorbid; Asthma; SARS-CoV-2;

Introduction

WHO has mentioned that Hypertension, Diabetes Mellitus and Obesity are considered to be common prevalence comorbidities in the global for the cause of coronavirus disease 2019 (COVID-19) (www.who.org). This result would have also influenced the geographical location of the country. The case studies presented in this paper gives us an overall outline of our comparative studies on prevalence of asthma in COVID-19 patients across the global.

Asthma is an inflammatory, highly ubiquitous, chronic and uncontagious respiratory ailment. Asthma is a chronic inflammation ailment of respiratory tract which causes lung disorder which affected over 330 million people worldwide as a long-term lung disease [1]. The swelling of the lungs airways and tightening of respiratory muscles are the considered as primary asthmatic symptoms. The breathing becomes difficult when air passage constricted due to the deposition of mucus. The constriction of lungs pathway triggers coughing and wheezing when the patient breathes out. Apart from this, many allergens responsible for allergies viz., bronco-constriction, respiratory tract infection, constriction of the lungs airway passages, obstruction of breathing, activate allergic responses etc [2]. Cytokines are mainly responsible for the inflammation.

The symptoms of Asthma are not same for all the persons. It depends on individuals. They are broadly classified in any categories;
(1) Exercise-induced bronco-constriction (EIB), usually expressed after physical activities,
(2) Occupational asthma is due to the irritants in the working places viz., dust, gases, chemical fumes etc.
(3) Allergy-induced asthma is due to airborne irritants in common places viz., pollen, mold spores, cockroach waste, pet dander, acid smell etc.

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(4) Non-allergic asthma is due to burnings irritants viz., air freshener, bleaching powder, cigarettes smoke, burning woods etc.
(5) Aspirin Exacerbated Respiratory Disease (AERD) also commonly knew as Aspirin-induced asthma (AIA) triggers while consuming aspirin or non-steroidal anti-inflammatory drugs.

The basic indications of asthma include; paroxysm of cough (during nights/ when laughing/ during exercise), Shortness of breath, Chest tightness, chest pain, difficulty while talking, anxiousness or panic and fatigue. Frequent wheezing is a most common asthmatic symptom in children.

The impact of respiratory infection will increase when respiratory viruses trigger asthma exacerbations [3, 4]. Earlier, the experts suspected that corona viruses trigger asthma exacerbations. Corona viruses (CoVs) mainly cause respiratory syndrome and tract infections, and hence these variants cause respiratory problem with severe asthma exacerbations in children and adults [5]. This is true in influenza virus [6,7,8]. Asthma is identified as one of the prevalence factor for severe COVID-19 illness as declared by European Academy of Allergy and Clinical Immunology (EAACI) [9] and the Centers for Disease Control (CDC) [10]. A clinical meta-analysis study by the researchers in the UK have reported that the asthma as one of the prevalence risk factor for COVID¬19 [11]. The latest investigation reveals that asthma is still controversial premorbid that could worsen SARS-CoV-2 (Virus responsible for COVID-19) progression. SARS-CoV-2 is a virus responsible for respiratory infection. On the contrary, epidemiologic studies have demonstrated prevalence of COVID-19 in asthmatic patients is lower [12,13,14]. The influence of asthma in the progression of COVID-19 is still unclear.

COVID-19 is a contagious zoonotic disease predominantly transmitted between human which has been proliferated from animals to humans is roots from β-group corona virus commonly known as Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) outspread among humans in the world [15]. SARS-CoV-2 rated third pathogenic virus leading to pandemic after the Middle East Respiratory Syndrome corona virus (MERS-CoV) and the Severe Acute Respiratory Syndrome corona virus (SARS-CoV) recorded [16,17]. On 31 December, WHO has declared COVID-19 following a case reported on ‘viral pneumonia’ in Wuhan, People’s Republic of China. WHO has published the current status of COVID-19 across the world in www.who.org. As on 15 May 2021, WHO has published that there have been 161,513,458 patients confirmed with COVID-19 including 3,352,109 deaths. A total of 1,264,164,553 vaccine doses have been administrated across the world.

