ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.676
Asthma Allergy Immunol 2021;19:174-182

RESEARCH ARTICLE

Received: 30.08.2021 • Accepted: 14.09.2021
Online Published: 14.12.2021

Atopy and Allergic Diseases Have No Impact on the Severity of COVID-19

Ali CAN[1], Deniz Eyice KARABACAK[1], Can TÜZER[1], Alpay Medet ALİBEYOĞLU[2], Murat KÖSE[2], Semra DEMİR[1], Suna BÜYÜKÖZTÜRK[1], Bahauddin ÇOLAKOĞLU[1], Asli GELİNCİK[1]

[1] Department of Internal Medicine, Division of Immunology and Allergic Diseases, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey
[2] Department of Internal Medicine, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Corresponding Author: Ali Can ✉ alican_4040@yahoo.com

ABSTRACT

Objective: The clinical features of COVID-19 range from asymptomatic disease to severe pneumonia or even death. Therefore, many researchers have investigated the factors that could affect the severity of COVID-19. We aimed to assess the impact of aero-allergen sensitization and allergic diseases on the severity of COVID-19.

Materials and Methods: We included 60 adult patients with symptomatic COVID-19 and allocated them into two groups equal in number as having severe and non-severe COVID-19. We evaluated the demographic features and allergic diseases in addition to clinical, laboratory and radiological findings of COVID-19. Skin prick tests (SPTs) with common aero-allergens, serum total IgE levels and blood eosinophil counts were evaluated 3 months after the patient's recovery from COVID-19.

Results: The mean age of the patients was 52 ± 11 years and 73.3% of the patients were male. There was no significant difference between the two groups in terms of age, gender, smoking habits, obesity and comorbidities. Although the frequency of sensitization to aero-allergens and the allergic diseases were similar, the history of allergic diseases in the family was higher in the severe group ($p<0.001$). The polysensitization in SPTs was associated with the presence of a cytokine storm during the infection ($p=0.02$). Total IgE levels and blood eosinophil counts were not significantly different between the two groups.

Conclusion: The presence of atopy or allergic diseases does not seem to be related to the severity of COVID-19. However, polysensitization and a family history of allergic diseases are more prominent in those having a cytokine storm and severe COVID-19, respectively.

Keywords: COVID-19, atopy, allergic disease, aero-allergen sensitization, cytokine storm

INTRODUCTION

After the declaration of the Coronavirus disease 2019 (COVID-19) as a pandemic in March 2020 by the World Health Organisation (WHO), extensive scientific efforts have been put forward by many health authorities that have increased our knowledge about the clinical course of the disease. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause a wide spectrum of clinical features ranging from asymptomatic infection to severe illness and even death. According to the WHO reports, more than 80 million COVID-19 cases have been formally confirmed and more than 1,8 million people have died until the end of the year 2020 (1). The main features of the severe COVID-19 are the presence of a cytokine storm, disseminated intravascular coagulation and/or acute respiratory distress syndrome (2).

Determining the clinical risk factors for severe COVID-19 is an important step in the planning of individual patient care. There are many factors such as old age, male gender, smoking, obesity and the presence of comorbidities including cardiovascular diseases, hypertension, diabetes and chronic respiratory disease that have all been shown to increase the mortality and morbidity rates in COVID-19 (3,4).

ORCID Ali Can / 0000-0001-8239-4071, Deniz Eyice Karabacak / 0000-0001-7627-8621, Can Tüzer / 0000-0002-8028-2647, Alpay Medet Alibeyoğlu / 0000-0002-3024-4036, Murat Köse / 0000-0001-5891-5164, Semra Demir / 0000-0003-3449-5868, Suna Büyüköztürk / 0000-0002-1899-5566, Bahauddin Çolakoğlu / 0000-0002-1851-9826, Asli Gelincik / 0000-0002-3524-9952

T helper 1 (Th1) cells have been found to play a significant role in the cytokine storm observed during the severe course of COVID-19 (2). Th1 and T helper 2 (Th2) responses are in balance in normal individuals but this balance is disrupted in favor of Th2 cells in allergic patients (5). In this sense, it has been speculated that the presence of atopy and/or allergic diseases could be protective against the occurrence of the severe course of COVID-19 considering the predominance of type 2 inflammation in such diseases. Studies examining the influence of atopy or allergic diseases on the course of COVID-19 have yielded conflicting results so far. While some authors reported that the presence of allergic diseases is associated with a more severe disease course (6), others have found that these diseases are related to less disease severity (7-9). This study aimed to investigate the possible relationship between atopic diseases and the severity of COVID-19 by determining the impact of the presence of aero-allergen sensitization and allergic diseases on the clinical course of COVID-19.

