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Investigating the association between allergic diseases and COVID-19 in 400 Iranian patients

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Abstract

Introduction: Allergic diseases could play a role of a predisposing factor for coronavirus disease 2019 (COVID-19). The aim of this study was to investigate allergic comorbidity and its association in COVID-19 patients.

Methods: Demographic data, clinical manifestations, laboratory reports, and radiologic findings, together with underlying comorbidity of patients, were studied. Allergic diseases were identified by using the standard GA²LEN questionnaire. The severity of COVID-19 was assessed by a visual analog scale (VAS) and an intensive care unit (ICU) report.

Results: Out of 400 COVID-19 patients admitted in the hospital, 158 (39.5%) presented with different allergic diseases, and a reverse association was observed between having allergic comorbidity and severity of COVID-19 infection ($P=0.005$, relative risk=0.96; 95% Confidence Interval (95% CI): 0.77–1.19). The respective frequency of asthma, allergic rhinitis (AR), chronic rhinosinusitis (CRS), atopic dermatitis, chronic urticaria, and food or drug allergy was 7.3%, 16%, 1.8%, 5%, 10% and 13.3%. Significantly, only AR was reversely associated with the severity of COVID-19 ($P=0.02$, relative risk=0.45; 95% CI: 0.77–1.19). Additionally, 43% of the patients presented hypoxemia, and 93.5% had chest CT scan involvement. Interestingly, patients with allergic diseases had significantly lower hypoxemia and chest CT involvement as compared with non-allergic patients ($P=0.002$ and 0.003, respectively).

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Conclusion: The results of this study established that allergic diseases were not determined to be a predisposing factor for the severe acute respiratory syndrome (SARS) due to coronavirus 2 (SARS-CoV-2) infection. Significantly, AR patients developed mild clinical manifestations of COVID-19 and admitted to ICU as compared to non-AR patients.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread globally, with sharp increase in Iran and some other countries. The disease causes severe pneumonia and other complications, including death in severely affected patients.^{1,2} Clinical manifestations of the COVID-19 infection reported so far include headache, fever, cough, shortness of breath, and breathing difficulties as well as taste and smell dysfunction. Generally, nasal symptoms and sore throat could be the result of viral airway infection, but in some severe cases, the infection could lead to pneumonia, SARS, renal failure, and death.^{3,6}

It has been reported that COVID-19 might result in severe conditions because of different comorbidities, including hypertension (HTN), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), cardiovascular disease, and obesity.⁷ A study conducted in China on the clinical characteristics of 1099 COVID-19 patients has demonstrated that 15.7% of patients had severe pneumonia.⁸

Allergic respiratory diseases, especially allergic rhinitis (AR), chronic rhinosinusitis (CRS), and asthma (AS), affect a large global population, and because of chronic inflammatory characteristics of these diseases, they may influence susceptibility to the SARS-CoV-2 infection and could be a cause of severe COVID-19.^{9,10} Presently, only few data are available to confirm a specific increased risk for COVID-19 in patients with underlying allergic diseases. However, another study from China has recently reported that these diseases could not be considered as risk factors for severe COVID-19 disease.⁵ Moreover, some data have depicted that the prevalence of asthma in the COVID-19 patients in China was less than 1%¹¹ whereas in the United States, prevalence of asthma was reported as 7–17%.^{12,13} Therefore, there may exist a risk for exacerbation of allergic diseases, especially asthma, triggered by SARS-CoV-2 as a respiratory viral infection.¹⁴

Owing to the epidemic status of COVID-19 in Iran, many studies have reported the clinical features of the disease; however, as far as the present study is concerned, there has been no study that assessed the frequency of allergic diseases and their association with COVID-19. Therefore, this study investigated the clinical and laboratory characteristics of COVID-19 patients admitted in wards, intensive care unit (ICU), and out patients department (OPD), associating severe and nonsevere conditions based on ICU admission and visual analog scale (VAS). Moreover, the frequency of allergic and other underlying diseases as associated comorbidity was determined in patients having COVID-19. Finally, association between COVID-19 and allergic diseases as a risk factor was examined.

