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TANAFFOS

Epidemiology of Asthma in Patients with COVID-19: Investigation of Respiratory Allergy as a Risk Factor for COVID-19 Severity

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Background: The outcome of coronavirus disease 2019 (COVID-19) is complicated by various comorbidities; asthma, a common chronic disease, may be considered one of these conditions. This study aimed to investigate the effect of asthma as a potential comorbid condition on the COVID-19 prognosis.

Materials and Methods: This retrospective study included all RT-PCR confirmed COVID-19 cases recorded on the Shiraz health department's electronic database from January to May 2020. A questionnaire was designed to collect information about patients' demographics, their history of asthma and other comorbidities, and the severity of COVID-19 by contacting them by phone.

Results: Of 3163 COVID-19 patients, 109 (3.4%) had self-reported asthma with a mean age of 42.7 ± 19.1 years. Most patients (98%) had mild-to-moderate asthma, while 2% had severe disease. Among asthmatic patients, fourteen (12.8%) were admitted to the hospital, and five (4.6%) died. Univariate logistic regression results showed that asthma had no significant effect on hospitalization (OR 0.95, 95% CI: 0.54-1.63) and mortality (OR 1.18, 95% CI: 0.48-2.94) in patients with COVID-19. Compared living and deceased patients with COVID-19, the pooled OR was 18.2 (95% CI: 7.3–40.1) for cancer, 13.5 (95% CI: 8.2–22.5) for age 40-70 years, 3.1 (95% CI: 2–4.8) for hypertension, 3.1 (95% CI: 1.8–5.3) for cardiac disease and 2.1 (95% CI: 1.3–3.5) for diabetes mellitus.

Conclusion: This study showed that asthma is not associated with an increased risk of hospitalization and mortality in patients with COVID-19. Further studies are needed to investigate the risk of different asthma phenotypes on the severity of COVID-19 disease.

Key words: Asthma; Coronavirus; COVID-19; Epidemiology

INTRODUCTION

After the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a global public health emergency in January 2020, various related investigations supported the increased risk of severe illness in patients with certain medical underlying diseases (1-3). Different studies showed that COVID-19 severity could be associated with several potential risk factors, including cancer, HTN (hypertension), chronic kidney diseases, pulmonary disorders, heart diseases, immune deficiency, DM (diabetes mellitus), obesity, and smoking (4-8).

Asthma is a significant burden on the health systems and affects approximately 300 million individuals of all ages worldwide, comprising 1-18% of the population in different countries (9,10). The provocation of asthma

occurs with various trigger factors, including allergens, air pollution, and viral infections (11-13). There is data and information about the impact of viral infections on emergency healthcare resources, hospitalization, and even death in patients with asthma (14). As for the viruses, it is also reported that defects in the production of various interferons as antiviral agents in some patients with asthma are related to an increased risk of asthma exacerbation (15). According to this evidence, asthma can be considered a risk factor for the severity of COVID-19.

Shortly after the global pandemic of COVID-19, the Centers for Disease Control and Prevention considered asthma a risk factor for the severity of the novel disease (16). Different studies indicate that asthma prevalence in patients with COVID-19 ranges from 9% to 25% (17); however, these reports remain unclear regarding the risk and associated outcomes for patients with asthma who contract COVID-19.

This study's primary aim was to determine the prevalence of asthma in inpatients and outpatients with COVID-19 disease. We also aimed to evaluate COVID-19 severity according to hospitalization and mortality in patients with asthma compared to those without asthma.

MATERIALS AND METHODS

This retrospective study included all PCR-confirmed patients with COVID-19 who were registered on the Shiraz health department's electronic database affiliated with the Shiraz University of Medical Sciences for five months, from January to May 2020. Shiraz is a city in South West of Iran with approximately 1.5 million inhabitants (in 2016). Shiraz health department serves as the only center for registration of all patients with COVID-19 in Shiraz, confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) results. Following the approval of the study protocol by the Shiraz University of Medical Sciences Ethics Committee (IR.SUMS.REC.1399.161), a total of 4950 patients with COVID-19 were included in this study. Asthma was defined based on the self-reported history of patients or their first-degree families in deceased patients.