MATERIALS and METHODS

Study Design

This prospective study was conducted at the adult allergy outpatient clinic in cooperation with the COVID-19 follow-up clinic at the Istanbul Faculty of Medicine between August and December 2020. Sixty adult patients with symptomatic COVID-19 who were diagnosed as positive with the SARS-CoV-2 polymerase chain reaction test and having compatible clinical features were included in the study. These patients were allocated into two groups as having severe and non-severe COVID-19 according to the diagnostic and treatment guideline for SARS-CoV-2 issued by the Chinese National Health Committee (trial version 7) (10). Three months after the recovery of COVID-19, an allergic diagnostic workup was performed at the allergy outpatient clinic.

To explore the association of allergic diseases and sensitization to aero-allergens with the risk of severe COVID-19, we compared the demographic, clinical and laboratory findings including the diagnostic work-up for allergic diseases of the two groups. The potential confounders on the severity of COVID-19 such as age, sex, obesity (BMI >30), smoking history, comorbidities including diabetes, hypertension and coronary artery disease were also examined.

The study was approved by the Ethics Committee of Istanbul Faculty of Medicine (approval number: 113240) and the Republic of Turkey Ministry of Health's permission (approval number: 2020-06-08T13_14_07) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Clinical and Severity Assessment of COVID-19

Demographic characteristics of the patients including age, gender, smoking habits, body mass index [BMI], comorbidities and family history of allergic diseases were evaluated. The data on clinical presentation and the course of COVID-19, and the initial laboratory and radiological findings of COVID-19 were collected from their medical records. Laboratory findings at the beginning of the COVID-19 diagnosis including complete blood counts, the liver function tests of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, the renal function tests including serum creatinine, C-reactive protein (CRP), procalcitonin (PCT), concentrations of D-dimer, prothrombin time (PT), ferritin and lactate dehydrogenase (LDH) and troponin T as a myocardial injury marker were collected from the patients' medical records. In addition, the chest computed tomography severity score (CT-SS) was used to assess the radiological severity with a threshold of 19.5 points for identifying the severe lung findings of COVID-19 (11).

Severe COVID-19 was defined as the presence of at least one of the following criteria: (a) respiratory distress with respiratory frequency ≥30/min; (b) pulse oximeter oxygen saturation ≤93% at rest; and (c) oxygenation index (artery partial pressure of oxygen/ inspired oxygen fraction, PaO2/FiO2) ≤300mmHg (10). Patients with none of these severity parameters were classified in the non-severe group. Patients were defined as having developed a cytokine storm according to the results of various clinical and laboratory findings (12). Cytokine storm development criteria were met when the patients fulfilled all the entry criteria and at least one criterion per each cluster as shown in Table I.

Diagnostic Work-Up for Allergy

We questioned the presence of previously diagnosed allergic diseases including allergic rhinitis (AR), allergic conjunctivitis and asthma and a detailed history was obtained regarding these allergic diseases. Patients were grouped according to their smoking habits as smokers, non-smokers and ex-smokers.

Table I. Predictive criteria for COVID-19 cytokine storm.

Entry criteria (must be all met)	Cut-off values
+Signs/sympotoms of COVID-19	
±RT-PCR positive for COVID-19	
+GGO by HRCT (or chest X-ray)	
Ferritin	> 250 ng/dl
C reactive protein	> 4.6 mg/dl
AND (one variable from each cluster)	
Cluster I	
Albumin	< 2.8 g/dl
Lymphocytes (%)	< 10.2
Neutrophil Absolute Number	> 11.4 K/mm^3
Cluster II	
ALT	> 60 U/L
AST	> 87 U/L
D-dimers	> 4,930 ng/ml
LDH	> 416 U/L
Troponin I	> 1.09 ng/mL
Cluster III	
Anion gap	< 6.8 mmol/L
Chloride	> 106 mmol/L
Potassium	< 4.9 mmol/L
BUN: Creatinine ratio	> 20 ratio

RT-PCR: Reverse transcriptase-polymerase chain reaction, **GGO:** Ground-glass opacity, **HRCT:** High-resolution computerized tomography, **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **LDH:** Lactate dehydrogenase, **BUN:** Blood urea nitrogen.