Tiredness, dry cough and fluctuating fever are the common symptoms of COVID-19 patients. The complex symptoms of COVID-19 patients were breathing problem, chest pain, movement difficulty and loss of speech, which are also the symptoms to the development of pneumonia and acute respiratory distress syndrome (ARDS).

Age and comorbidity such as diabetes Mellitus, cardiovascular disease, allergies etc., may be risk factors for SARS-CoV-2 affected people [18]. It is consistent with the chronic inflammation and airways dysfunction characterizing asthma. These comorbidities elevate the frequency and severity of respiratory infections in COVID-19 patients with prevalence of asthma, such as is the

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case with influenza [19]. Diabetes mellitus and asthma were the most common comorbidities among younger patients admitted in hospitals for COVID-19 in the USA [20].

People with asthma have the fear that they may be at higher risk for COVID-19. The Centre for Disease Control and Prevention (CDC&P) and World Health Organization (WHO) have reported that people with asthma are more susceptible to becoming severely ill with COVID-19 [21, 22]. The virus responsible for the common cold (also known as Rhinovirus) is an effective stimulus of asthma exacerbations [23]. Asthma exacerbations are often triggered by Rhinovirus which is vulnerable for an increase in airway eosinophilic inflammation. COVID-19 is the fourth most prevalent comorbidity behind hypertension, obesity, and diabetes.

The influence of asthma on SARS-CoV-2 cannot be eliminated. The database reveals that the intensity of SARS-CoV-2 infection is low in patients with asthma compared to without patients without asthma. The risk of mortality in elderly patients is highly associated with age and comorbidities in the COVID-19 with asthma. Elderly patients with Asthma and comorbidities need extra attention to avoid disease progression to respiratory failure or death [24,25]. Asthmatic patients who take Inhaled corticosteroids (ICS) exhibited low probability for hospitalization due to COVID-19 [26]. Patients infected by SARS-CoV-2 exhibited a reduction in blood eosinophils. More severe Asthmatic condition has been indicated as a risk factor for COVID-19 mortality [27].

Objective

The primary objective of our analyzing various case studies is to explore the possible association of bronchial asthma in COVID-19 patients and to understand the prevalence of its occurrence. During our case studies, we have considered that validated cases published by various researchers in the peer reviewed journals for correctness. Most of the studies reveals that patients who have infected with COVID-19 doesn't have the risk of hospitalization or need mechanical breathing assistance compared to patients without asthma.

Discussions

Case study – 1

Centre for Disease control and prevention (CDC&P), USA has reported that pervasiveness of asthma is about 17% in COVID-19 patients as compared to the Asiatic reports showed a low prevalence. However, the asthma prevalence of 4.2% is reported in China, where asthma is under-diagnosed and under-treated [28,29,30,31].

Analysis

In the meta-analysis, we have explored the report of 502 positive COVID-19 patients database from multiple hospitals in Louisiana, USA including 72 asthmatic patients and 430 non-asthmatic patients.

