

# Atopic Dermatitis in COVID-19 Pandemic: A Systematic Review

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**Abstract:** **Background:** Atopic dermatitis is characterized by immune dysregulation, which may predispose toward worse COVID-19 outcomes but there are still conflicting results in the literature regarding the frequency of allergic diseases in COVID-19 patients. **Purpose:** To analyze the effect of having an atopic dermatitis on COVID-19 disease severity. **Method:** This journal analyzes 18 journals that explain about atopic dermatitis in COVID-19 pandemic. **Conclusion:** No significant association of AD with COVID-19 severity

**Keywords:** Atopic dermatitis, COVID-19, disease severity

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents an unprecedented global health crisis and continues to wreak havoc on health care systems and to claim a mounting number of lives. Disease causes SARS with a significant morbidity and mortality.<sup>1,2</sup>

Atopic dermatitis (AD) is an inflammation skin in the form of chronic residue dermatitis, accompanied by itching and on certain body parts especially on the face in infants (infantile phase) and flexural part of the extremities (in childhood). Atopic dermatitis often occurs in infants and childhood; about 50% disappear by adolescence, sometime can persist, or even just starting to appear as adults. In the United States, Atopic dermatitis (AD) is affecting 2% to 3% of the general population and 7% of adults. The term "atopy" has been introduced by Coca and Cooke in 1923, the origin of the word "atopos" (out of place) which means different, and it means a skin disease that is not normal, both the site of the affected skin and course of the disease.<sup>3,4</sup>

Atopic dermatitis patients have been found to account for an increasing prevalence of emergency department (ED) visits in the United States, which would currently place them at high risk of contracting COVID-19, especially for those receiving immunosuppressants. Increased hand washing and disinfectant use, and the prolonged wearing of masks and gloves, can lead to an increase in hand and facial dermatitis.

Higher stress levels during this time may increase the risk of atopic dermatitis flares.<sup>5</sup>

There are conflicting results in the literature regarding the frequency of atopic dermatitis in COVID-19 patients. The effect of having an atopic dermatitis on COVID-19 disease severity has been little studied. We provide a review with a focus on atopic dermatitis in COVID-19.<sup>6</sup>

## 2. Method

### Literature Identification

Literature related to atopic dermatitis in COVID-19 was identified through an electronic database in December 2021. The databases used were Google Scholar and Science Direct. To maximize the search for journals, the keywords were atopic dermatitis, COVID-19, pandemic, dermatology.

### Inclusion and Exclusion Criteria

The inclusion criteria in this review were original research articles on atopic dermatitis in COVID-19. Exclusion criteria were not original research articles and did not discuss atopic dermatitis in COVID-19.

## 3. Result

This search from the Google Scholar and Science Direct database yields a total of 210 with 110 journals from Google Scholar and 100 journals from Science Direct. After reading the abstracts from the journals, 18 journals were found that met the inclusion criteria.

No	Author/ Location/ Year	Research Methods	Participants	Key Points
1	Kridin K, et al/ Israel/ 2021	A Case Control Study	78.073 patients with AD and positive COVID-19 from February 27, 2020 - January 6, 2021	3618 (4.6%) tested positive for COVID-19. The majority of patients had a mild AD (n = 2526, 92.1%), whereas 286 patients (7.9%) followed a moderate-to-severe course. During the pandemic, 174 patients (4.8%) were treated by systemic agents, and 30 patients (0.8%) were managed by phototherapy. The majority of COVID-19-positive patients with AD experience a subclinical infection. However, 1.1% of patients died after the infection, and 6.0% developed complications necessitating hospitalization. Coronavirus disease 2019-associated hospitalization was independently predicted by undergoing extended systemic corticosteroid treatment during the pandemic, older age, Arab ethnicity, comorbid cardiovascular diseases, metabolic syndrome, COPD, CRF, malignancy, and depression. Metabolic syndrome, CRF, COPD, and depression, but not AD-