Skin prick tests (SPTs) with common inhalant allergens including house dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farinea), molds (Aspergillus fumigatus, Alternaria alternata) and pollens (Grass mix[Holcus lanatus, Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis, Festuca pratensis], Artemisia vulgaris, Chenopodium album, Olea europaea, Urtica dioica, Plantago lanceolata, Betula verrucosa) (Lincoln Diagnostics, Decatur, IL, USA) were performed. Grass mix was accepted as one allergen in the skin prick test. Polysensitization was defined when more than one allergen sensitization was present (13). Serum total IgE levels and peripheral eosinophil counts were measured with peripheral blood samples.

Statistical Analysis

Categorical variables were summarized as frequencies, percentages and continuous variables were described as mean±standard deviation (SD) or median and interquartile ranges (IQR) depending on the distribution of the data. The variables were investigated using analytical methods (Kolmogrov-Smirnov/Shapiro-Wilktest) to determine whether or not they were normally distributed. The Chi-square test or Fisher's exact test (when chi-square test assumptions did not hold due to low expected cell counts) was used to compare proportions in different groups. Student's t-test and Mann-Whitney U test were used to compare the continuous variables among groups as appropriate. The tests with a p value of <.05 were considered as statistically significant. All the analyses were performed with the use of SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and Allergic Clinical Findings of the Study Population

The mean age of the patients was 52 ± 11 years. The majority (73.3%) of the patients were male. Approximately one in 10 patients (11.7%) were at normal weight, while about half (46.7%) of the patients were obese. Twenty (33.3%) patients were smokers among whom the average smoking history was 30 package years. Five (8.3%) patients were ex-smokers and the average time after quitting smoking until now was 3 years. Twenty-five (41.6%) patients were non-smokers (Table II).

More than half (n=33) of the patients had comorbid diseases including diabetes mellitus (n=18), hypertension (n=17), coronary heart disease (n=8), hyperlipidemia (n=8), hypothyroidism (n=6) and benign prostatic hypertrophy (n=3) while 23.3% of the patients had allergic diseases including allergic rhinitis (n=8), allergic conjunctivitis (n=5) and asthma (n=4). Five patients had more than one allergic disease and 23.3% of the patients had a family history of an allergic disease (Table II).

More than half (51.7%) of the patients revealed positive SPT results to at least one aero-allergen and the most common positivity was for pollens. The most common allergen sensitivities detected among patients in order of frequency were grass-mix pollen (n=14), Dermatophagoides pteronyssinus (n=13),

Table II. Comparison of the demographic and clinical features of the patients with severe and non-severe COVID-19