Materials and methods

Data collection of the COVID-19 patients

This case series study was conducted in the general hospital affiliated to the Bushehr University of Medical Sciences (BPUMS), Iran. All the 400 patients tested positive for SARS-CoV-2 infection (identified by using Reverse Transcriptase-Polymerase Chain Reaction [RT-PCR] test) participated in this study. The patients were split in three groups: 68 patients were admitted in ICU, 270 were admitted in wards, and 62 were treated as OPD patients. Demographic data and clinical manifestations of the COVID-19 patients, including fever, general condition, respiratory, and gastrointestinal (GI) indications were recorded by trained medical staff in a questionnaire. The severity of COVID-19 was assessed at the time of admission using VAS. Patients admitted in the ICU were considered as severe cases. Laboratory findings and computed tomographic (CT) scan of the chest of each patient were obtained and evaluated from the electronic medical record system of the hospital. In addition, we assessed other underlying diseases, such as diabetes mellitus, hypertension, cardiovascular, brain, liver, thyroid, and kidney disorders of the patients by self-reporting. This study was approved by the Ethics Committee of the Bushehr University of Medical Sciences, Bushehr, Iran (ethical approval code: IR.BPUMS.REC.1399.083).

Identification of allergic diseases in COVID-19 patients

For identification and epidemiological investigation of allergic diseases in the COVID-19 patients, we used the standard questionnaire of the Global Allergy and Asthma European Network (GA²LEN).¹⁵ For this questionnaire, details of all allergic disorders, such as AR, allergic rhinoconjunctivitis (ARC), chronic rhinosinusitis, asthma, chronic urticaria (CU), atopic dermatitis (AD), and food or drug allergy, were obtained as self-reported by the patients based on the questions about the diseases as stated in the GA²LEN questionnaire. Furthermore, other physicians also diagnosed the stated diseases, including COPD.

Statistical analysis

Descriptive statistics such as mean value and standard deviation (SD) of laboratory findings and the frequency distribution of age groups, gender, smoking status, allergic diseases, underlying diseases, and COPD in the COVID-19 patients were determined. Association between

demographic characteristics and clinical data of the patients was evaluated using Chi-square test. Moreover, Chi-square test was also used for assessing the correlation between allergic diseases, COPD, and other underlying comorbid diseases and the COVID-19 manifestations and its severity (admission in ICU and VAS). Differences in laboratory findings were compared using two independent *t*-tests, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA).

Results

In this study, 400 COVID-19 patients (51.2% males and 48.8% females) were enrolled. The mean (SD) age of all the patients was 49.2 with a range of 17–92 years. Of the 400 patients, 62 (15.5%) were OPD patients, and 270 (67.5%)

and 68 (17%) were admitted in wards and ICU, respectively. Demographic and clinical data of the patients are provided in [Table 1](#).

Clinical manifestations of COVID-19 patients

The most common clinical manifestations of the patients were chest tightness/dyspnea (78.5%), fatigue (77.3%), cough (69%), and fever (64%). Severity of the patient's clinical manifestations based on self-reported VAS was mild (41%), moderate (47%), and severe (12%). There was an association between having fever ($P = 0.005$), chest tightness/dyspnea ($P < 0.001$), severe headache ($P = 0.01$), anosmia/hyposmia ($P < 0.001$), and GI manifestations ($P < 0.001$) and treatment of OPD patients. On the other hand, there was an association between having cough ($P = 0.01$), chest tightness/dyspnea ($P = 0.01$), anosmia/hyposmia ($P = 0.01$), and diarrhea ($P = 0.01$) and admission in wards ([Table 2](#)).

Table 1 Demographic and clinical data of COVID-19 patients.