An anonymous questionnaire was adapted from the COVID-19 case questionnaire published by NSW health (18), the international study of asthma and allergies in children (ISSAC) (19), and also a review of related literature. This questionnaire comprised three parts. In part A (demographic data), information about age, sex, education, smoking status, history of HTN, cancer, cardiac diseases, diabetes mellitus (DM), kidney diseases, neurological diseases, pulmonary diseases, and obesity were collected and recorded. In part B (allergy-related information), history and severity of asthma (mild to moderate and severe, severe asthma was defined by the need for daily oral or high doses of inhaled corticosteroids (ICS), the use of steroids for asthma, allergic rhinitis (AR), and allergic rhinitis type were recorded. In part C of the COVID-19 questionnaire, information about the symptoms, such as fever, cough, headache, body pain, loss of taste and smell, and nausea, was obtained and recorded. The severity of COVID-19 infection was determined based on home treatment and hospital or ICU admission (through yes-or-no questions). A technician called the cell phone numbers to obtain the information and fill out the questionnaire. If someone didn't answer the first time, the technician called him again. The technician obtained deceased patients' information by interviewing their closest family members. The estimated filling time for the questionnaire was 10 minutes for each patient.

Statistical analysis

Qualitative variables were expressed as numbers (n), and percentages (%), and quantitative variables were presented by means and standard deviations (SD) and bar charts. Chi-square, Fisher's exact tests, and univariate logistic regression were applied to assess the relationship between asthma (yes or no) and the demographic and clinical variables. A p-value of less than 0.05 was considered statistically significant in all statistical analyses. Statistical analyses were performed using IBM SPSS version 22 (IBM Corporation, Armonk, NY, USA).

RESULTS

All patients with COVID-19 were from Shiraz, Iran. A total of 3163 questionnaires were completed, and 1901 were excluded because there was no response to the calls. The mean age of all patients with COVID-19 was 38.5±16.9 years, ranging from 6 months to 102 years. Among them, 109(3.4%) patients had self-reported asthma. The mean age of COVID-19 patients with asthma was 42.7± 19.1 years, ranging from 9 to 85 years. Table 1 presents the primary demographic data of COVID-19 patients with and without asthma. There were 1211(38.3%) asymptomatic patients whose infection was only confirmed based on the positive RT-PCR results.

Table 1. The main demographic characteristics of COVID-19 patients with and without asthma

Characteristics		Total n=3163	Asthma n=109(%)	Non asthma n=3054(%)	*P*
Sex	Male	1268	47(2.5)	1206(95.1)	**<0.001†**
	Female	1895	62(4.9)	1848(97.5)	
Age (years)	<40	1939	50(2.7)	1887(97.3)	**<0.001†**
	40-70	1087	43(4.0)	1044(96.0)	
	>70	137	14(10.2)	123(89.8)	
Education	Primary school	60	8(13.3)	52(86.7)	**<0.001†**
	High school	311	6(1.9)	305(98.1)	
	Advanced	52	0(0.0)	52(100.0)	
Tobacco exposure	Yes	536	20(3.7)	516(96.3)	0.691†
	No	2627	89(3.4)	2538(96.6)	
Mortality	Expire	125	5(4.0)	120(96.0)	0.729†
	Alive	3038	104(3.4)	2934(96.6)	
Hospitalization	Hospital	319	11(3.4)	308(96.6)	0.780†
	ICU	104	3(2.9)	101(97.1)	

†Chi-square test

As shown in Table 1, sex and age were significantly different between COVID-19 patients with and without asthma. Among 109 asthmatic patients, 107 (98.1%) had mild-to-moderate disease, and 2(1.9%) had severe asthma. Seventy-three (70.8%) of asthmatic patients regularly used ICS, while only 2 used low doses of a systemic corticosteroid with high doses of ICS.

There were 258 individuals (8.4%) with a history of AR among the studied patients. Their mean age was 37.7±14.1 years, with a female to male ratio of 117 to 147. Around 34.5% had perennial AR, and 65.5% had seasonal AR.

The outcomes of the logistic regression on the current data of patients with COVID-19 showed that symptoms of body ache, cough, fever, headache, and nausea were significantly more common in asthmatic patients compared with non-asthmatic ones (Figure 1).

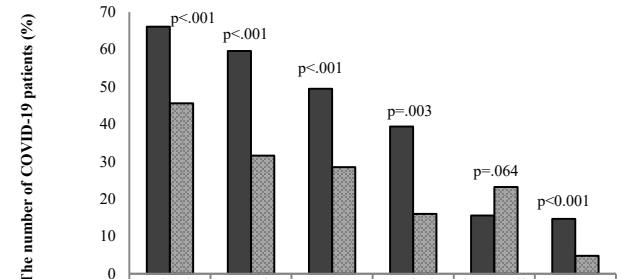

Figure 1. The comparison of the symptoms of COVID-19 infection in asthmatic and non-asthmatic patients

The number of COVID-19 patients without comorbidity was 2479 (78.3%). The prevalence of various comorbidities, including cancer, cardiac diseases, DM, HTN, kidney disease, lung disorder, and neurological diseases in patients with COVID-19 based on their asthma status is shown in Table 2. The results of univariate logistic regression and Fisher Exact test showed that cardiac comorbidities (p=.004) and lung diseases (p<001) were significantly different between COVID-19 patients with and without asthma. There was no patient with a history of obesity among all cases with COVID-19. Therefore, we could not consider obesity in our analysis.

