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Letters

Asthma in older adults with severe coronavirus disease 2019
Clinical outcomes and predictors of mortality

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To date, numerous studies have evaluated the relationship between coronavirus disease 2019 (COVID-19) and asthma; however, the impact of asthma on COVID-19–associated outcomes remains controversial and not fully understood.[1-3] It is possible that these contradictions can be explained in terms of asthma heterogeneity. There are data to suggest that asthma in older adults is phenotypically different from that in young patients, particularly when physiological changes associated with the aging process are taken into account.[4] Because old age is a well-known factor of a poor prognosis in COVID-19,[5] it is of great interest to study the course of COVID-19 in older patients with asthma.

This observational study was conducted in the Pulmonology department of a university-affiliated hospital between May 12, 2020 and December 27, 2020. Given that this was a retrospective study, the requirement for informed consent was waived. We enrolled patients older than 65 years old with physician-diagnosed asthma admitted with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by real-time polymerase chain reaction, radiological findings compatible with severe COVID-19 pneumonia, and blood oxygen saturation on admission of less than 92% (on room air). The exclusion criteria were nonasthma chronic lung diseases. The diagnostic criteria of allergic asthma were those of the guidelines of the Global Initiative for Asthma: exposure to the allergen induces or aggravates the symptoms and the skin prick test and serum specific immunoglobulin E test exhibiting positive responses to at least 1 allergen.[6] Demographic, clinical, and laboratory data were recorded at admission. We recorded the Charlson comorbidity index (CCI), which calculates the score for comorbidities according to the relative risks of 19 major diseases, including ischemic heart disease, diabetes, and hypertension. We also analyzed the outcomes of COVID-19, such as transfer to the intensive care unit, the need for noninvasive and invasive mechanical ventilation, and 28-day mortality.

The objectives of this study were: (1) to investigate the influence of asthma in older adults on COVID-19 outcomes, and (2) to identify predictors of in-hospital mortality of older patients with asthma and COVID-19. Cox proportional hazard models were used to estimate the association between asthma and in-hospital mortality; the models were adjusted for age, sex, and comorbidities.

Of the 2435 patients hospitalized with COVID-19 infection, 69 patients met the necessary diagnostic criteria (2.8%). Baseline characteristics of the study population are detailed in Table 1. Most patients had a nonallergic asthma phenotype (44 patients, 63.8%) and multiple comorbidities (the median CCI was 5.3). A total of 19 of the included patients (27.5%) were receiving Global Initiative for Asthma step 4 to 5 therapies; 12 patients (17.4%) and 4 patients (5.8%) were treated before admission with maintenance oral steroids and biologic therapy (omalizumab [n = 2], mepolizumab [n = 2]), respectively.

During hospitalization, all patients received the standard therapy including prophylactic enoxaparin, intravenous dexamethasone, and tocilizumab. Supplemental oxygen was administered in all patients (100%); noninvasive ventilation and invasive mechanical ventilation were used in 6 (8.6%) and 7 (10.1%) patients, respectively. Twelve patients (17.3%) were transferred to the intensive care unit and the 28-day mortality rate was 13% (9 patients). All patients who died had nonallergic asthma. There was a significant difference in the proportion of patients with severe asthma among deceased and surviving patients (56% vs 13%; P =.01). Patients who died from COVID-19 used maintenance oral steroids more often than survivors (44% vs 13%, P =.04).

Patients who died had higher CCI, higher body temperature at admission, higher respiratory rate, and a higher baseline blood neutrophil count, neutrophil/lymphocyte ratio, fibrinogen, lactate dehydrogenase, glucose levels, and C-reactive protein at day 5 compared with survivors. The Cox regression analysis identified the following variables predicting poor outcomes: CCI (risk ratio [RR], 1.67 [1.11-2.53]), body temperature (RR, 3.73 [1.31-10.6]), severe asthma (RR, 2.75 [1.08-6.99]), nonallergic asthma (RR, 7.95 [1.06-14.30]), and the long-term oral steroid use (RR, 2.57 [1.01-6.53]). The risk of death was not associated with an increased or decreased eosinophil count (Cox regression; P =.57 and P =.53 for percentage and absolute values, respectively).