Variable	Total patients, N (%)	ICU admissions, N (%)	Non-ICU admissions (Outpatients and wards admission) N (%)	P-value
Males	205 (51.2)	40 (10)	165 (41.2)	0.1
Females	195 (48.8)	28 (7)	167 (58.8)	
Age group (years)				
<30	45 (11.2)	4 (1)	41 (10.2)	0.00
30–39	83 (20.8)	10 (2.5)	73 (18.2)	
40–49	88 (22)	9 (2.2)	79 (19.7)	
50–59	65 (16.3)	9 (2.2)	56 (14)	
≥60	119 (29.7)	35 (8.7)	84 (21)	
Fever	256 (64)	44 (17.2)	212 (82.8)	0.5
Cough	276 (69)	47 (17)	229 (83)	0.5
Fatigue	309 (77.3)	46 (14.9)	263 (83.5)	0.03
Chest tightness/dyspnea	314 (78.5)	61 (19.4)	253 (80.6)	0.008
Severe headache	160 (40)	18 (11.3)	142 (88.8)	0.008
Anosmia/hyposmia	51 (12.8)	3 (5.9)	48 (94.1)	0.001
Nausea and vomiting	126 (31.5)	19 (15.1)	107 (84.9)	0.2
Diarrhea	88 (22)	10 (11.4)	78 (87.6)	0.07
Abdominal pain/dyspepsia	82 (20.5)	8 (9.8)	84 (90.2)	0.03
Anorexia	225 (56.3)	29 (12.9)	196 (87.1)	0.01
Oral aphthous	20 (5)	3 (15)	17 (85)	0.5
Smoking	109 (27.3)	22 (5.5)	87 (21.7)	0.05
Allergic diseases (self-reported)				
Allergic rhinitis	64 (16)	5 (7.8)	59 (92.2)	0.02
Allergic rhinoconjunctivitis	52 (13)	5 (9.6)	47 (90.4)	0.08
Chronic rhinosinusitis	7 (1.8)	0	7 (100)	0.2
Asthma	29 (7.3)	2 (6.9)	27 (93.1)	0.09
Atopic dermatitis	20 (5)	1 (5)	19 (95)	0.1
Chronic urticaria	40 (10)	3 (7.5)	37 (92.5)	0.06
Total	158 (39.5)	16 (10.8)	142 (89.2)	0.005
Comorbid diseases (self-reported)				
Hypertension	99 (24.8)	30 (30.3)	69 (69.7)	0.00
Diabetes mellitus	78 (19.5)	17 (21.8)	61 (78.2)	0.1
Thyroid disorders	26 (6.5)	6 (21.3)	20 (76.9)	0.2
Fatty liver	108 (27)	23 (21.3)	85 (78.7)	0.1
Cardiovascular disorders	65 (16.3)	22 (33.8)	43 (66.2)	0.00
Brain diseases	25 (6.3)	11 (44)	14 (56)	0.001
Kidney diseases	32 (8)	9 (28.1)	23 (71.9)	0.07
Total	260 (65)	53 (20.4)	207 (79.6)	0.009

Table 2 Clinical manifestations and paraclinical data of COVID-19 patients with or without allergic comorbidity.

Variable	Patients with allergic comorbidity, N (%)	Patients without allergic comorbidity, N (%)	P-value
Gender			0.00
Male	63 (30.7)	142 (69.3)	
Female	95 (48.7)	100 (51.3)	
Age group (years)			0.02
<30	23 (51.1)	22 (48.9)	
30–39	42 (50.6)	41 (49.4)	
40–49	35 (39.8)	53 (60.2)	
50–59	22 (33.8)	43 (66.2)	
≥60	36 (30.5)	82 (69.5)	
Fever	104 (65.8)	152 (62.8)	0.3
Cough	112 (70.9)	164 (67.8)	0.2
Fatigue	126 (79.7)	153 (75.6)	0.2
Chest tightness/dyspnea	126 (79.7)	188 (77.7)	0.3
Severe headache	75 (47.5)	85 (35.1)	0.009
Anosmia/hyposmia	32 (20.3)	19 (7.9)	0.00
Nausea and vomiting	70 (44.3)	56 (23.1)	0.00
Diarrhea	37 (23.4)	51 (21.1)	0.3
Abdominal pain/dyspepsia	36 (22.8)	46 (19)	0.2
Anorexia	94 (59.5)	131 (54.1)	0.1
Oral aphthous	11 (7)	9 (3.7)	0.1
Severity of symptoms (VAS; self-reported)			0.3
Mild	70 (44.3)	94 (38.8)	
Moderate	73 (46.2)	115 (47.5)	
Severe	15 (9.5)	33 (13.6)	
WBC (total number)	6900±313	7200±283	0.4
Neutrophil (%)	73.3±12	74.4±12	0.3
Lymphocyte (%)	19.5±9.8	18.4±10.3	0.3
Platelets (n)	215000±8000	212000±5000	0.8
ESR (mm/h)	45.1±2.1	46.6±1.7	0.5
CRP (mg/L)	61±3.7	66.1±2.9	0.2
SGOT (IU/L)	42.7±2.7	44.8±2.3	0.5
SGPT (IU/L)	45.5±3	46.2±3.1	0.8
AP (IU/L)	202.3±11.3	198.2±5.2	0.7
Hypoxemia (SpO ₂ <93%)	54 (34.2)	118 (49)	0.002
CT, chest involvement			0.003
No	18 (11.5)	8 (3.3)	
Mild	24 (15.3)	39 (16.3)	
Moderate	68 (43.3)	92 (38.8)	
Severe	47 (29.9)	102 (42.3)	

WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; AP: alkaline phosphatase.