Demographic and clinical characteristics	Severe COVID-19 (n=30)	Non-severe COVID-19 (n=30)	p
Age, mean ± SD, years	52 ± 11	52 ± 11	NS
Male/female, n	22/8	22/8	NS
Smokers, n (%)	9 (30)	11 (36.6)	NS
Family history of allergic diseases, n (%)	11 (36.7)	3 (10)	**<0.001**
Presence of comorbid diseases, n (%)	15 (50)	18 (60)	NS
Obesity, n (%)	13 (43.3)	15 (50)	NS
Diabetes mellitus, n (%)	9 (30)	9 (30)	NS
Hypertension, n (%)	8 (26.7)	9 (30)	NS
Coronary heart disease, n (%)	3 (10)	5 (16.7)	NS
Hyperlipidemia, n (%)	5 (16.7)	3 (10)	NS
Hypothyroidism, n (%)	3 (10)	3 (10)	NS
Benign prostatic hypertrophy, n (%)	1 (3.3)	2 (6.7)	NS
Presence of allergic diseases, n (%)	6 (20)	5 (16.7)	NS
Allergic rhinitis, n (%)	6 (20)	2 (6.7)	NS
Allergic conjunctivitis, n (%)	2 (6.7)	3 (10)	NS
Asthma, n (%)	2 (6.7)	2 (6.7)	NS
Skin test positivity, n (%)	16 (53.3)	15 (50)	NS
Pollens, n (%)	14 (46.6)	12 (40)	NS
House dust mites, n (%)	8 (26.6)	10 (33.3)	NS
Molds, n (%)	2 (6.7)	0 (0)	NS
Number of positive SPT results, median(IQR)	1 (0-3)	1 (0-2)	NS
Clinical findings of COVID-19			
Fatigue, n (%)	30 (100)	22 (73.3)	**0.002**
Shortness of breath, n (%)	30 (100)	18 (60)	**<0.001**
Headache, n (%)	21 (70)	18 (60)	NS
Fever, n (%)	24 (80)	13 (43.3)	**0.003**
Cough, n (%)	21 (70)	13 (43.3)	**0.03**
Back pain, n (%)	17 (56.7)	14 (46.7)	NS
Diarrhea, n (%)	13 (43.3)	14 (46.7)	NS
Chest pain, n (%)	16 (53.3)	10 (33.3)	NS
Loss of smell, n (%)	13 (43.3)	13 (43.3)	NS
Nausea-Vomiting, n (%)	17 (56.7)	7 (23.3)	**0.008**
Losing weight, n (%)	15 (50)	9 (30)	NS
Sore throat, n (%)	12 (40)	11 (36.7)	NS
Runny nose, n (%)	8 (26.7)	1 (3.3)	**0.01**
Laboratory and radiologic findings of COVID-19 (Unit;reference range)			
ALT (U/L; 5-45)	96 (55-207)	24 (18-53)	**<0.001**
AST (U/L; 5-42)	78 (54-125)	24 (18-39)	**<0.001**
Creatinine (mg/dl; 0.7-1.4)	0.95 (0.8-1.1)	0.9 (0.76-1.08)	NS
LDH (U/L;135-250)	457 (408-561)	213 (187-256)	**<0.001**

Table II continue

Albumin (g/dl; 3.2-5.5)	3.3 (2.9-3.5)	4.3 (3.8-4.6)	**<0.001**
Ferritin (ng/ml; 30-400)	1131 (651-1909)	177 (76-320)	**<0.001**
CRP (mg/dl; 0-5)	113 (73-171)	7 (3-38)	**<0.001**
PCT (ng/ml; 0-0.05)	0.22 (0.08-0.45)	0.05 (0.02-0.07)	**<0.001**
Troponin T (pg/ml; 0-14)	8 (7-10)	6 (3-11)	NS
Total bilirubin (mg/dl; 0.2-1.2)	0.6 (0.5-0.8)	0.4 (0.3-0.6)	**<0.001**
PT (s;10-15)	14 (14-15)	13 (12-14)	**<0.001**
Platelets($\times10^9$/L; 155-375)	165 (132-225)	203 (173-238)	**0.04**
Leukocytes ($\times10^9$/L; 4.3-10.3)	9.22 (7.40-12.0)	6.64 (6.16-7.45)	**<0.001**
Neutrophils ($\times10^9$/L; 2.8-11)	6.99 (5.58-9.96)	3.95 (3.37-4.84)	**<0.001**
Lymphocytes ($\times10^9$/L; 1.2-3.6)	0.68 (0.54-0.92)	1.75 (1.27-2.3)	**<0.001**
Eosinophils ($\times10^9$/L; 0.05-0.6)	0.01 (0.01-0.01)	0.09 (0.01-0.1)	**<0.001**
Baseline eosinophils($\times10^9$/L; 0.05-0.6)	0.2 (0.10-0.22)	0.2 (0.1-0.2)	NS
Total IgE (IU/ml; 0-100)	39 (19-100)	58 (19-100)	NS
D-dimer (μg/L; 0-550)	1710 (1068-5615)	420 (338-765)	**<0.001**
Severe radiological involvement, n (%)	22 (73.3)	0 (0)	**<0.001**

Note: Measurement of laboratory parameters is shown as median (IQR). **NS:** Non-significant, **SPT:** Skin prick test

Dermatophagoides farinea (n=12), Artemisia vulgaris (n=6), Chenopodium album (n=4), Betula verrucosa (n=3), Plantago lanceolate (n=2), Olea europaea (n=2), Urtica dioica (n=2), Aspergillus fumigatus (n=2) and Alternaria alternate (n=1). We found that while 38.7% of the patients had two allergen positivity 22.6% had only one allergen positivity in SPTs (Table II).