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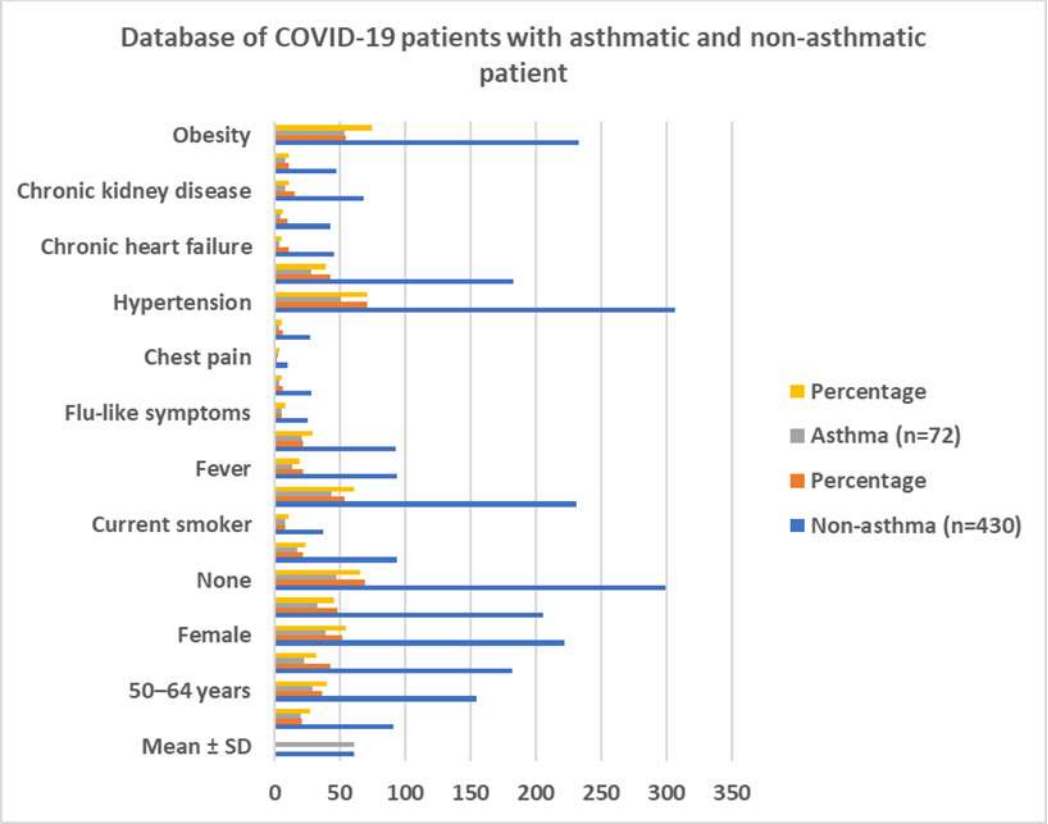

Figure 1. Database of COVID-19 patients with asthmatic and non-asthmatic patient [25]

The statistical analysis reveals that the presence of asthma in COVID-19 patients was not associated with greater odds of complications, and hence prolonged hospital stay or ICU admission [32]. The COVID-19 is also not associated with higher hospitalization rates but may depend on the distribution of the angiotensin-converting enzyme-2 (ACE2) in the respiratory pathway. Diabetes and hypertension (high BP) may increase ACE2 expression, whereas inhaled-corticosteroid (ICS) use may decrease ACE2 expression, hence leading to more difficulty with viral entry [33,34]. ACE2 expression is low in case of patients with asthma and predominantly allergic phenotype [34].

Still it is not clear about the ACE2 expression to overall COVID-19 susceptibility and disease severity. Unfortunately, database does not have inhaled-corticosteroid information of the patients to clarify the possible benefits of these medications as has been suggested [35]. In contrast to having asthma, having COPD increases the risk for severe COVID-19 in the hospitalized patients [36,37]. This comorbidity is associated with increased ACE2 expression in the lung tissue and small airways [18].

Case study – 2

Anthony P. Sunjaya and his team members have done Sidik-Jonkman random effects meta-analysis of COVID-19 patients with and without asthmatic condition across the world using binomial distribution model and calculated the confidence intervals using Wilson score test. 587280 COVID-19 patients were included in the 57 different case studies. Among these COVID-

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19 patients, 7.46% patients had prevalence of asthma as illustrated in the tables 1, 2 & 3. Among them, 9.61% patients had non-severe asthmatic condition against 4.13% severe asthmatic. Meta-analysis showed a 14% patients had reduced risk in acquiring COVID-19 and 13% reduction in hospitalization of COVID-19 patients with asthma compared with those without asthma as discussed in table 1 and table 2 [38]. Three different continental databases have been taken for the analysis viz America, Europe and Asia.