Allergic comorbidity in COVID-19 patients

The total frequency of allergic comorbidity in COVID-19 patients was 158 (39.5%), and it was reversely associated with the severity of COVID-19 as required for admission in ICU ($P=0.005$, relative risk=0.96; 95% CI: 0.25–0.81). Moreover, a relationship was established between having allergic comorbidity and OPD treatment for COVID-19 ($P=0.02$, relative risk=1.7; 95% CI: 1.03–2.8). Frequency of allergic diseases in COVID-19 patients is shown in [Figure 1](#). The number of patients having asthma was 29 (7.3%). However, no relationship was established between having

asthma and admission in wards ($P=0.4$) or OPD treatment ($P=0.1$). Importantly, only two patients (0.5%) with asthma had acute clinical manifestations of COVID-19 and admitted in the ICU. In addition, of the total number of patients with COVID-19, 64 (16%) had AR; of these 22 (5.5%) were treated as outpatients and 23 (5.7%) were admitted in wards (self-reported). Furthermore, a relationship was observed between having AR and OPD treatment ($P=0.002$); however, no relationship was established between having AR and admission in wards ($P=0.1$). We had only two patients with CRS and nasal polyp (CRSwNP). The frequency of having food or drug allergy and COPD was 13.3% and 6.8%,

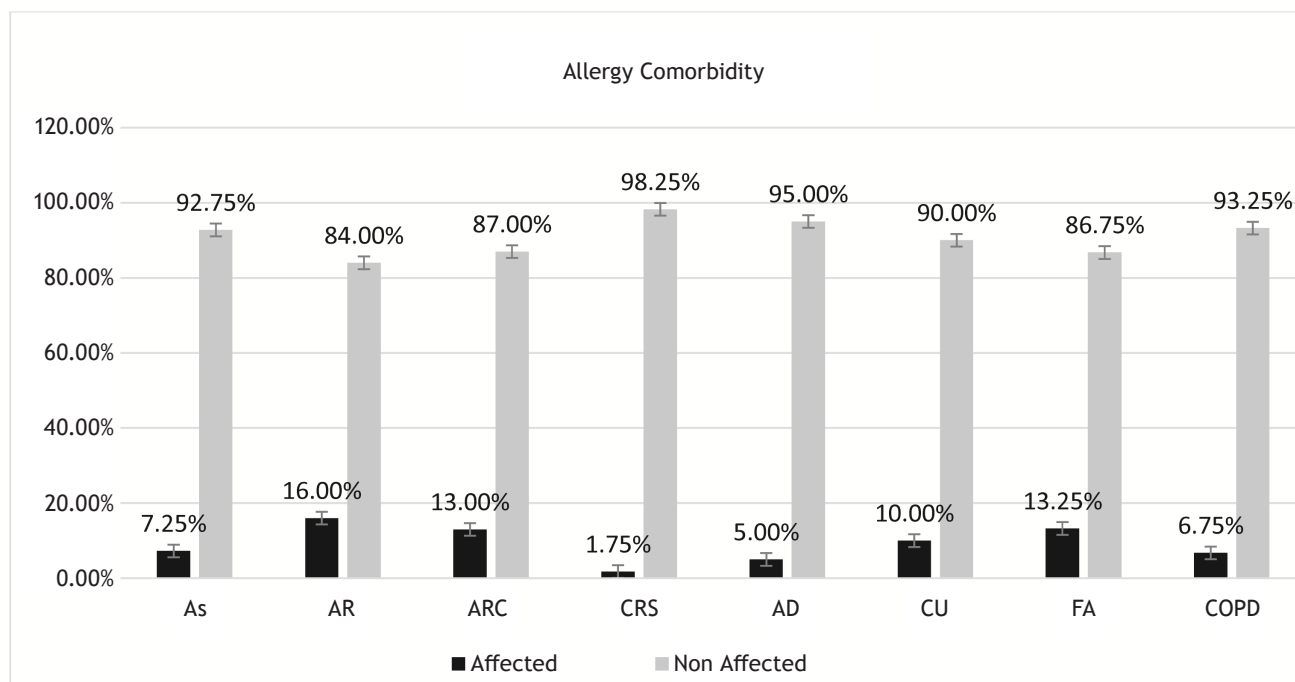


Figure 1. The frequency of allergic diseases in COVID-19 patients. AR: Allergic rhinitis; ARC: Allergic rhinoconjunctivitis; CRS: Chronic rhinosinusitis; AS: Asthma; CU: Chronic urticaria; AD: Atopic dermatitis; FA: Food allergy; COPD: Chronic obstructive pulmonary disease

respectively. It is important to note that no relationship was demonstrated between having comorbidity of atopic dermatitis ($P=0.02$), chronic urticaria ($P=0.02$), or COPD ($P=0.002$) and OPD treatment.

Moreover, in the past 12 months, 3.5% of the patients had reported wheezing or whistling sound in the chest, 2.5% had shortness of breath, 2.5% had an attack of cough, and 2.5% had sputum in the chest. Further, a relationship was demonstrated between having a cough attack and both OPD treatment and patients admitted in wards ($P=0.04$ and 0.01 , respectively). Only 1% of the patients reported reduced feeling or loss of smell in the past 12 months.

It was observed that 54 (34.2%) of the total patients with allergic comorbidity had hypoxemia. A significant difference was observed between having allergic comorbidity and lower presence of hypoxemia during COVID-19 ($P=0.002$, relative risk=0.54; 95% CI: 0.35–0.81). In addition, 94 (23.5%) of the total patients had both allergic and other underlying diseases. In addition, no association was observed between having both allergy and some above-mentioned underlying diseases and severity of COVID-19 ($P>0.05$). The frequency of underlying diseases in COVID-19 patients is shown in Table 1. Finally, 40 (10%) of the total patients were smokers and have allergic diseases simultaneously. However, this condition was not associated with the severity of COVID-19 ($P>0.05$).