In a recently published study, Eggert et al[7] reported that among patients with asthma positive for SARS-CoV-2, the allergic asthma phenotype was associated with a reduced risk of hospital admissions, meaning that certain phenotypes of asthma may be protective. The role of allergic asthma diminishes with age; hence a different phenotype presents in older adults with normal eosinophils and elevated sputum neutrophils.[4] Interestingly, in our study, all deceased patients had a nonallergic asthma phenotype. In addition, as recently reported in a study by Schleich et al,[4] older adults with asthma are characterized by poorer lung function and higher bronchial neutrophilic inflammation. Recent publications have suggested that allergic status and type 2 inflammation may decrease susceptibility to SARS-CoV-2 infection and protect against the most severe consequences of COVID-19.[8] Ferastraoaru et al[9] in their retrospective study found that, in patients with asthma, preexisting blood eosinophilia greater than or equal to 150 cells/mL was protective from COVID-19–associated admission. In our cohort of older adults with asthma, we were unable to find differences in eosinophilia levels between deceased and surviving patients. However, it cannot be ruled out that the blood eosinophil counts did not differ significantly owing to the outpatient and inpatient use of systemic steroids. In our study, therapy with

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Table 1
Demographic, Clinical, and Laboratory Characteristics of Older Patients With Asthma and Severe Coronavirus Disease 2019

Parameters	Allpatients(n = 69)	Survived patients(n = 60)	Deceasedpatients(n = 9)	*P* value[a]
Age, y	71 (67-80)	70 (66-80)	72 (68-85)	.33
Sex (male/female)	30/39	24/36	6/3	.16
Smoking history, pack-y	45 (32-50)	48 (45-55)	32 (20-45)	.52
BMI, kg/m^2	28.2 (24.7-33.2)	28.1 (23.2-33.8)	28.0 (27.3-32.4)	.69
CCI, points	5.3 (4-7)	5.0 (3-6)	7.0 (6-7.5)	.003
Arterial hypertension, n (%)	31 (44.9)	25 (41.7)	6 (66.7)	.30
Ischemic heart disease, n (%)	18 (26.1)	14 (23.3)	4 (44.4)	.26
Atrial fibrillation, n (%)	25 (36.2)	20 (29.0)	5 (55.6)	.52
Obesity, n (%)	30 (43.5)	25 (41.7)	5 (55.6)	.42
Diabetes mellitus, n (%)	20 (28.9)	17 (28.3)	3 (33.3)	.54
Chronic kidney disease, n (%)	9 (13.0)	6 (10.0)	3 (33.3)	.14
Allergic asthma phenotype, n (%)	22 (31.9)	22 (36.7)	0 (0)	.05
Oral steroids, n (%)	12 (17.4)	8 (13.3)	4 (44.4)	.04
Biologic therapy, n (%)	4 (5.8)	4 (6.7)	0 (0)	.58
Body temperature, °C[b]	37.1 (36.9-37.6)	37.0 (36.8-37.5)	37.8 (37.5-38.5)	.006
Respiratory rate, min^{-1}	23 (22-24)	23 (22-24)	25 (24-26)	.02
Heart rate, min^{-1}	83 (74-94)	82 (74-95)	84 (75-90)	.57
SpO_2/FiO_2	207 (175-229)	209 (171-229)	206 (187-323)	.64
Leukocytes, 10^9/L	6.2 (4.7-8.9)	6.1 (4.6-8.2)	8.9 (6.1-9.3)	.13
Neutrophils, 10^9/L	4.6 (2.8-10.8)	3.8 (2.8-6.2)	7.3 (5.1-8.2)	.05
Lymphocytes, 10^9/L	0.9 (0.6-1.4)	1.0 (0.7-1.4)	0.7 (0.4-0.9)	.06
Neutrophil/lymphocyte ratio	4.5 (2.6-10.3)	3.5 (2.3-7.2)	10.7 (7.1-11.2)	.02
Eosinophils, %	0.6 (0.3-2.0)	1.0 (0.3-3.0)	0.4 (0.2-1.3)	.15
Eosinophils, 10^9 /L	0.1 (0.07-0.2)	0.1 (0.03-0.2)	0.1 (0.07-0.1)	.46
Fibrinogen, g/L	5.1 (4.2-8.9)	4.9 (3.9-7.8)	11.4 (10.3-12.4)	.04
D-dimer, mg/L	0.9 (0.4-1.1)	0.7 (0.4-1.2)	1.0 (0.8-5.0)	.21
CRP at admission, mg/L	40.0 (14.4-73.2)	34.9 (10.6-70.9)	50.0 (35.1-105.9)	.17
CRP at day 5, mg/L	17.7 (3.5-30.2)	8.6 (2.8-24.3)	39.1 (20.3-170.9)	.007
Creatinine, μmol/L	90.8 (80.2-103.3)	90.2 (78.4-100.1)	97.8 (82.4-110.9)	.39
Glucosa, mmol/L	6.6 (5.7-8.1)	6.5 (5.5-7.8)	8.0 (7.3-10.2)	.02
ALT, U/L	28.7 (17.7-42.8)	30.4 (16-44)	24.5 (19.2-58)	.79
AST, U/L	34.4 (25-49.6)	31.5 (24.9-47.3)	36.5 (28-60.5)	.59
LDH, U/L	536 (399-694)	445 (382-664)	701 (532-1155)	.03
CT, % of lung involvement	30 (25-70)	30 (25-50)	50 (25-75)	.66