				related variables, were independent predictors of COVID-19-associated mortality. <sup>1</sup>
2	Naziroglu T, Aksu K/ Turkey/ 2020.	A retrospective cross-sectional study was conducted in patients diagnosed with COVID-19 in a state hospital in Istanbul, Turkey.	235 adults with COVID-19	235 adults with COVID-19 (mean age, 45.3 years; 139 [59.1%] male). Among study population, 16 (6.8%) subjects had one of the three atopic symptoms, which were wheezing, rhinitis, or eczema. Among the subjects with atopic status, four (1.7%) subjects had wheezing, eight (3.4%) had rhinitis, and four (1.7%) had eczema within the last 12 months. Although atopic status is associated with 3.1 times higher odds for mild disease, being atopic or not being atopic was not found to be associated with COVID-19 severity (P = .054). <sup>6</sup>
3	Ragamin A, et al/ Netherland/ 2021	A Retrospective study.	913 patients in 2020, 698 patients in 2019, 591 patients in 2018	Caretakers who perceived their child as more vulnerable experienced more COVID-19-related stress (p < 0.001). Furthermore, 9.7% of all caretakers indicated that the AD severity of their child worsened during the first COVID-19 wave, while 71.5% did not report changes in severity or AD and in 10.4% AD improved. <sup>7</sup>
4	Rakita U, et al/ Washington USA/ 2021.	A retrospective analyzed data from George Washington University (GWU) medical records for patients treated for SARS-CoV-2	430 patients	No association of AD with COVID-19 morbidity. AD patients may be more susceptible to acquiring SARS-CoV-2 infection, though findings are inconclusive. Current evidence indicates that AD patients are not at increased risk of mechanical ventilation, hospitalization, longer hospital stay, intensive care unit admission or death. AD is not associated with various other COVID-19 outcomes, including supplemental oxygen therapy, lingering symptoms and acuity level of initial care. <sup>8</sup>
5	Hernandez N, et al/ Colombia/ 2021	A Cross-sectional study from web survey	212 AD patients	116 out of 155 (75%) reported AD worsening with mild, moderate, and severe worsening in 70.3%, 18.7%, and 10.3% of patients, respectively. Only 2/155 (1.3%) patient tested positive for SARS-CoV-2. When SARS-CoV-2 positive patients were compared to the percentage of patients with comorbidities, psychiatric disorders, sleep disturbances, immunosuppressive therapy (prednisolone, methotrexate, azathioprine, and dupilumab), and disease flare, there was a statistically significant association only with the presence of comorbidities (p=0.03; Chi2 Test). <sup>9</sup>
6	Grieco T, et al/ Italy/ 2021.	A prospective cohort study	80 Italian patients aged ≥18 years, with moderate-to-severe AD, and treated with dupilumab	There was no statistically significant difference between AD-COVID patients and non-AD COVID patients in any of the outcomes examined such as hospitalization, acute respiratory distress syndrome, sepsis, mechanical ventilation, mortality, and severe COVID. Subgroup analysis also revealed that AD-COVID patients with a one-year history of immunosuppressant use had no significant difference in any of the listed outcomes as well compared to AD-COVID patients without history of immunosuppressants. AD patients who contract COVID are not at higher risk for more severe COVID outcomes compared to COVID patients without AD. Likewise, AD patients with a history of systemic immunosuppressants are also not at a higher risk for COVID complications compared to AD patients without a history of systemic immunosuppressants. <sup>10</sup>
7	Pakhchian H, et al/ Washington USA/ 2021.	A retrospective cohort study	2,408 record patients	Dupilumab does not impose an increased risk of SARS-CoV-2 infection or COVID-19 complications in patients with AD. Dupilumab should be continued and considered as a safe drug for moderate-to-severe AD during the pandemic. <sup>11</sup>
8	Kridin K, et al/ Israel/ 2021	A population-based cohort study was conducted to compare AD patients treated by dupilumab with those treated by prolonged systemic corticosteroids (≥ 3 months), phototherapy, and azathioprine or mycophenolate mofetil, regarding the incidence of COVID-19 and its complications.	AD patients treated by dupilumab (n = 238), treated by prolonged systemic corticosteroids (≥ 3 months; n = 1,023), phototherapy (n = 461), and azathioprine or mycophenolate mofetil (MMF; n = 194).	Dupilumab does not impose an increased risk of SARS-CoV-2 infection or COVID-19 complications in patients with AD. Dupilumab should be continued and considered as a safe drug for moderate-to-severe AD during the pandemic. No events of COVID-19-associated mortality occurred in the dupilumab, phototherapy, and azathioprine/MMF groups. The risk of COVID-19, COVID-19-associated hospitalization, and COVID-19-associated mortality was not statistically different between patients treated by dupilumab and systemic corticosteroid. <sup>12</sup>
9	Stingeni L, et	A prospective cohort	19 adolescents affected by	A total of 1831 patients were included, with 1580/1831 (86.3%)

