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The effects of systemic immunomodulatory treatments on COVID-19 outcomes in patients with atopic dermatitis: results from the global SECURE-AD registry

Keywords: atopic dermatitis, COVID-19, systemic therapy, dupilumab

Word count: 3789
Table and figure count: 2 tables, 4 figures

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.18613

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Funding sources: The SECURE-AD register is supported through a grant for skin disease registries held by Alan Irvine (National and International Skin Registries; NISR) as well as the National Institute for Health Research Biomedical Research Centre at Guy's & St Thomas' NHS Foundation Trust and King's College London as well as by research funding of the Department of Dermatology, University of Amsterdam.

Conflict of interest disclosures:

- A.H. Musters: none.
- C. Broderick: received support for attending meetings and/or travel from Abbvie (Attendance at British Association of Dermatologists annual meeting 2021).
- D. Prieto-Merino: none.
- A. Chiricozzi: received consulting fees from AbbVie, Almirall, Biogen, Fresenius Kabi, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme and UCB Pharma; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Almirall, Leo Pharma, Lilly, Janssen, Novartis, and Sanofi Genzyme.
- G. Damiani: none.
- K. Peris: none.
- S. Dhar: none.
- A. De: none.
- E. Freeman: Royalties UpToDate: COVID-19 Dermatology Author; Other financial or non-financial interests: Member of American Academy COVID-19 Task Force (unpaid).
- B.W.M. Arents: none.
- T. Burton: none.
- A.L. Bosma: none.
- C.-C. Chi: none.
- G. Fletcher: none.
- A.M. Drucker: none.
- K. Kabashima: received grants or contracts form Japan tobacco Inc., Kao, LEO Pharma, Chugai Pharmaceutical, Maruho, Pola Pharma, Abbvie, Eli Lilly, Sanofi, and Pfizer, Kose, and Kyorin Pharmaceutical; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from LEO Pharma, Japan tobacco Inc., P&G Japan, Eli Lilly Japan, Tanabe Mitsubishi, Ono Pharmaceutical, Kyowa Kirin, Pola Pharma, AbbVie, and Sanofi.
- E.F. de Monchy: none.
- M. Panda: none.
- D. Wall: is employed (as an Health Informatician) by National and International Skin Registry Solutions (NISR), a charity limited by guarantee, that develops national and international patient registries; NISR provided funding to support the development of the SECURE-AD platform and resources required to launch and maintain the project. He provided expertise specifically regarding this; consultancy fees from Eli Lilly and Company; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Fondation Rene

Touraine; Support for attending meetings and/or travel from Pfizer and Janssen (To attend virtual British Association of Dermatologists meeting 2020/2021).

- C. Vestergaard: received consulting fees from AbbVie, Almirall, Leo Pharma, Eli Lilly, Novartis, Sanofi Genzyme; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Almirall, Leo Pharma, Lilly, Novartis, and Sanofi Genzyme.
- E. Mahé: received grants or contracts from Sanofi and Abbvie; Consulting fees from Sanofi and Abbvie.
- L. Bonzano: none.
- L. Kattach: received consulting fees from AbbVie; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; Support for attending meetings and/or travel from Lilly to attend the BNDG and BAD conferences.
- M. Napolitano: received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events.
- M.F. Ordoñez-Rubiano: received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, Abbvie and Leo Pharma.
- E. Haufe: none.
- C. Patruno: received consulting fees from AbbVie, Eli Lilly, Novartis, Pierre Fabre, Pfizer, Sanofi, and Leo Pharma; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Eli Lilly, Novartis, Pierre Fabre, Pfizer, Sanofi, and Leo Pharma.
- A.D. Irvine: received consulting fees from Arena, Amirall, Pfizer, Regenron, Sanofi, Novarti, Abbvie, Benevolent Ai, and Lilly; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Leo, Abbvie, Lilly, and Sanofi; Participation on a Data Safety Monitoring Board or Advisory Board for Novartis (paid); Leadership or fiduciary role in other board, society, committee or advocacy group at International Eczema Council (unpaid) and Irish Hospital Consultants Association (unpaid).
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- C. Flohr: received grants from NIHR UK/EU Horizon 2020 (TREAT and SOFTER trial/ BIOMAP and Trans-Foods consortia (CI/PI), Sanofi (Investigator-led microbiome research programme) and Pfizer (Investigator-led microbiome research programme).

Data availability statement:

Please contact the corresponding author for data access requests.

Abstract

Background: Limited data are available on the effects of systemic immunomodulatory treatments on COVID-19 outcomes in patients with atopic dermatitis (AD).