Clinical, Laboratory and Radiological Findings of COVID-19

The distribution of the symptoms, the laboratory and radiological findings are shown in Table II. All patients were symptomatic during the COVID-19 and the most common symptom was fatigue (86.6%). The blood leukocyte count was normal in most of the patients (75%) whereas it was high in 23.3% and low in 1.7% of the patients on the day of hospital admission. Blood neutrophil counts were also normal in 83.3%, high in 11.7% and low in 5% of the patients. More than half of the patients (53.3%) had lymphopenia. Eosinopenia was common in 61.7% of the patients during COVID-19 whereas blood eosinophil counts measured 3 months after recovery were mostly normal (95%). The eosinophil counts were significantly lower at the time of admission when compared to levels 3 months after recovery in all patients (p<0.0001). Other laboratory results including higher serum concentrations of CRP (76.7%), D-dimer (68.3%), PCT (65%), LDH (63.3%) and ferritin (51.7%) were found in all patients.

Pulmonary infiltrations in chest tomography were detected in the majority of the patients (88.3%) and these infiltrations were usually bilateral (96.2%). According to the radiological severity evaluation, these were graded as severe in 22 (36.7%) patients and non-severe in 38 (63.3%).

Comparison of the Findings of the Patients with Severe and Non-Severe COVID-19

The clinical findings of COVID-19 including fatigue (p=0.02), fever (p=0.003), cough (p=0.03), nausea/vomiting (p=0.08), runny nose (p=0.01) and shortness of breath (p<0.001) were higher in the severe group but there were no significant differences in terms of other clinical findings. While AST (p<0.001), ALT (p<0.001), LDH (p<0.001), ferritin (p<0.001), CRP (p<0.001), PCT (p<0.001), total bilirubin (p<0.001), D-dimer (p<0.001), PT values (p<0.001), leukocyte (p<0.001) and neutrophil counts (p<0.001) were higher, serum albumin levels (p<0.001), platelet (p=0.04), lymphocyte (p<0.001) and eosinophil counts (p<0.001) were lower in the severe group than in the non-severe group. Severe radiological involvement was more frequent in the severe group than in the non-severe group (p<0.001). The demographic

features such as age, gender, obesity, smoking history and clinical characteristics including comorbidities were similar in both groups (Table II).

While there were no significant differences between the two groups in terms of the presence of allergic diseases, a family history of allergic diseases was more common in the severe group ($p<0.001$). The positivity rate of SPTs with aeroallergens was similar in both groups and there was no difference between the two groups in terms of the number of positive SPT results. The results of the diagnostic workup for allergic diseases among the two groups are shown in Table II.

The presence of an allergic disease and the family history of allergic diseases were similar in patients with and without a cytokine storm. However, the presence of polysensitization in SPTs was higher in patients who had experienced a cytokine storm during COVID-19 ($p=0.02$). There was no difference in serum baseline eosinophil counts and total IgE levels in patients with and without cytokine storm (Table III).

DISCUSSION

This novel prospective study investigates the role of atopy and allergic diseases on the severity of COVID-19 by matching other confounding risk factors in both groups that affect disease severity irrespective of initially knowing the presence of allergic complaints. Our main finding is that the presence of atopy and allergic diseases confirmed with allergic diagnostic workup does not seem to affect the severity of symptoms seen during the infection since the frequency of allergic diseases, SPT results with aero-allergens, serum total IgE levels and baseline blood eosinophil counts were found to be similar between the severe and non-severe COVID-19 patients. However, patients with a family history of allergic diseases had a more severe infection. In addition, the number of positive allergens in SPTs was higher in patients who had developed a cytokine storm during the infection.

After the COVID-19 infection had turned into a pandemic, many studies focused on determining the factors affecting the severity of the disease. At first, it was claimed that the allergic diseases are not a risk factor of severe COVID-19 (14). In a subsequent large study of 530 hospitalized COVID-19 patients, it was stated that the COVID-19 infection was milder in patients with an atopic disease (7). In this retrospective study, atopy was confirmed with SPTs with aero-allergens or specific IgE positivity in some patients within the whole group before hospitalization but patients with mild symptoms who had spent the disease duration at their homes were not included in the study. In addition, risk factors for more severe infection including gender and the number of patients were not well-balanced among the patient groups. However, a further nation-wide cohort study showed that the COVID-19 infection was more severe in atopic patients (6). In this study, while severe COVID-19 was associated with allergic rhinitis, it was interestingly more frequent in non-allergic asthmatics than in allergic asthmatic patients (6). In the current study, the analyzed data was obtained from medical records from the past 3 years that may cause an underestimation in the diagnosis of allergic diseases. Since the methodology of these studies and the studied populations are different, a conclusive statement seems hard to reach. In this sense, we believe that the detailed allergy diagnostic work-up that we have performed during face-to-face visits in all patients irrespective of allergic complaints and the prospective design of our study has improved the strength of our data.