Table 1. Statistics of COVID-19 positive patients with Asthma in America

America		**COVID-19 Positive**	
Country	**City**	**Asthma (n)**	**Overall (n)**
USA	Washington	8	77
USA	Georgia	19	217
USA	Seattle	3	24
USA	New York	868	11565
USA	San Francisco, Boston	4	80
USA	Veterans Affair	102	1162
USA	California	23	174
USA		2546	21647
Mexico		3417	119528

In USA, 154474 different positive COVID-19 patients (mean age of 59.97) have been considered during the study. Among the total sample, 6990 COVID-19 patients had Asthma. It is almost 4.5% of the total affected patients. The possibility of hospitalization recorded among the COVID-19 patients who have diagnosed with Asthma and consumes inhaled corticosteroids (ICSs) was recorded almost zero.

Another study from the USA and UK signifies the presence of asthma among COVID-19 patients was high. The database reveals that the occurrence of asthma in COVID-19 patients was 14.4% against the national asthma prevalence report which claims 8% to 9% in the USA.
In Europe, 166510 different positive COVID-19 patients in the mean age of 56.29 have been considered during the study. Among the total sample, 13366 COVID-19 patients had Asthma. It is almost 8% of the total affected patients.

Table 2. Statistics of COVID-19 positive patients with Asthma in Europe & UK

Europe		**COVID-19 Positive**	
Country	**City**	**Country**	**City**
France, Italy, Spain, Belgium, Switzerland		93	1420
France,		3	35

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Switzerland			
Brazil		4	81
Italy	Lombardy	29	1043
Italy	South Lombardy, Liguria	1	40
Spain	Catalonia	9025	132034
Spain	Madrid	115	2226
Germany	Hamburg	2	12
UK		3569	26855
UK	North Bristol	21	95
UK	Southeast London	65	452

The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC), UK has given the meta-analysis report on 16,749 patients where, it has reported 14% asthma prevalence in the COVID-19 patients. A similar study from Biobank, UK reported that only 17.9% of COVID-19 patients have the prevalence of asthma. The second study Biobank, UK has reported that about 13% of COVID-19 patients have the prevalence of asthma. It revealed that adult and old age patients with asthma had a greater risk factor for the cause of severe COVID-19.

Table 3. Statistics of COVID-19 positive patients with Asthma in Asia [27]

Asia		**COVID-19 Positive**	
Country	**City**	**Country**	**City**
China	Wuhan	8	863
China	Zhejiang Province	6	788
China	Beijing	2	63
China	Shenzhen	1	55
China	Jiangsu Province	0	80
China	Ningbo	0	127
China	West China	1	34
China	Chongqing	0	43
Hong Kong		0	8
South Korea		1498	5213
Thailand	Bangkok	0	11
Iraq		2	15
Iran		307	14991

In Asia, 22325 different positive COVID-19 patients in the mean age of 44 have been considered during the study. Among the total sample, 1828 COVID-19 patients had Asthma. It is almost 8.2% of the total affected patients. The meta-analysis of COIVID-19 patients' database reveals that the prevalence of asthma in COVID-19 patients in Asia is in proportional with the global prevalence of asthma in COVID-19 patients. Asthma prevalence in COVID-19 patients who have been hospitalized in China was low.

Case study – 3

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Ting Wu [39] published the study that among 41,282 COVID patient cases from 18 studies, including 3,940 asthma patients, the prevalence of asthma was only 0.08 with an overall 12 as shown in figure 2. In their study from the database obtained, they have revealed that the asthma doesn't increase the risk of severity in COVID-19 patient.