Objective: To investigate COVID-19 outcomes in patients with AD treated with or without systemic immunomodulatory treatments, using a global registry platform.

Methods**:** Clinicians were encouraged to report cases of COVID-19 in their patients with AD in the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Atopic Dermatitis (SECURE-AD) registry. Data entered from April 1st 2020 to October 31st 2021 were analyzed using multivariable logistic regression. The primary outcome was hospitalization from COVID-19, according to AD treatment groups.

Results**:** 442 AD patients (mean age 35.9 years, 51.8% male) from 27 countries with strongly suspected or confirmed COVID-19 were included in analyses. 428 (96.8%) patients were treated with a single systemic therapy (n=297[67.2%]) or topical therapy only (n=131[29.6%]). Most patients treated with systemic therapies received dupilumab (n=216). 14 patients (3.2%) received a combination of systemic therapies. 26 patients (5.9%) were hospitalized. No deaths were reported. Patients treated with topical treatments had significantly higher odds of hospitalization, compared to those treated with dupilumab monotherapy (odds ratio (OR) 4.65[95%CI 1.71-14.78]), including after adjustment for confounding variables (adjusted OR (aOR 4.99[95%CI 1.4-20.84]). Combination systemic therapy which did not include systemic corticosteroids was associated with increased odds of hospitalization, compared to single agent non-steroidal immunosuppressive systemic treatment (OR 8.09[95%CI 0.4-59.96], aOR 37.57[95%CI 1.05-871.11]). Hospitalization was most likely in patients treated with combination systemic therapy which included systemic corticosteroids (OR 40.43[95%CI 8.16-207.49], aOR 45.75[95%CI 4.54-616.22]).

Conclusions**:** Overall, the risk of COVID-19 complications appears low in patients with AD, even when treated with systemic immunomodulatory agents. Dupilumab monotherapy was associated with lower hospitalization than other therapies. Combination systemic treatment, particularly combinations including systemic corticosteroids, was associated with the highest risk of severe COVID-19.

Abstract word count: 296

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19), is associated with a highly variable disease course, ranging from asymptomatic infection to severe disease resulting in hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and death.[1] Older age, male sex, non-white ethnicity, obesity, diabetes and underlying immunosuppression are important factors associated with a more severe and protracted disease course and increased mortality rates.[1, 2]

Atopic dermatitis (AD, also known as atopic eczema) is a complex chronic inflammatory skin disease. Both genetic and environmental factors play a role in AD pathogenesis. AD is characterized by skin barrier dysfunction and altered cell-mediated immunity.[3, 4] Compared to the general population, cutaneous and systemic infections are more common in patients with AD,[5] therefore it is plausible that SARS-CoV-2 infection, as well as the risks associated with COVID-19, could be affected by intrinsic immune dysregulation in AD.

A recent epidemiological study using electronic healthcare records demonstrated that many inflammatory skin diseases, including AD, acne, psoriasis, and cutaneous lupus, were associated with higher risk of COVID-19, even after controlling for age, gender, ethnicity, obesity and deprivation status.[6] However, patients with these inflammatory skin diseases had an overall lower odds of mechanical ventilation.[6]

Patients with moderate-to-severe AD are often treated with systemic immunomodulatory therapy, including systemic corticosteroids and conventional systemic therapies, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil. More recently, biologics such as dupilumab and tralokinumab, and small immunomodulatory molecules including the Janus Kinase inhibitors (JAKi) baricitinib, upadacitinib, and abrocitinib,[7-9] have been approved in several countries for the treatment of AD. Clinicians and patients must consider the potentially increased risk of infection associated with immunomodulatory treatments, especially in the context of a global pandemic, as differing mechanisms of action and levels of immunosuppression may impart variable risks of serious infections.[10-14] Contrastingly, some degree of immunomodulation may have beneficial effects on the rate of SARS-CoV-2 infection,[15] and targeting of specific immune pathways could reduce the development of a hyper-inflammatory state in severe COVID-19[16-19] a hypothesis supported by the recent World Health Organization recommendation for using baricitinib in the treatment of severe or critical COVID-19.[20]

Responding to the urgent need to better understand the determinants of COVID-19 outcomes and whether immunomodulatory treatments for AD affect the risk of morbidity and mortality, the SECURE-AD (Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion – Atopic Dermatitis) Physician Registry was launched in April 2020. The primary aim of the SECURE-AD study was to evaluate the effects that different systemic immunomodulatory AD treatments have on COVID-19 outcomes.