Th2 responses are mostly associated with defensive responses to helminths and inflammation caused by allergens (15). Th2 responses are dominant in allergic or atopic individuals (5). On the other hand, it has been reported that type 2 immune modulation decreases the expression of angiotensin-converting enzyme 2, the receptor used by the SARS-CoV-2 to enter the cell (16,17). Furthermore, Th1 cells related hyperinflammation play a major role in cytokine storm, the most important cause of mortality in COVID-19 (2). Therefore, it was speculated that in patients with dominant type 2 inflammation due to the presence of allergic diseases or atopy, the course of COVID-19 might be less severe than in patients without atopy (7). However, we did not observe such an association in our study with objective laboratory parameters related to Th2 responses in severe and non-severe COVID-19 patients. In previous studies, serum total IgE levels (8) and blood eosinophil counts (8,18) were evaluated. In addition to these tests, the SPTs performed in all COVID-19 patients in our study strengthened our findings.

The presence of an allergic disease in the family history was associated with a severe course of COVID-19 and polysensitization was more frequent in patients having a cytokine storm during the infection in our study. However the atopic status in our patients does not seem to affect

Table III. Comparison of the demographic and clinical features of the patients with and without cytokine storm

Demographic and clinical characteristics	Presence of cytokine storm (n=18)	Lack ofcytokine storm(n=42)	p
Age, mean ± SD, years	51± 9	52 ± 12	NS
Male/female, n	15/3	29/13	NS
Smokers, n (%)	5 (27.8)	15 (35.7)	NS
Family history of allergic diseases, n (%)	7 (38.9)	7 (16.7)	NS
Presence of comorbid diseases n (%)	9 (50)	24 (57.2)	NS
Obesity, n (%)	8 (44.4)	20 (47.6)	NS
Diabetes mellitus, n (%)	5 (27.8)	13 (31)	NS
Hypertension, n (%)	6 (33.3)	11 (26.2)	NS
Coronary heart disease, n (%)	2 (11.1)	6 (14.3)	NS
Hyperlipidemia, n (%)	4 (16.7)	4 (10)	NS
Hypothyroidism, n (%)	1 (5.6)	5 (11.9)	NS
Benign prostatic hypertrophy, n (%)	1 (5.6)	2 (4.8)	NS
Presence of allergic diseases, n (%)	4 (22.2)	7 (16.7)	NS
Allergic rhinitis, n (%)	4 (22.2)	4 (9.5)	NS
Allergic conjunctivitis, n (%)	2 (11.1)	3 (7.1)	NS
Asthma, n (%)	1 (5.6)	3 (7.1)	NS
Skin test positivity, n (%)	12 (66.7)	19 (45.2)	NS
Pollens, n (%)	10 (55.6)	16 (38.1)	NS
House dust mites, n (%)	7 (38.9)	11 (26.2)	NS
Molds, n (%)	2 (11.1)	0 (0)	NS
Number of positive SPT results, median(IQR)	2 (0-4)	0 (0-2)	**0.02**
Clinical findings of COVID-19			
Fatigue, n (%)	18 (100)	34 (81)	**0.04**
Shortness of breath, n (%)	18 (100)	30 (71.4)	**0.01**
Headache, n (%)	12 (66.7)	27 (64.3)	NS
Fever, n (%)	16 (88.9)	21 (50)	**0.005**
Cough, n (%)	15 (83.3)	19 (45.2)	**0.006**
Back pain, n (%)	8 (44.4)	23 (54.8)	NS
Diarrhea, n (%)	9 (50)	18 (42.9)	NS
Chest pain, n (%)	13 (72.2)	13 (31)	**0.003**
Loss of smell, n (%)	7 (38.9)	19 (45.2)	NS
Nausea-Vomiting, n (%)	9 (50)	15 (35.7)	NS
Losing weight, n (%)	10 (55.6)	14 (33.3)	NS
Sore throat, n (%)	9 (50)	14 (33.3)	NS
Runny nose, n (%)	5 (27.8)	4 (9.5)	NS
Laboratory and radiologic findings of COVID-19 (Unit;reference range)			
ALT (U/L; 5-45)	142 (70-254)	33 (20-59)	**<0.001**
AST (U/L; 5-42)	100 (69-188)	32 (20-55)	**<0.001**
Creatinine (mg/dl; 0.7-1.4)	1 (0.8-1.1)	0.9 (0.79-1.1)	NS
LDH (U/L;135-250)	540 (453-673)	234 (198-311)	**<0.001**