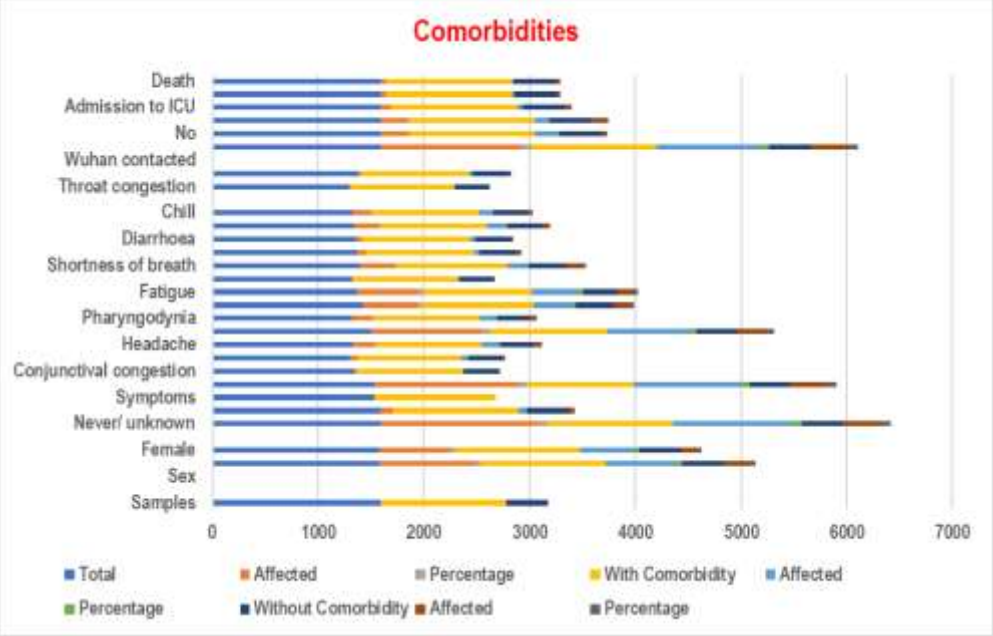

Figure 2. Meta-analysis of prevalence of asthma in COVID-19 patients with comorbidities

Case study – 4

Lacey B. Robinson [40] studied 562 COVID-19 patients with asthma and 2686 COVID-19 patients with non-asthma in their meta-analysis using data taken from the Mass General Brigham Health Care System, Boston, USA as given in the figure 3. Among the 562 COVID-Asthma patients, 199 patients were hospitalized, 15 were under ventilator and 7 were died. Among the 2686 COVID without Asthma patients, 487 patients were hospitalized, 107 were under ventilator and 69 were died. The Body mass index (mean, SD, kg/m2) of asthma patients are 31.8 and COVID Asthma patients are 7.2; and the Body mass index for non-asthma patients are 29.8 and COVID non-Asthma patients are 6.4. The Charlson comorbidity index for asthma patients are 2.1 and COVID Asthma patients are 2.5; also Charlson comorbidity index for non-asthma patients are 1.0 and COVID non-Asthma patients are 2.1.

The mean age of COVID-19 patients (both asthmatic and non-asthmatic) were around 51 years. More than 50% of COVID patients were in 26 to 75 years age. COVID-19 is affected majorly to male population.

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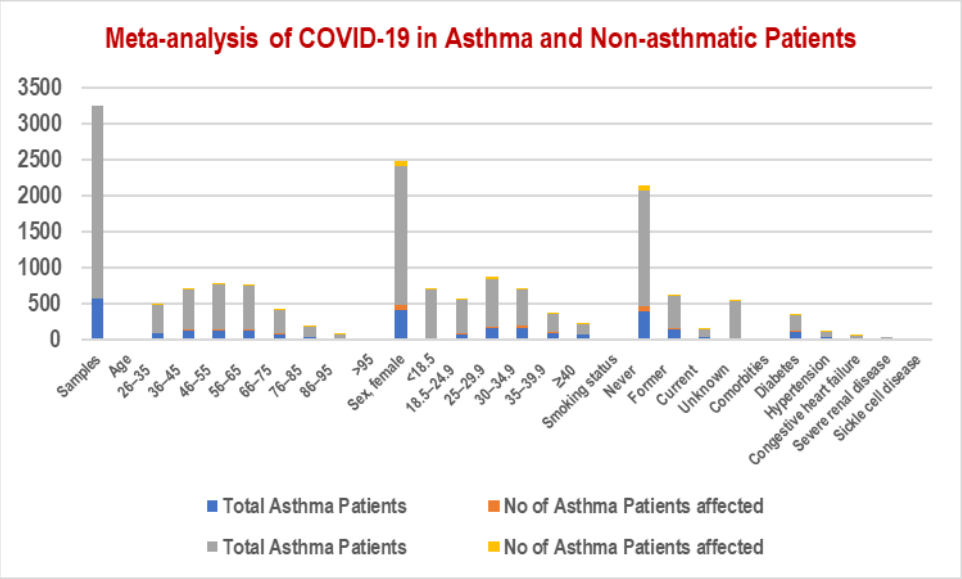