Discussion

To the best of our knowledge, this is the first study conducted in Iran considering patients with COVID-19 and its association with the comorbidity of allergic diseases. In the

present study, 400 patients, including ward/ICU admissions and OPD patients, infected with SARS-CoV-2 were examined for allergic diseases.

The total frequency of allergic comorbidity among COVID-19 patients was 39.5%, and it was reversely associated with the severity of COVID-19 manifestations in such a manner that these patients had significantly lower admissions in the ICU than the patients with no signs of allergy. However, there was a significant association between having allergic comorbidity and OPD treatment of COVID-19. Several studies having assessed the association between respiratory viral infection, such as respiratory syncytial virus (RSV) and exacerbation of respiratory allergic diseases, reported that viral infections of the respiratory tract are associated with exacerbation of diseases.^{16,17} It was confirmed that angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), which are expressed in airway epithelial cells, were identified as the main receptors of SARS-CoV-2. Moreover, other studies have reported that patients with allergic respiratory diseases have downregulated ACE2 expression in nasal and bronchial epithelial cells. Further, another study has established that use of inhaled corticosteroids (ICS) was associated with the downregulation of both ACE2 and TMPRSS2 receptors.¹⁸⁻²⁰ Taken together, despite having the presence of allergic diseases in a large proportion of general population; these were not determined to be a predisposing factor for the SARS-CoV-2 infection.

In addition, our study established that asthma was present in 7.3% of the patients, including admitted and OPD patients. According to our previous study, the prevalence of asthma in the region was 10% in general population.²¹ However, in the present study, we noticed that frequency

of asthma among the admitted COVID-19 patients was 5.2%. Therefore, our data revealed that asthmatic patients are less likely to develop COVID-19 as compared to general population. However, a US study conducted on 1526 patients identified with COVID-19 has reported that 14.4% of the patients had asthma. Other recent studies from the United States have demonstrated that the prevalence of asthma in the admitted COVID-19 patients was 7–17%.^{7,13,14} Contrary to the present study, a study conducted in China did not identify any asthmatic case among 140 COVID-19 patients.⁵ Thus, the controversy over prevalence of asthma could be related to geographic variations or different methods of assessment and epidemiologically identified asthma. In addition, our findings were in line with a US study which evidenced that there was no association between asthma comorbidity and the severity of COVID-19 as required for ICU care.¹⁴