	al/ Italy/ 2021.	study	moderate to severe AD who started dupilumab from January to October 2020.	continuing therapy during pandemic. Most patients were treated with dupilumab (86.1%, 1576/1831) that was interrupted in only 9.9% (156/1576) of cases, while systemic immunosuppressive compounds were more frequently withdrawn. Treatment interruption was due to decision of the patient, general practitioner, or dermatologist in 39.9% (114/286), 5.6% (16/286), and 30.1% (86/286) of cases, respectively. Fear of increased susceptibility to SARS-CoV-2 infection (24.8%, 71/286) was one of the main causes of interruption. Sixteen patients (0.9%) resulted positive to SARS-CoV-2 infection; 3 of them (0.2%) were hospitalized but no cases of COVID-related death occurred. Conclusions: Most AD patients continued systemic treatments during COVID pandemic and lockdown period, without high impact on disease control, particularly dupilumab-treated patients. <sup>13</sup>
10	Chiricozzi A, et al/ Italy/ 2021.	A cross-sectional, multicentric, observational study was conducted in 35 Italian centers.	The DA-COVID registry included 1831 patients with moderate-to-severe AD presenting demographic and clinical characteristics. Overall, 142/1831 (7.7%) patients were lost to follow-up throughout the observation period.	No significant differences in outcomes for patients (n=275) based on atopic disease were noted: ICU admission, 43% versus 44.7% (atopic versus no atopic disease, respectively; p=0.84); supplemental oxygen use, 79.1% versus 73.6% (p=0.36); intubation rate, 35.8% versus 36.5% (p=0.92); and mortality rate, 13.4% versus 20.7% (p=0.19). Severity of COVID-19 in hospitalized patients does not differ based on atopic status. <sup>14</sup>
11	Timberlake D, et al/ Columbus/ 2021.	Retrospective chart review on all patients testing positive for SARS-CoV-2 over 2 months at a major adult and pediatric tertiary referral center hospital	275 Patients	Did not find a statistically significant elevated risk for infection with COVID-19 in patients with Atopic disease. <sup>15</sup>
12	Yiu ZZN, et al/ Manchester UK/ 2021.	A cross-sectional study using data extracted from the Salford Royal NHS Foundation Trust (SRFT) electronic patient records (EPRs) of inpatient and outpatient visits.	13.162 patients	In total 269.299 patients were tested within the UC CORDS, with a 3,64% positive test rate (n = 9808, average age 42 years). Of these, 5,387 patients with AD were tested for SARS-CoV-2 and had a 2,95% (n = 159, average age 34 years) infection rate, which was lower than in those without AD (3,66%, n = 9.649, average age 42 years) (P = 0,0063). This observation was significant in women with AD compared with those without (2,7% vs. 3,46%, P = 0,022), but was not significant in men (3,3% vs. 3,89%, P = 0,14). There were similar proportions of COVID-19-positive men with and without AD (49% vs. 47%, P = 0,70). <sup>16</sup>
13	Nguyen C, et al/ California/ 2021.	A retrospective cross-sectional study was conducted using the University of California COVID Research Data Set (UC CORDS), a Health Insurance Portability and Accountability Act secure medical records dataset for patients tested for SARS-CoV-2 across University of California medical centres	269.299 patients	Patients with AD did not have significantly increased risk for SARS-CoV-2 infection, including those on immunomodulatory medications (prednisone or methotrexate). The hospitalization rate of SARS-CoV-2-positive patients with AD was not significantly different from those without AD. The mortality rate for SARS-CoV-2-positive patients with AD on prednisone was not significantly different from those without AD. <sup>17</sup>
14	Wu JJ, et al/ California/ 2022	A retrospective cohort study	The AD and non-AD cohorts included 39,417 and 397,293 subjects,	Dupilumab was associated with lower risk of contracting COVID-19 infection compared with other systemic medications. Based on the current evidence, dupilumab does not appear to increase COVID-19 risk in patients with AD. The literature reports less severe outcomes in atopic patients affected by COVID-19 <sup>18</sup>
15	Guterres D, et al/ Brazil/ 2020.	A Prospective Study	300 patients	Markers of COVID-19 disease severity do not differ based on asthma or atopic status in pediatric patients. In children, like adults, the presence of asthma or atopy does not appear to alter the risk of severe COVID-19. <sup>19</sup>
16	Timberlake D, et al/ Ohio/ 2020.	A retrospective chart review	49 patients	Atopic Rhinitis and eczema were associated with lower odds of COVID-19 related hospitalization. There was no difference in mortality between the groups with and without atopy. <sup>20</sup>

17	Keswani A, et al/ Washington/ 2020.	A cohort retrospective medical record review	1.043 patients	Most biologics and conventional immunotherapies, such as methotrexate, cyclosporine, and azathioprine when based on the doses and indications in dermatology, did not appear to increase the risk of viral vulnerability. They are most likely safe to be used during the COVID-19 pandemic. No positive correlation was observed between the development of COVID-19 infection and the use of immunosuppressive and immunomodulatory therapies. <sup>21</sup>
18	Mansouri P, et al/ 2021	A cross-sectional study	703 patients	No positive correlation was observed between the development of COVID-19 infection and the use of immunosuppressive and immunomodulatory therapies. <sup>22</sup>