Figure 3. Meta-analysis of COVID-19 in Asthma and Non-asthmatic Patients

A study of database collected from Boston based healthcare system reveals that the COVID-19 patients with pre-existing asthma is associated with the hospitalization and also the support of the mechanical ventilation but mortality was low. It also reveals that the COVID-19 patients with asthma have multiple comorbidity viz., diabetes mellitus and hypertension. Meta-analysis of patients' data reveals that mean body mass index was higher in asthma patients than others.

Case study – 5

522 patients (Male: Female:: 3:1) database of all the ages has been accessed. More than 50% of COVID patients were in the middle age (21 to 50 years). Among the COVID-19 patients, more than 70% of the affected people were identified as asymptomatic at the time of diagnosis as illustrated in the figure 4, which were the major challenge for treatment. Cough and tight breathing were the common symptoms among COVID-19 patients. Symptomatic clinical sign were predominant in old age patients than youngsters. COVID-19 were higher with a patients multiple comorbid conditions. Mortality is recorded higher in old age COVID-19 patients.

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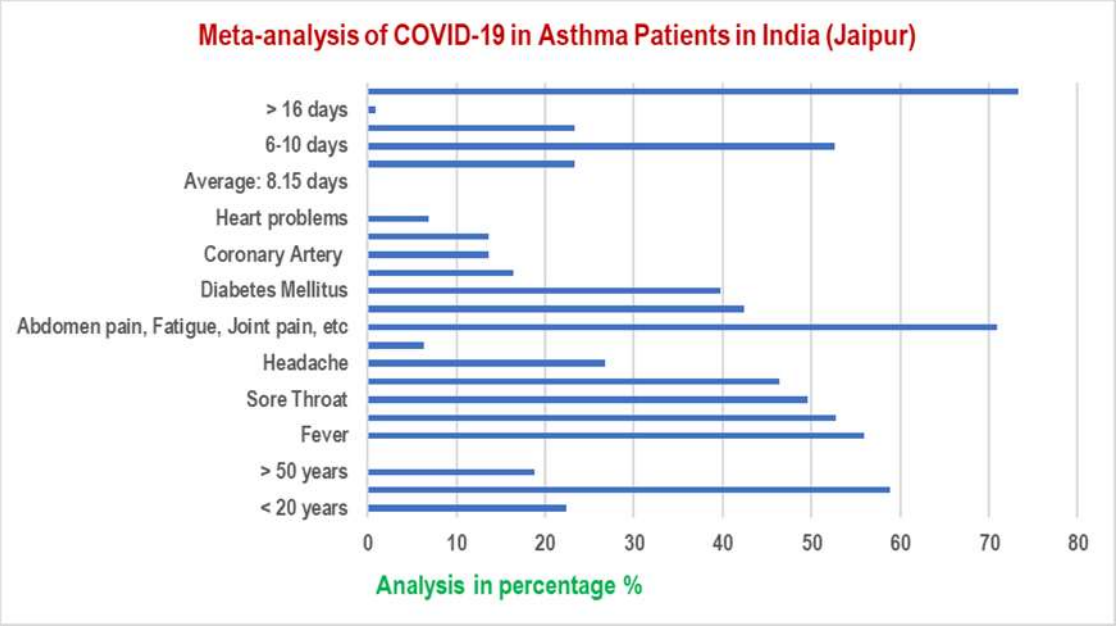