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCI, Charlson comorbidity index; CRP, C-reactive protein; CT, computed tomography; FiO_2, inspired oxygen fraction; IQR, interquartile range; LDH, lactate dehydrogenase; SpO_2, oxygen saturation.
NOTE. Continuous variables are presented as median value (IQR).
[a]Mann-Whitney test was used.
[b]The highest temperature during the day was recorded.

maintenance oral steroids in older adults with asthma was a risk factor for poor prognosis. Similar data were presented in a recent study by Adir et al,[10] who also reported that systemic steroid use was significantly associated with an increased risk of severe COVID-19 and all-cause mortality. In contrast to the study by Adir et al,[10] in our study, all patients had severe COVID-19 and all received intravenous dexamethasone during hospitalization. Despite this, long-term use of steroids turned out to be a factor of poor prognosis.

Our study has several limitations. It was a retrospective study performed in a single-center, and statistical analysis and interpretation of our study results are further limited by its relatively small sample size.

Therefore, our study provided evidence that nonallergic asthma phenotype, asthma severity, systemic steroid use, and comorbidities may be risk factors for poor outcomes in older patients with asthma and severe COVID-19. However, further large cohort studies are needed to evaluate the effect of asthma severity and phenotypes on COVID-19 outcomes in older adults.

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References

1. Heffler E, Detoraki A, Contoli M, et al. COVID-19 in severe asthma network in Italy (SANI) patients: clinical features, impact of comorbidities and treatments. *Allergy*. 2021;76(3):887–892.
2. Rosenthal JA, Awan SF, Fintzi J, Keswani A, Ein D. Asthma is associated with increased risk of intubation but not hospitalization or death in coronavirus disease 2019. *Ann Allergy Asthma Immunol*. 2021;126(1):93–95.
3. Avdeev S, Moiseev S, Brovko M, et al. Low prevalence of bronchial asthma and chronic obstructive lung disease among intensive care unit patients with COVID-19. *Allergy*. 2020;75(10):2703–2704.
4. Schleich F, Graff S, Guissard F, Henket M, Paulus V, Louis R. Asthma in elderly is characterized by increased sputum neutrophils, lower airway caliber variability and air trapping. *Respir Res*. 2021;22(1):15.

5. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763–1770.
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021. Available at: http://www.ginasthma. Accessed September 28, 2020.
7. Eggert LE, He Z, Collins W, et al. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19 [e-pub ahead of print]. *Allergy*. doi:10.1111/all.14972, accessed September 28, 2020.
8. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol*. 2020;146(1):203–206. e3.
9. Ferastraoaru D, Hudes G, Jerschow E, et al. Eosinophilia in asthma patients is protective against severe COVID-19 illness. *J Allergy Clin Immunol Pract*. 2021;9(3):1152–1162. e3.
10. Adir Y, Humbert M, Saliba W. COVID-19 risk and outcomes in adult asthmatic patients treated with biologics or systemic corticosteroids: nationwide real-world evidence. *J Allergy Clin Immunol*. 2021;148(2):361–367. e13.

Delayed angioedema after administration of the severe acute respiratory syndrome coronavirus 2 messenger RNA vaccine

The coronavirus disease 2019 (COVID-19) pandemic has led to millions of deaths worldwide and continues to be a public health threat. Administration of COVID-19 vaccines safely and markedly decreases the chance of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and prevents severe COVID-19. Their widespread use is imperative to ending the pandemic. Since their implementation, various adverse reactions to the messenger RNA (mRNA) COVID-19 vaccines have been reported, with the most common being delayed cutaneous reactions, and, rarely, anaphylaxis.[1–3] Here, we present 3 cases of delayed angioedema after mRNA COVID-19 vaccination (Table 1).