The mortality rate in our patients with COVID-19 was 3.9% (n=125), with a median age of 53.5± 21.5 years ranging from 6 months to 95 years. There was a significant correlation between age and mortality in these patients (p<0.01), but we did not find any correlation between smoking status and mortality. Seventy-one of 125 (56.8%) patients who passed away due to COVID-19 had no comorbidity. Among 125 deceased patients with COVID-

19, the most frequent comorbidities were HTN in 30 (24%), DM in 19 (15.2%), and cardiac disease in 17 (13.6%), followed by cancer in 11(8.8%) and asthma in 5 (4%). Moreover, no mortality was observed due to neurological diseases, kidney disorders, and lung diseases in patients with COVID-19 infection.

Five of 103 (3.8%) patients with asthma who expired due to COVID-19 had mild-to-moderate asthma, while two also had perennial allergic rhinitis. According to the information obtained from the relatives of the deceased patients, all had a history of HTN, three had cardiac diseases, and one had DM. The results of univariate logistic regression (unadjusted model) showed that asthma did not have any significant effect on hospitalization (OR 0.95, 95% CI: 0.54-1.63) and mortality (OR 1.18, 95% CI: 0.48-2.94).

The cancer had the highest odds ratio of mortality among COVID-19 patients (18.2), followed by age between 40 and 70 years (13.5), HTN (3.1), cardiac disease (3.1), and diabetes (2.1) (Table 3).

Table 2. Clinical co-morbidities of patients with COVID-19 with and without asthma

Characteristics		Total	Asthma n=109	Non asthma n=3054	*P*
Cancer	Yes	27	0(0.0)	27(100.0)	0.386‡
	No	1895	109(3.5)	3027(96.5)	
Cardiac disease	Yes	163	14(8.6)	149(91.4)	**0.004**†
	No	3000	95(3.2)	2905(96.8)	
Diabetes mellitus	Yes	255	70(2.7)	248(96.3)	0.522†
	No	2627	102(3.5)	2806(96.5)	
Hypertension	Yes	308	12(3.9)	296(96.1)	0.649†
	No	2855	97(3.4)	2758(96.6)	
Kidney disease	Yes	3054	0(0.0)	58(100.0)	0.128‡
	No	45	109(3.5)	2996(96.5)	
Lung disease	Yes	46	7(15.2)	39(84.8)	**<0.001**†
	No	3117	102(3.3)	3015(96.7)	
Neurological disease	Yes	66	2(3.0)	64(97.0)	0.852†
	No	3097	107(3.5)	2990(96.5)	

†Chi-square test, ‡Fisher Exact test

Table 3. Effect of some risk factors on mortality rate in patients with COVID-19 infection

Characteristics	Expire n (%)	Alive n (%)	Unadjusted OR(95%CI)	Adjusted OR(95%CI)
Smoking	18 (3.4)		0.82(0.49-1.36)	-
Age > 40 years			Reference	-
Age 40-70 years	53(4.9)	1034(95.1)	**13.54(8.16-22.45)*****	**11.05(6.28-19.42)*****
Age >70	31(22.6)	106(77.4)	**5.70(3.51-9.28)*****	**5.46(3.26-9.13)*****
Cancer	11(40.7)	16(59.3)	**18.23(7.27-40.16)*****	**19.29(8.40-44.32)*****
Cardiac disease	17(10.4)	146(89.6)	**3.12(1.80-5.34)*****	1.79(0.98-3.29)
Diabetes mellitus	19(7.5)	236(92.5)	**2.13(1.28-3.53)****	1.06(0.59-1.89)
Hypertension	30(9.7)	278(90.3)	**3.14(2.04-4.81)*****	1.29(0.76-2.16)
Kidney disease	0(0.0)	58(100)	-	-
Pulmonary disease	0(0.0)	46(100)	-	-
Asthma	5(4.6)	104(95.4)	1.18(0.47-2.94)	-

*<0.05, **p<.001, ***p<.001

DISCUSSION

Serious concerns have been raised about COVID-19 infection in asthmatic individuals. In the current study, among 3163 patients with COVID-19, 109(3.4%) had self-reported asthma. The prevalence of asthma is 8.9% in the general Iranian population; however, the rate of asthma among our patients with COVID-19 was approximately less than half of this figure. Recent studies reported a rate of 14.4% asthma among 1526 patients with COVID-19 in the USA and an asthma prevalence of 17.9% among patients with COVID-19 in the UK (20,21). At the beginning of the COVID-19 pandemic, which was when our study was conducted, the assumption that any chronic diseases could be a mortality risk factor was common, and consequently, patients with asthma were overcautious in protection by isolating themselves at home and wearing a face mask exaggeratedly and remote management of their asthma.