Figure 4. Meta-analysis of COVID-19 in Asthma Patients in India (Jaipur)

The extensive study of various case studies carried by different researchers on different countries around the world revealed that COVID-19 patients with asthma were not reported with higher risk of hospitalization and mortality compared with the COVID-19 patients without asthma.

Conclusion

We have studied the COVID-19 research and study papers published by the researchers on COVID-19 with the prevalence of asthma since its emergence in December 2019. From the first pandemic wave, we have understood that asthma should be under control to curb the possibility of serious exacerbations occurrence. As the world prevalence of asthma is less than 5%, we conclude that the chronic asthma is not responsible for the development of COVID-19 and mortality; also, it is not a premorbid condition for COVID-19. Doctors and the researchers are unable to declare the claim of possibilities of asthmatic condition as premorbid among COVID-19 patients. Asthma itself had lower risk factor for the prognosis of COVID-19.

In conclusion, the relationship between the SARS-CoV-2 coronavirus disease and chronic asthma lung disease are still unformulated. Meta-analysis of database illustrates that inhaled-corticosteroid effective to control the exacerbation in case of Asthmatic COVID-19 patients [4,41].

References (APA 6th edition)

[1] Global Asthma Network The global asthma report Auckland, New Zealand: *Global Asthma Network;* 2018.

[2] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-covid-19.

[3] Ishmael Faoud T. The inflammatory response in the pathogenesis of asthma. *J. Am. Osteopathic Assoc.* 2011;111(11 Suppl 7): S11–S17.

[4] Zheng XY et al, "Regional, age and respiratory-secretion-specific prevalence of respiratory viruses associated with asthma exacerbation: a literature review", *Arch Virol.* 2018;163(4): 845–53.

[5] Bergmann CC, Silverman RH. "COVID-19: Coronavirus replication, pathogenesis, and therapeutic strategies". *CCJM*. 2020;87(6):321–327.

[6] McIntosh K et al, "The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children", *J Pediatr*. 1973;82(4): 578–90.

[7] Nicholson KG, Kent J, Ireland DC., "Respiratory viruses and exacerbations of asthma in adults", *BMJ*. 1993;307(6910):982–6.

[8] Sposato B, et al., "Influenza A H1N1 and severe asthma exacerbation", *Eur Rev Med Pharmacol Sci.* 2010;14(5):487–90.

[9] Brough HA, et al. "Managing childhood allergies and immune-deficiencies during respiratory virus epidemics - The 2020 COVID-19 pandemic: A statement from the EAACI-section on pediatrics",*Pediatr Allergy Immunol*. 2020; 31(5):442–448.

[10] Garcia M, et al, "Centers for Disease Control and Prevention 2019 novel corona virus disease (COVID-19) information management: addressing national health-care and public health needs for standardized data definitions and codified vocabulary for data exchange". *J Am Med Inform Assoc*. 2020; 27(9):1476–1487.

[11] Williamson EJ, et al., "Factors associated with COVID-19-related death using OpenSAFELY", *Nature.* 2020;584 (7821):430–436.

[12] Lupia T, et al, "2019 novel coronavirus (2019-nCoV) outbreak: a new challenge:,*J Glob Antimicrob Resist.* 2020; 21:22–27.

[13] Zhang JJ, et al, "Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan. China", *Allergy.* 2020;75 (7):1730–1741.

[14] Li X, et al. "Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan", *J Allergy Clin Immunol*. 2020;146 (1):110–118.

[15] Mackenzie John S., Smith David W. "COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't", *Microbiol. Australia.* 2020:MA20013. doi: 10.1071/MA20013.