The frequency of other allergic diseases such as AR, chronic rhinosinusitis, atopic dermatitis, chronic urticaria, and food or drug allergy in COVID-19 patients was 16%, 1.8%, 5%, 10% and 13.3%, respectively. In addition, the present data depicted that the severity of COVID-19 required for admission in ICU was significantly lower in AR patients, which is not in agreement with the outcome of Chinese study pointing no allergic disease.⁵

We also assessed comorbidities of both allergic and other underlying diseases such as diabetes mellitus, hypertension, cardiovascular, brain, liver, thyroid, and kidney disorders in COVID-19 patients. Interestingly, our data demonstrated that 23.5% of COVID-19 patients had allergic and other underlying diseases as comorbidities. Furthermore, the above-mentioned comorbidities were not associated with the severity of COVID-19. However, recent studies have demonstrated that some underlying diseases such as diabetes mellitus and cardiovascular diseases are the risk factors for COVID-19.^{7,22} The result of our study suggested that comorbidity of allergic diseases and the use of corticosteroids may be downregulating ACE2 and TMPRSS2 receptors, leading to a decrease in the risk of SARS-CoV-2 infection in patients with underlying diseases.¹⁹ In addition, the present study has established that although 10% of the patients had allergic diseases and smoking habit simultaneously, they depicted no association with the severity of COVID-19. Moreover, COPD as an underlying disease witnessed in 6.8% of the patients was not associated with the severity of COVID-19. In the study conducted in China, only two (1.4%) of the 140 patients were reported with COPD, which confirmed that COPD played a minor role in the exacerbation of COVID-19.⁵

Noticeably, the results of the present study indicated that 93.5% of COVID-19 patients had involvement of chest CT scan, and 43% of them presented hypoxemia. Zhang et al. have reported the presence of bilateral ground-glass and patchy opacity in CT scan or X-ray in 89.6% of COVID-19 patients.⁵ Interestingly, our data indicated that patients with allergic diseases had significantly lower hypoxemia and involvement of chest CT.

The data from the present study was in line with other studies expressing that males were more affected with COVID-19 compared to females among admitted and OPD

patients, and the number of males with COVID-19 admitted in ICU was higher than females (10% vs. 7%, respectively). In addition, males were significantly less likely to present allergic diseases than females (30.7% vs. 48.7%, respectively). Further, the data established that most of the patients frequently referred with COVID-19 were aged 60 years and above, and more admissions in ICU were made from this age group than other groups. In addition, the highest frequency of allergic diseases was determined in the age group of 30–35 years.^{4,5,23} Therefore, we conclude that allergic diseases which are more frequent in younger age groups could be due to factors that alleviate the severity of COVID-19 symptoms. However, further investigations are required to determine why these conditions lead to better COVID-19-related outcomes.

The most common symptoms reported in the patients of our study were chest tightness/dyspnea, fatigue, cough, and fever. On the other hand, the study from China has reported that fever, cough, and fatigue were the prior symptoms determined in COVID-19 patients.⁵ Therefore, the frequency of COVID-19 symptoms may vary with diversity in populations.

Limitations

There were several limitations to our study. The first was that since some of the data were obtained from the electronic medical record system of the hospital, we were limited to performing specific tests, such as immunoglobulin E (IgE), for more accurate diagnosis of allergic diseases. The second limitation was that critically ill patients admitted in ICU and wards were less cooperative in answering the related questions.

Conclusion

The present study established that allergic diseases and asthma, present in a large proportion of general population, were not predisposing factors for SARS-CoV-2 infection. Interestingly, the patients with AR developed mild symptoms of COVID-19, and significantly fewer were admitted in ICU as compared to non-AR patients. Moreover, allergic conditions as underlying diseases in COVID-19 patients were not associated with the severity of the disease or the number of admissions in ICU. Finally, the data revealed that more males were affected by COVID-19 and admitted in ICU compared to females.

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Conflict of interest

There were no conflicts of interest in this study.

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