#### 4. Discussion

COVID-19, caused by the coronavirus SARS-CoV-2, has become pandemic. The impact of SARS-CoV-2 infection on the immune system and its modulation or suppression by pharmacological intervention has been dissected in detail with regards to clinical implications of the various cytokines and cellular functions affected. A further level of complexity opens up as soon as we look at diseases whose pathogenesis and therapy involve different immunological signalling pathways, which are potentially affected by COVID-19. Medical treatments must often be reassessed and questioned in connection with this infection. However, there is still considerable uncertainty in this regard and we are currently in a phase of almost exponentially growing data on various diseases in the context of SARS-CoV-2 infections. The medical knowledge as well as the literature on COVID-19 and its treatment options is growing at an overwhelming pace.<sup>23</sup>

Atopic dermatitis (AD) is common, chronic, inflammatory skin diseases, affecting 2% to 3% of the general population and 7% of adults in the United States, respectively. Disease mechanisms are multifactorial, with immune dysregulation important for this condition, and mainstays of treatment immune modulation. Systemic treatment is recommended for AD patients with severe disease or recalcitrant to topical therapy. Immunocompromised patients are highly vulnerable to infections, which is particularly concerning in the context of the COVID-19 pandemic.<sup>4</sup>

Increased hand washing and disinfectant use, and the prolonged wearing of masks and gloves, can lead to an increase in hand and facial dermatitis. Higher stress levels during this time may increase the risk of atopic dermatitis flares. Liberal use of moisturizers, especially on the hands, should be counselled. To decrease risk of contracting coronavirus disease 2019, patients are encouraged to purchase moisturizers in bulk or order for delivery, and providers are encouraged to prescribe 90-day supplies of medications such as topical steroids to minimize repeated trips to the pharmacy. As the COVID-19 era has changed the behaviour of all individuals, and since previous reports about its possible impact on AD patients remained speculative.<sup>5,9</sup>

Atopic dermatitis patients have been found to account for an increasing prevalence of emergency department (ED) visits in the United States. Atopic dermatitis patients have a higher incidence of anxiety and depression than healthy controls. Stress and social isolation during quarantine may exacerbate these conditions. Recommending support groups through the

National Eczema Association, engaging in moderate physical exercise, and stressreduction techniques may benefit atopic dermatitis patients' emotional well-being and increase resilience.<sup>5</sup>

When SARS-CoV-2 positive patients were compared to the percentage of patients with comorbidities, psychiatric disorders, sleep disturbances, immunosuppressive therapy (prednisolone, methotrexate, azathioprine, and dupilumab), and disease flare, there was a statistically significant association only with the presence of comorbidities.<sup>9</sup>

Dupilumab targets IL-4 and IL-13, elements of the type 2 immune response. As type 1 and type 2 immune responses crossregulate each other, suppression of type 1 immunity can potentially facilitate uncontrolled or persistent viral and bacterial infections. Nonetheless, dupilumab has been associated with a reduced infection rate in AD patients.<sup>4</sup>

Dupilumab, an anti-interleukin (IL)-4/IL-13 human monoclonal antibody, is the first biologic treatment approved by the European Medicines Agency and the Food and Drug Administration in 2017 for the treatment of moderate-to-severe atopic dermatitis (AD) in patients who are candidates for systemic therapy. The drug is a powerful suppressor of type 2 cytokine production, being an inhibitor of IL-4/IL-13 receptors. It is also currently being evaluated for its potential application in other allergic diseases, including asthma and chronic rhinosinusitis with nasal polyps.<sup>10</sup>

Data on the tolerability and response to biologic therapies for type 2 immune disorders in the context of coronavirus disease 2019 (COVID-19) are currently lacking. Grieco T, et al survey aimed at assessing the adherence of patients to dupilumab therapy and the risk of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A total of 80 patients with atopic dermatitis treated with dupilumab completed a web-based survey. Of the 80 patients, 7 discontinued dupilumab owing to concerns and difficulties related to COVID-19. Our sample was highly susceptible to viral infection owing to the frequency of risk factors including living in high SARS-CoV-2 burden areas, such as in Northern Italy; having co-morbidities, such as asthma, diabetes, and cardiovascular disease; and being of advanced age. Older patients in our sample are particularly exposed to the risk of COVID-19-related cytokine storm, triggered by excessive interleukin-4 production and type 2 immune response. One patient contracted SARS-CoV-2 infection without the progression of COVID-19 despite continuing scheduled dupilumab treatment. Because evidence on the appropriate management of biologic therapy

in the setting of COVID-19 is lacking, the collection of clinical data from patients in treatment with dupilumab is a valuable addition to current clinical practice. Our survey provides a contribution to the understanding of the tolerability and response to dupilumab during COVID-19 and suggests a feasible and effective approach to patients being treated with biologics even when social distancing is required.<sup>10</sup>

