Association between atopic dermatitis and COVID-19 infection: A case-control study in the All of Us research program

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Background: There is an incomplete understanding of the risk of COVID-19 infection in atopic dermatitis (AD) patients.

Objective: To evaluate the risk of COVID-19 infection in AD patients in a large, diverse cohort.

Methods: A case-control study of the All of Us cohort to analyze the association between AD and COVID-19. Comorbidities and risk factors were compared between cases and controls using multivariable analyses.

Results: In a cohort of 11,752 AD cases with 47,008 matched controls, AD patients were more likely to have a COVID-19 diagnosis (4.2% vs 2.8%, $P < .001$). AD remained significantly associated with COVID-19 in multivariable analysis (odds ratio, 1.29; $P < .001$) after adjusting for demographic factors and comorbidities.

Limitations: Ascertainment of AD and COVID-19 cases using electronic health records and lack of clinical data on AD severity or therapy and COVID-19 outcomes.

Conclusion: AD is associated with increased odds of COVID-19 infection even after controlling for common comorbidities. (JAAD Int 2022;6:77-81.)

Key words: atopic dermatitis; COVID-19; epidemiology.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin disorders. There is uncertainty regarding the risk of infection with SARS-CoV-2, the causative virus of COVID-19, in AD patients. The pathophysiology of AD is complex and multifactorial, though it is known to involve immune dysregulation and activity of Th2 cytokines such as interleukin (IL) 4 and IL-13.[1] Current systemic treatments for AD such as dupilumab, an anti-IL-4 receptor α monoclonal antibody, have immunomodulatory properties with indeterminate effects on the risk of COVID-19 infection.[2-4]

There is an incomplete understanding of the relationship between AD and the risk of COVID-19 infection. For example, inconsistent data in the literature concerning COVID-19 infection rates in AD patients, with some studies finding an increased incidence of infection and others showing no significant difference.[5-7] Here, we aim to evaluate the association between AD and COVID-19 infection among adults in the All of Us research program, a National Institutes of Health database with health data from over 250,000 Americans, focusing on populations that have traditionally been underrepresented in research.[8]

MATERIALS AND METHODS

We performed a nested, matched, case-control study of the All of Us cohort, including adults

18 years of age and older from 2018 to the present. The All of Us program was designed to provide longitudinal health data for the advancement of precision medicine in the United States, with a priority to recruit participants that are historically underrepresented in biomedical research. Aggregate data are collected through a combination of survey responses, physical measurements, electronic health record (EHR) data, and genomic information from the donation of biospecimens. Participants are asked to complete additional surveys after enrollment, allowing for the collection of data on updated medical history, health care access and use, and more recently, questions concerning COVID-19.[9]

AD cases were identified in All of Us through EHR data using *International Classification of Diseases, Tenth Revision, Clinical Modification* code L20 and/or Systemized Nomenclature of Medicine code 24079001. COVID-19 cases were identified using *International Classification of Diseases, Tenth Revision, Clinical Modification* code U07.1 and/or Systemized Nomenclature of Medicine code 840539006. Age, sex, and race-matched controls were selected for each AD case through nearest-neighbor propensity score matching without replacement.

We compared comorbidities between cases and controls using Pearson's χ^2 test or Fisher's exact test for categorical variables and the unpaired *t* test for continuous variables. In multivariable analyses, we used logistic regression to determine whether AD and other comorbidities were associated with COVID-19 infection. Multivariable models were built by including universal confounders (age, sex), a priori associations, and covariates with a significance of $P < .1$ in univariable analysis, followed by backward elimination of covariates with a significance of $P > .1$ or with evidence of collinearity.

RESULTS

In the total cohort of 214,206 All of Us participants, we identified 11,752 cases of AD (average age 59; SD, 16; 68% female) and 47,008 matched controls. Age, sex, and race/ethnicity were well matched between cases and controls (all $P > .99$). AD cases were more likely to have a diagnosis of COVID-19 (4.2% vs 2.8%; $P < .001$) compared to controls (Table I). AD cases were also significantly more likely to have higher

CAPSULE SUMMARY

- Atopic dermatitis is associated with increased COVID-19 infection after controlling for common comorbidities.