Case 1

A 21-year-old man with a history of chronic rhinitis tolerated his first Pfizer-BioNTech COVID-19 mRNA vaccine without adverse symptoms. Two-and-a-half days after his second dosage (given 3 weeks later), he developed erythematous plaques and wheals on his thigh with subjective tongue swelling. The rash was evanescent but persisted despite antihistamine treatment, becoming more diffuse for more than 30 hours. Five days after his second dosage, he developed marked swelling of his lips with dysphagia, prompting evaluation in the emergency department (ED), where he was found to be normotensive and tachycardic. On physical examination, he was noted to have an urticarial rash on his neck and face, and swelling of the posterior pharynx, tongue, upper lip, and periorbital area. In the ED, he was given 0.3-mg intramuscular epinephrine, 125-mg intravenous methylprednisolone, 20-mg intravenous famotidine, 50-mg intravenous diphenhydramine, and 10-mg oral cetirizine. The patient's angioedema began to improve within 8 hours and completely resolved within 24 hours. He denied previous episodes of angioedema and reported no further episodes in the subsequent 7 months.

Case 2

A 33-year-old man with a history of type 1 diabetes mellitus, allergic rhinitis, peanut allergy, and eosinophilic esophagitis tolerated his first Pfizer-BioNTech COVID-19 mRNA vaccine without immediate adverse symptoms. After 30 hours, he developed throat tightness, dysphagia, and dyspnea. He self-administered 0.3-mg intramuscular epinephrine and presented to the ED, where he was noted to be hypertensive and tachycardic. Physical examination revealed dysphonia, dyspnea, and tripoding. Flexible laryngoscopy revealed grape-sized uvular swelling and edema of the false vocal folds. He received another dosage of 0.3-mg intramuscular epinephrine, 50-mg intravenous diphenhydramine, and 125-mg intravenous methylprednisolone. Because of the severity of his symptoms, he was started on a continuous intravenous epinephrine infusion that was weaned overnight as the angioedema improved. Serum tryptase level drawn in the ED was normal. The patient denied ingestion of peanuts before symptom onset and had no previous history of angioedema. He received his second Pfizer-BioNTech vaccine 6 months after this reaction without complications. He reported no further episodes of angioedema in the subsequent 9 months after his first vaccination.

Case 3

A 33-year-old woman with a history of episodic idiopathic urticaria, asthma, venom hypersensitivity, and Cushing syndrome on long-term low-dose corticosteroids tolerated her first Pfizer-BioNTech COVID-19 mRNA vaccine without immediate complications. After 1 day, she developed a pruritic, erythematous rash on her chest, throat tightness, and dyspnea, and presented to the ED where she was noted to be normotensive, tachycardic, and mildly febrile. Physical examination revealed lip and tongue angioedema, urticaria involving arms and chest, muffled voice, and decreased breath sounds. Flexible laryngoscopy revealed edematous vocal cords. She was urgently intubated. Serum tryptase levels during symptoms were normal. She received 2 doses of 0.3-mg intramuscular epinephrine, 50-mg oral diphenhydramine, 125-mg intravenous methylprednisolone, and 20-mg oral famotidine. Owing to her symptom severity, she was started on a continuous intravenous epinephrine infusion, which was weaned after 8 hours, and her angioedema resolved by 14 hours. She was advised not to receive dose 2 of the Pfizer-BioNTech COVID-19 vaccine. She denied a previous history of angioedema and reported no further episodes in the subsequent 7 months.

Anaphylaxis to mRNA COVID-19 vaccines is estimated to occur in 2.5 to 11.1 cases per million doses.[1,4,5] In these cases, diffuse erythematous rash, generalized urticaria, angioedema, wheezing, dyspnea, hypotension, nausea, and vomiting were typically observed within 15 to 30 minutes of administration.[2,4–6] In contrast, the mean time to symptom development in our 3 cases was 39 hours and, when available, serum tryptase levels collected at the time of symptoms were within the reference range. Urticaria has been reported to develop within 1 to 3 days after vaccination but, in these reports, there was no association with angioedema.[3,7] Delayed local cutaneous reactions with erythema, induration, and tenderness, which developed approximately 8 days and 2 days after first and second vaccinations, respectively, have also been described.[3,7] However, our cases did not have involvement of the injection site.

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