[16] He Chunting., "Highly pathogenic coronaviruses: thrusting vaccine development in the spotlight", *ActaPharmaceutica Sin. B*. 2020;10(7):1175–1191.

[17] Zhou F, et al. "Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, *Lancet*. 395(10229), 1054-1062, 2020.

[18] Weill Cornell Medicine COVID-19: why is it mild for some, deadly for others? New York, *New York: Weill Cornell Medicine;* 2020.

[19] US Centers for Disease Control and Prevention Flu & people with asthma Atlanta, *Georgia: Centers for Disease Control and Prevention.*

[20] Garg S, et al. "Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET", *14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep.* 2020;69:458–464.

[21] US Centers for Disease Control and Prevention Precautions regarding COVID-19 and asthma Atlanta, *Georgia: Center for Disease Control and Prevention;* 2020.

[22] World Health Organization Coronavirus disease (COVID-19) advice for the public Geneva *Switzerland: World Health Organization;* 2020.

[23] Busse WW, Lemanske RF, Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet.* 2010;376:826–834.

[24] Sang Chul Lee etc, "Impact of comorbid Asthma on severity of coronavirus disease (COVID-19)", *Scientific Reports, Nature,* (2020)10:21805.

[25] Yuanyuan Wang et al, "Does Asthma increases the mortality of patients with COVID-19?: A systematic review and meta-analysis, *Int. Archives of allergy and immunology,* 2021; 182: 76.

[26] Jose Luis Izquierdo et al. "The impact of COVID-19 on patients with Asthma", *European Respiratory Journal,* No.57, 2021.

[27] Pignatti P et all, "Impact of COVID-19 on patients with Asthma", *Int J Tuberc Lung Dis. 2020 Nov 1*;24(11):1217-1219.

[28] Zhang J-j et all, "Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China", *Allergy.* 2020;75(7): 1730-1741.

[29] Li X et al, "Risk factor for severity and mortality in adult COVID-19 inpatients in Wuhan", *J Allergy Clinical Immunology*, 2020;146(1): 110-118.

[30] Garg S et al, "Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed corona virus disease 2019 - COVID-NET", *Morb Mortal Wkly Rep,* 2020; 69(15): 458-464.

[31] Huang K, "Prevalence, Risk factors and management of Asthma in China: a national cross sectional study, *Lancet,* 2019; 394(10196): 407-418.

[32] Mohammad H Hussein et al, "Asthma in COVID-19 patients: An extra chain fitting around the neck?', *Respir Med.* 2020 Dec; 175: 106205.

[33] Peters MC et al, "COVID-19-related genes in sputum cells in asthma: relationship to demographic features and corticosteroids", *Am J Respir Crit Care Med.* 2020;202:83–90.

[34] Jackson DJ et al. "Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2", *J Allergy Clin Immunol.* 2020;146:203–206.

[35] Halpin DMG et al. "Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection?", *Lancet Respir Med.* 2020;8:436–438.

[36] Richard Broadhurst et al, "Asthma in COVID-19 Hospitalizations: An Overestimated Risk Factor?", *Ann Am Thorac Soc.* 2020 Dec; 17(12): 1645–1648.

[37] Leung JM, Y et al., "ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19", *Eur Respir J.* 2020;55:2000688.

[38] Anthony P. Sunjaya et al, "Asthma and risk of infection, hospitalization, ICU admission and mortality from COVID-19: Systematic review and meta-analysis", *J Asthma.* 2021 : 1–14.

[39] Ting Wu et al, "Asthma does not influence the severity of COVID-19: a meta-analysis", *J Asthma.* 2021 : 1–7.

[40] Lacey B. Robinson et al, "COVID-19 severity in asthma patients: a multi-center matched cohort study", *J Asthma.* 2020 : 1–14.

[41] Ong KY et al, "Managing Asthma in the COVID-19 pandemic and current recommendations from professional bodies: a review", *J. Asthma,* 2020;1-8.