A retrospective cross-sectional study was conducted in 235 adults patients diagnosed with COVID-19 in a state hospital in Istanbul, Turkey. The result of this study, being atopic or not being atopic was not found to be associated with COVID-19 severity.<sup>6</sup>

A retrospective analyzed data from George Washington University (GWU) medical records for patients treated for SARS-CoV-2 amount 430 patients, no association of AD with COVID-19 morbidity. AD patients maybe more susceptible to acquiring SARS-CoV-2 infection, though findings are inconclusive. Current evidence indicates that AD patients are not at increased risk of mechanical ventilation, hospitalization, longer hospital stay, intensive care unit admission or death. AD is not associated with various other COVID-19 outcomes, including supplemental oxygen therapy, lingering symptoms and acuity level of initial care.<sup>8</sup>

European task force on atopic dermatitis recommend for AD patients treated with immune-modulating therapy at times of SARS-Cov-2 pandemic.

- 1) To continue all immune-modulating treatments, including immunosuppressive therapy, since exacerbations of underlying diseases can have a large negative impact on patients' immunity.
- 2) To strictly follow the recommendations for patients at risk issued by the local health authorities in each European country.
- 3) To carefully observe hygienic procedures using hand wash and disinfectants. Non-irritant soap substitutes should be used in the same way as directed for soap. Moisturizers should be applied afterwards.<sup>24</sup>

Following the sanitary recommendations for more frequent hand washing and disinfection procedures during the pandemic, the prevalence of hand eczema is rising significantly, even among persons not previously affected. Basic topical treatment with emollients, as well as specific treatment with topical corticosteroids and calcineurin inhibitors should be initiated or continued according to current guidelines without any specific requirements, including UV- light therapies. Since exacerbations of the skin disease may negatively affect the patients' immunity, systemic treatment in eczema patients should be continued for all immunomodulating drugs including immunosuppressive therapy, as consented and advised by the European Task Force on Atopic Dermatitis (ETFAD).<sup>23</sup>

If a patient on systemic treatment is diagnosed with COVID-19, interdisciplinary risk assessments are necessary on whether to continue or pause systemic treatment, preferably in tertiary care centers. In atopic dermatitis, immune-

modulating medication may also control the severity of asthma/chronic obstructive lung disease and other comorbid conditions. Hence, termination of a stable treatment regimen with immune-modulating drugs may not be beneficial. However, in patients with exclusive skin disease such as hand eczema, pausing of immune-modulating therapies seems to be less problematic in case of COVID-19, since flare-ups of the skin disease may be acceptable during the critical time of the viral infection. Whenever immunomodulating therapy is stopped, patients need to be supplied with ample topical treatment and detailed instructions to control the skin disease for the following weeks. Close monitoring of comorbid diseases is important in these individuals. Targeting specific cytokines may even benefit patients with COVID-19, since therapeutic cytokine blockade without affecting viral clearance may inhibit hyperinflammatory host responses.<sup>23</sup>

The pandemic increased AD flares with mild worsening of the disease in the majority of our patients. Although itching remained moderate, a main concern was the presence of sleep disturbances, anxiety, and a sensation of uncertainty, which in turn could have influenced disease flaring. Other causes for disease worsening included increased hand washing, the lack of use of gentle soaps, and the prolonged use of gloves or masks which has been confirmed in this study, as main areas involved were the face, upper extremities, and hands.<sup>9</sup>

AD-COVID patients with a one-year history of immunosuppressant use had no significant difference in any of the listed outcomes as well compared to AD- COVID patients without history of immunosuppressants. AD patients who contract COVID are not at higher risk for more severe COVID outcomes compared to COVID patients without AD. Likewise, AD patients with a history of systemic immunosuppressants are also not at a higher risk for COVID complications compared to AD patients without a history of systemic immunosuppressants.<sup>11</sup>

## 5. Limitation

This journal only explain about relationship between atopic dermatitis and COVID-19

## 6. Conclusion

No significant association of AD with COVID-19 severity

## 7. Conflict of Interest

No conflict of interest

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