The present study indicated significant sex differences between COVID-19 patients with and without asthma. The Global Allergy and Asthma Network of Excellence (GA2LEN) questionnaire demonstrated that the prevalence of asthma was more common in women than men in Southwestern Iran, but this was not significant (10). Although our finding that COVID-19 is more prevalent in women with asthma is consistent with a study conducted in France (22), the sex difference among patients with asthma is yet to be elucidated.

The findings of this study demonstrated that the prevalence of COVID-19 was significantly higher in the elderly with asthma. Advanced age is associated with a decline in humoral and cellular immunity in patients with asthma (23). Airway remodeling that involves structural changes in the airway walls of patients with asthma is due to a chronic inflammatory response (24) and could be considered an influential factor in the elderly (25). It would be feasible to assume that the decreased immunity and alternations in the lung tissue structure following remodeling in asthmatic patients may increase the risk of contracting COVID-19 (23-25). Additionally, less-educated asthmatic patients had a higher prevalence of COVID-19, which indicates ignorance of protection measures.

The findings of this study demonstrated that COVID-19 patients with asthma are not at a higher risk for hospitalization than those without the disease. Similar to our results, a study conducted by Chhiba et al. did not find any significant differences in hospitalization rates due to COVID-19 in patients with asthma after adjustment for demographic data (20). Moreover, in our study, the lower rate of hospitalization in patients with asthma may be due to the fact that most patients had mild-to-moderate asthma.

Only two patients (1.9%) with severe asthma contracted COVID-19. The diagnosis of a severe form of the disease in our study was based on the need for the administration of systemic corticosteroids or high daily doses of ICS; therefore, it is possible that some patients were erroneously excluded.

COVID-19 symptoms were more common in patients with asthma than their non-asthmatic counterparts; however, this may be attributed to their fear of the primary disease and exaggerated symptoms.

In our study, over one-third of the patients with COVID-19 had no self-reported comorbidities; this could be because approximately 30% of the patients were asymptomatic. Among our patients with COVID-19, the three most prevalent comorbidities were HTN, DM, and cardiovascular disease. HTN was self-reported, and people with high blood pressure are reported to be at higher risk of contracting the virus. Clark et al. reported that the underlying mechanism through which hypertension increases the risk of contracting COVID-19 is complex and may be attributed to the underlying co-morbidity (26). Similar to our study, a meta-analysis in patients with COVID-19 revealed that HTN was the most prevalent comorbidity, followed by DM and cardiovascular disease (3). Obesity is demonstrated to be associated with severe forms of COVID-19 (8), and as none of our patients were obese, we could not investigate this relationship in our study. A previous study indicated that asthma might have

a weak association with cardiovascular disease (27); therefore, further investigations are needed to determine why these comorbidities are common in asthmatic patients with COVID-19.

In patients with asthma, the mortality rate was similar to those without the disease during the study period (approximately 4%); therefore, it can be asserted that our results suggested that asthma had no significant effect on the mortality rate in patients with COVID-19. Low risk of asthma could be due to the differences in immune responses or the protective effects of certain asthma medications (28). Halpin and colleagues suggested that using ICS in asthma patients can prevent the coronaviruses' entry into the airways. Furthermore, due to ICS usage, patients with asthma may have lower expression of ACE2, which is necessary for the binding of the virus (29). More studies are needed to describe asthmatic patients' genetic background and cytokine profile in response to COVID-19 infection.

Our findings indicated that cancer, age between 40 to 70 years old, HTN, cardiac diseases, and DM significantly increase the mortality rate in patients with COVID-19. Studies by Kim et al. and Guan et al. reported that various comorbidities increase the mortality rate in patients with COVID-19 (30,31).

One limitation of our study was the self-reported quality of information obtained regarding asthma, its medication, and other comorbidities were subjective and potentially erroneous. Another limitation was that we could not collect and interpret all laboratory values and radiological findings because questionnaires were self-reported by the patients. Moreover, our study was based on the reports in the first months of 2020, which might have changed during the following months.

CONCLUSION

The results of our study demonstrated that the prevalence of asthma was 3.4% in patients with COVID-19, and asthma was not associated with hospitalization or mortality rate in patients with COVID-19. It is proposed that clinicians envisage the risk of severe COVID-19 in the elderly and patients with cancer, HTN, cardiac disease, and DM.

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