Table II continue

Albumin (g/dl; 3.2-5.5)	3.3 (2.9-3.5)	4.1 (3.4-4.4)	**<0.001**
Ferritin (ng/ml; 30-400)	1561 (825-2110)	278 (103-658)	**<0.001**
CRP (mg/dl; 0-5)	140 (97-197)	28 (4-74)	**<0.001**
PCT (ng/ml; 0-0.05)	0.36 (0.17-0.53)	0.05 (0.03-0.11)	**<0.001**
Troponin T (pg/ml; 0-14)	8 (7-11)	7 (3-10)	NS
Total bilirubin (mg/dl; 0.2-1.2)	0.6 (0.5-0.8)	0.5 (0.4-0.6)	**0.008**
PT (s;10-15)	15 (14-16)	13 (12-14)	**0.002**
Platelets($\times10^9$/L; 155-375)	154 (93-208)	198 (168-238)	**0.02**
Leukocytes ($\times10^9$/L; 4.3-10.3)	10.73 (8.4-13.04)	6.82 (6.34-8)	**<0.001**
Neutrophils ($\times10^9$/L; 2.8-11)	6.87 (6.35-11.37)	4.4 (3.67-6.62)	**<0.001**
Lymphocytes ($\times10^9$/L; 1.2-3.6)	0.64 (0.4-0.8)	1.45 (0.89-2.05)	**<0.001**
Eosinophils ($\times10^9$/L; 0.05-0.6)	0.01 (0.01-0.01)	0.55 (0.01-0.1)	**0.001**
Baseline eosinophils($\times10^9$/L; 0.05-0.6)	0.2 (0.1-0.2)	0.2 (0.1-0.22)	NS
Total IgE (IU/ml; 0-100)	40 (28-109)	51 (17-100)	NS
D-dimer (µg/L; 0-550)	1945 (1270-8075)	610 (375-1397)	**<0.001**
Severe radiological involvement, n (%)	15 (83.3)	7 (16.7)	**<0.001**

Note: Measurement of laboratory parameters is shown as median (IQR). **NS:** Non-significant, **SPT:** Skin prick test.

their infection course at present. This observation is difficult to explain considering conflicting data about COVID-19 in relation to atopy. However, we may speculate that atopy in the family history can play a role as a risk factor for the development of atopic diseases in the future and can therefore act as a risk factor for more severe viral infections (19). Interestingly, it was shown that serum interferon (IFN) levels, which are known to act in the anti-viral defense mechanisms, are higher in monosensitized individuals than in polysensitized individuals in a previous study (20). Patients with an allergic disease can have a decreased secretion of IFN-I and IFN-III in the epithelial cells of the airway in relation to various respiratory viral infections (21). There are other studies supporting that interferon production is defective in individuals with atopic asthma and atopic dermatitis compared to normal individuals (22,23). We can speculate that polysensitization seen among our patients with a cytokine storm may be related to decreased interferon secretions, which in turn may cause a severe course of the COVID-19.

There are a few limitations of our study. Our single-center study with a small sample size and a short follow-up time can be considered as limited to draw a definite conclusion. However, the prospective design with its detailed allergy diagnostic work-up in every symptomatic COVID-19 patient is the strongest feature of our study. In addition, the number of asthmatic patients among our patients was very low to make conclusive suggestions. Finally, the allergy work-up was performed after the recovery of the infection, considering the risk of viral transmission during face-to-face contacts, which may cause an underestimation in determining atopy since it was not performed during the infection. However, we believe a three-month period is not too long after a contagious infection.