- Patients with atopic dermatitis should be aware of the potential increased risk of COVID-19 and should emphasize preventative measures such as vaccination.

mean body mass index (30.3 vs 29.9; $P < .001$), to have hypertension (59.4% vs 48.9%; $P < .001$), hyperlipidemia (63.5% vs 47.3%; $P < .001$), type II diabetes mellitus (DM) (27.7% vs 20.2%; $P < .001$), sleep apnea (9.6% vs 6.8%; $P < .001$), cardiovascular disease (15.6% vs 10.5%; $P < .001$), malignancy (22.0% vs 15.6%; $P < .001$), and autoimmune disease (15.0% vs 7.9%; $P < .001$). AD remained significantly associated with COVID-19 in multivariable analysis (odds ratio, 1.29; $P < .001$) after adjusting for demographic factors and comorbidities such as body mass index, hypertension, hyperlipidemia, type II DM, and autoimmune disease (Table II). In a sensitivity analysis, we calculated E-values to measure potential residual confounding and found that a confounder would need to have an odds ratio of 1.9 to fully explain the association between AD and COVID-19.[10]

DISCUSSION

Among the All of Us cohort, we found that individuals with AD had a 29% increase in odds of having COVID-19 infection. This large-scale study provides an additional piece of evidence demonstrating an increased incidence of COVID-19 among AD patients, even after controlling for common comorbidities and known COVID-19 risk factors such as hypertension and type II DM. Our findings confirm previously identified associations between AD and various comorbidities, including hypertension, type II DM, sleep apnea, cardiovascular disease, malignancy, and autoimmune disease.[11-13] Many of these AD comorbidities have also been well-documented as significant risk factors for COVID-19 infection and risk factors for severe infection with poor outcomes in particular.[14-16] Although our results were attenuated slightly in multivariable analysis after considering these potential confounding factors, the relationship between AD and COVID-19 remained statistically significant.

There are limited studies investigating COVID-19 infection in AD patients (Table III). In one retrospective cohort study looking at 39,417 AD patients with matched controls, the incidence rate ratio of COVID-19 after adjustment for comorbidities was 1.18 (95% CI, 1.12-1.24) or 1.31 (95% CI, 1.11-1.53) depending on the method of sensitivity analysis, which was similar to the findings of our study. This study also found a slightly lower risk of COVID-19

infection in AD patients treated by dupilumab (incidence rate ratio, 0.66; 95% CI, 0.52-0.83).[5] In contrast, a cross-sectional study looking at 5387 patients with AD tested for COVID-19 found a positive test rate of 2.95%, which was a lower infection rate than non-AD patients (3.66%, P = .0063). However, this study did not control for potential confounding variables.[6] Another retrospective cohort study looking specifically at 238 AD patients treated with dupilumab found no significant difference in infection rates or COVID-19 outcomes compared with AD patients on other systemic therapies such as systemic corticosteroids, phototherapy, or azathioprine and mycophenolate mofetil.[4] Finally, in a retrospective study that included 18,360 AD patients, the odds ratio of COVID-19 infection in AD patients after adjustment for comorbidities was 1.48 (95% CI, 1.06-2.06; P = .020).[7]

The immunopathologic mechanisms that may connect AD and COVID-19 infection remain incompletely elucidated. Since AD comorbidities and COVID-19 risk factors are similar, certain risk factors may increase the risk of infection in AD patients more than others. Interestingly, a recent study has demonstrated a link between higher levels of IL-13 and COVID-19 infections and higher IL-4 and IL-13 levels in patients with more severe disease.[17] Hyperactivation of these cytokines in AD patients may predispose them to COVID-19. It may explain why AD patients on dupilumab, which targets and inhibits IL-4 and IL-13, do not exhibit higher infection rates. However, AD has not been associated with increased COVID-19 severity or complications in other epidemiologic studies.[18] Asthma, which shares a similar immunologic profile to AD with IL-4 and IL-13-mediated airway inflammation, has also not been correlated with an increased risk of COVID-19 infection or severe disease.[19-21] Several hypotheses have been proposed to explain these findings, including the variable role of type 2 immune response in responding to SARS-CoV-2, as well as other physiological changes in asthma, asthma medications, and behavioral factors.[22]

The strengths of our study include a large number of participants and the diversity of our cohort with a focus on groups traditionally underrepresented in biomedical research.

Table I. Clinical characteristics of AD cases versus age, sex, and race matched controls in All of Us

	Matched controls	AD cases	P value
N	47008	11752	
Age, mean (SD)	59.16 (16.22)	59.15 (16.22)	.994
Female (%)	31781 (67.6)	7946 (67.6)	.998
Race/ethnicity (%)			1.000
Asian	1632 (3.5)	409 (3.5)	
Black	8159 (17.4)	2038 (17.3)	
Hispanic	7224 (15.4)	1805 (15.4)	
Other	1420 (3.0)	355 (3.0)	
White	28573 (60.8)	7145 (60.8)	
COVID-19 (%)	1313 (2.8)	492 (4.2)	<.001
Ever smoker (%)	19159 (40.8)	4547 (38.7)	<.001
BMI, mean (SD)	29.87 (7.52)	30.32 (7.58)	<.001
Hypertension (%)	23007 (48.9)	6979 (59.4)	<.001
Hyperlipidemia (%)	22218 (47.3)	7458 (63.5)	<.001
Type II DM (%)	9513 (20.2)	3253 (27.7)	<.001
Atrial fibrillation (%)	4049 (8.6)	1198 (10.2)	<.001
Sleep apnea (%)	3185 (6.8)	1131 (9.6)	<.001
Ischemic heart disease (%)	3351 (7.1)	1312 (11.2)	<.001
Stroke (%)	2110 (4.5)	739 (6.3)	<.001
Cardiovascular disease (%)	4951 (10.5)	1829 (15.6)	<.001
HIV (%)	693 (1.5)	288 (2.5)	<.001
HCV (%)	1394 (3.0)	452 (3.8)	<.001
Thyroiditis (%)	1022 (2.2)	493 (4.2)	<.001
Hypothyroidism (%)	7319 (15.6)	2582 (22.0)	<.001
Hyperthyroidism (%)	1302 (2.8)	652 (5.5)	<.001
Malignancy (%)	9377 (19.9)	3603 (30.7)	<.001
Autoimmune disease* (%)	3732 (7.9)	1764 (15.0)	<.001