CONCLUSION

The current study indicates that the presence of allergic diseases and sensitization to aeroallergens does not affect the likelihood of more severe COVID-19. However, the presence of polysensitization and a family history of allergic diseases can be considered as a sign for a cytokine storm and a more serious infection, respectively. To date, it is hard to reach a consensus on the relationship between COVID-19 and atopic/allergic diseases. Further multicenter large cohort studies searching inflammatory markers are needed to verify the possible relationship between atopic diseases and COVID-19.

ACKNOWLEDGEMENTS

The study received no funding sources.

CONFLICT of INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19): situation report. 2020 Access date: 1 January 2021. Available from: http://www.who.int.
2. Azkur AK, Akdis M, Azkur D, Sokolowska M, Veen W, Brügggen MC, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020;75: 1564-81.
3. Rod JE, Oviedo-Trespalacios O, Cortes-Ramirez J. A brief-review of the risk factors for covid-19 severity. Rev Saude Publica 2020;54:60.
4. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. Int J Infect Dis 2020;94: 91-5.
5. Romagnani S. Immunologic influences on allergy and the TH1/TH2 balance. J Allergy Clin Immunol 2004;113:395-400.
6. Yang JM, Koh HY, Moon SY, Yoo IK, Ha EK, You S, et al. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. J Allergy Clin Immunol 2020;146:790-8.
7. Scala E, Abeni D, Tedeschi A, Manzotti G, Yang B, Borrelli P, et al. Atopic status protects from severe complications ofCOVID-19. Allergy 2021;76:899-902.
8. Shi W, Gao Z, Ding Y, Zhu T, Zhang W, Xu Y. Clinical characteristics of COVID-19 patients combined with allergy. Allergy 2020;75: 2405-8.
9. Wang L, Foer D, Bates DW, Boyce JA, Zhou L. Risk factors for hospitalization, intensive care, and mortality among patients with asthma and COVID-19. J Allergy Clin Immunol 2020;146: 808-12.
10. Pei-Fang Wei , editors. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl) 2020;133(9):1087-95.
11. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, Luo Y, Gao C, Zeng W. Chest CT severity score: An imaging tool for assessing severe COVID-19. Radiol Cardiothorac Imaging 2020;2(2):e200047.
12. Caricchio R, Gallucci M, Dass C, Zhang X, Gallucci S, Fleece D, et al. Preliminary predictive criteria for COVID-19 cytokine storm. Ann Rheum Dis 2021;80:88-95.
13. Migueres M, Davila I, Frati F, Azpeitia A, Jeanpetit Y, Barrand ML, et al. Types of sensitization to aeroallergens: Definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. Clin Transl Allergy 2014;4:16.
14. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang TB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730-41.
15. Licona-Limón P, Kim LK, Palm NW, Flavell RA. TH2, allergy and group 2 innate lymphoid cells. Nat Immunol 2013;14:536-42.
16. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426:450-4.
17. Chhapola Shukla S. ACE2 expression in allergic airway disease may decrease the risk and severity of COVID-19. Eur Arch Otorhinolaryngol 2020;278:2637-40.
18. Xie G, Ding F, Han L, Yin D, Lu H, Zhang M. The role of peripheral blood eosinophil counts in COVID-19 patients. Allergy 2021;76:471-82.
19. Turner KJ. Epidemiology of atopic disease. In: Lessof MH, Lee TH, Kemeny CM, editors. Allergy: An international textbook. Williams & Wilkins; Baltimore: 1987.337-46.
20. Prigione I, Morandi F, Tosca MA, Silvestri M, Pistoia V, Ciprandi G, Rossi GA. Interferon-gamma and IL-10 may protect from allergic polysensitization in children: Preliminary evidence. Allergy 2010;65(6):740-2.
21. Edwards MR, Strong K, Cameron A, Walton RP, Jackson DJ, Johnston SL. Viral infections in allergy and immunology: How allergic inflammation influences viral infections and illness. J Allergy Clin Immunol 2017;140:909-20.
22. Papadopoulos NG, Stanciu LA, Papi A, Holgate ST, Johnston SL. A defective type 1 response to rhinovirus in atopic asthma. Thorax 2002;57:328-32.
23. Campbell DE, Fryga AS, Bol S, Kemp AS. Intracellular interferon-gamma (IFN-gamma) production in normal children and children with atopic dermatitis. Clin Exp Immunol 1999;115:377-82.