BMI, Body mass index; *DM*, diabetes mellitus; *HCV*, hepatitis C virus.
*Autoimmune disease includes systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, thyroiditis, vitiligo, and alopecia areata.

The limitations of our study include ascertainment of AD and COVID-19 cases using EHR data and a lack of clinical data such as on AD severity, AD therapy, or COVID-19 symptoms, severity, hospitalization, and mortality. Additionally, identifying COVID-19 cases through diagnosis codes may have excluded asymptomatic infections or symptomatic infections that were never confirmed through testing. Another limitation of this study is that patients with AD may have more contact with the health care system and thus are more likely to be tested for or diagnosed with COVID-19. There may also be other unmeasured confounders of the association between AD and COVID-19. Further studies are needed to determine the immunopathologic links between AD and COVID-19 infection and whether certain AD

Table II. Univariable and multivariable association of comorbidities with COVID-19

Covariates	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age	1.00 (1.00-1.00)	.263	0.99 (0.99-0.99)	<.001
Male	0.92 (0.83-1.01)	.095	1.04 (0.93-1.15)	.531
AD	1.52 (1.37-1.69)	<.001	1.29 (1.15-1.44)	<.001
BMI	1.03 (1.03-1.04)	<.001	1.01 (1.01-1.02)	<.001
Hyperlipidemia	1.75 (1.59-1.93)	<.001	1.48 (1.31-1.68)	<.001
Hypertension	2.10 (1.90-2.33)	<.001	1.65 (1.46-1.88)	<.001
Type II DM	2.31 (2.10-2.55)	<.001	1.42 (1.27-1.60)	<.001
Autoimmune disease	1.42 (1.27-1.60)	<.001	1.45 (1.26-1.67)	<.001

AD, Atopic dermatitis; *BMI*, body mass index; *DM*, diabetes mellitus.

Table III. Summary of literature evaluating association of AD and COVID-19

Study	Subjects (N)	Results	Conclusions
Wu et al[5]	39,417 AD patients with matched controls (US)	1. IRR of COVID-19 in AD patients = 1.18 (1.11-1.53, *P* < .0001) or 1.31 (1.11-1.53, *P* = .001), depending on sensitivity analysis 2. IRR of COVID-19 in AD patients on dupilumab = 0.66 (0.52-0.83, *P* < .0001)	AD was associated with increased risk of COVID-19 infection. Dupilumab was associated with decreased risk of COVID-19 infection in AD patients.
Nguyen et al[6]	5387 AD patients (US)	COVID-19 infection rate in AD vs non-AD patients = 2.95% vs 3.66%, *P* = .0063	AD was associated with a decreased rate of COVID-19 infection.
Kridin et al[4]	238 AD patients on dupilumab (Israel)	1. HR of COVID-19, dupilumab vs systemic corticosteroids = 1.13 (0.61-2.09, *P* = .699) 2. HR of COVID-19, dupilumab vs phototherapy = 0.80 (0.42-1.53, *P* = .500) 3. HR of COVID-19, dupilumab vs azathioprine and MMF = 1.10 (0.45-2.65, *P* = .840)	No difference in COVID-19 infection rates in AD patients on dupilumab vs systemic corticosteroids, phototherapy, or azathioprine and MMF.
Patrick et al[7]	18,360 AD patients (US)	OR of COVID-19 in AD patients = 1.48 (1.06-2.06, *P* = .020)	AD was associated with increased odds of COVID-19 infection.
Current study	11,752 AD patients with matched controls (US)	OR of COVID-19 in AD patients = 1.29 (1.15-1.44, *P* < .001)	AD was associated with increased odds of COVID-19 infection.

AD, Atopic dermatitis; *IRR*, incidence rate ratio; *HR*, hazard ratio; *MMF*, mycophenolate mofetil; *OR*, odds ratio.

comorbidities or treatments modify the risk of COVID-19 infection.

Conflicts of interest

None disclosed.

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