Methods

Study design, setting and patients

The SECURE-AD Physician Registry is a global web-based registry, launched through international collaboration between clinicians, researchers, and patients with AD (https://www.covidderm.org/). The study was promoted by national and international dermatology and patient partner organizations (see Acknowledgements). Clinicians were encouraged to report all cases of COVID-19 in patients with AD, and were required to register using their name, email and hospital affiliation. Ethical approval was granted by the Leeds Research Ethics Committee (20/YH/0135) and by the Irish National Research Committee for COVID-19-related Health Research (NREC COVID-19).

AD patients of all ages and any AD severity with suspected or confirmed COVID-19 (including asymptomatic patients detected through public health screening) were eligible for inclusion. Clinicians were asked to allow sufficient time to pass to observe disease progression, experience partial or complete recovery, hospitalization or death. Patients with AD taking immunomodulatory medication for an indication other than AD were excluded.

Data collection and outcomes

Anonymized observational data were collected using a web-based case report form (CRF), hosted on the OpenAppIT Clinical Insight platform (Dublin, Ireland). A single CRF was completed for each patient which included demographics (age, sex, ethnicity, country of residence), patient characteristics (body mass index (BMI), smoking status, co-morbidities, concomitant medications), date of diagnosis and AD disease activity (prior to and during COVID-19), and details of AD treatments. Although additional ethnicity options were pre-specified, ethnicity data were condensed (White, South Asian, Other, Unknown) for the regression analysis due to sample sizes.

Clinicians reported COVID-19 disease course and outcomes (duration of symptoms, persistence of COVID-19 symptoms at the time of reporting, death due to COVID-19, Emergency Department (ED) attendance, hospitalization, length of hospital stay, intensive care unit (ICU) admission, ventilation requirement, and flare (exacerbation) of AD during COVID-19). Hospitalization due to COVID-19 was selected as the primary measure of severe COVID-19 in our cohort due to low numbers of reported ICU admissions or mechanical ventilation. The web-based CRF was not altered since it was launched on April 1st 2020, so data on COVID-19 vaccination status were not collected.

CRFs were carefully designed to avoid traceability and only anonymized data were submitted to SECURE-AD. In line with the Declaration of Helsinki (1975, revised 2013), written consent from patients was not required.[21] All data were collected and processed exclusively for the promotion of scientific and medical research, carried out in the public interest.

Data collection was harmonized with concurrent efforts studying other immune-mediated inflammatory diseases (IMIDs), for example SECURE-Alopecia, SECURE-IBD, PsoProtect, and the Global Rheumatology Alliance.[22-24]

Statistical analysis

Based on data availability, drug class and mechanisms of action, we created immunomodulatory treatment groups. We summarized demographics and clinical characteristics and COVID-19 outcomes of the study population using descriptive statistics.

To minimize the risk of over-fitting logistic regression models for hospitalization by including each comorbidity as an individual variable, we created a cohort-specific “comorbidity score”, using

each patient's comorbidities and Body Mass Index (BMI). Presence or absence of comorbidities (asthma, other lung diseases including COPD, cardiovascular disease, hypertension, diabetes and stroke) and BMI were used to model the risk of hospitalization from COVID-19. This model gives a higher coefficient to the comorbidities that better predict hospitalization (irrespective of AD treatments) and these coefficients are used as the weights in our comorbidity score.

We report two main analyses to evaluate the effects of immunomodulatory therapies on COVID-19 outcomes. Firstly, to evaluate the effects of individual systemic treatments, patients receiving topical therapy only or a single systemic therapy for AD (i.e. systemic monotherapy) were analyzed separately to those receiving systemic therapies in combination. Treatment groups in the monotherapy analysis were: topical treatment only, dupilumab, methotrexate, ciclosporin, systemic corticosteroids, other conventional immuno-suppressant treatments (azathioprine and mycophenolate mofetil), JAKi, and other systemic treatments (including tralokinumab and other biologic and small molecule treatments (omalizumab and apremilast)). 95% confidence intervals (95%CI) associated with percentages experiencing COVID-19 outcomes were calculated by Pearson-Klopper method, using R's binom package v1.1-1.[25] Logistic regression was used to generate odds ratios (OR) and 95%CI for hospitalization according to immunomodulatory treatment groups, using dupilumab monotherapy as the reference group. Regression models were then adjusted for age, sex, ethnicity and each patient's comorbidity score.

Secondly, we evaluated the effect of systemic therapies used in combination, stratified according to whether the combination included systemic corticosteroids. The following systemic treatment groups were created: any non-steroidal immunosuppressive systemic treatment (NSISS) as monotherapy (reference group), systemic corticosteroids as monotherapy, combination treatment not including systemic corticosteroids, and combination treatment including systemic corticosteroids. Patients receiving topical therapies only were excluded from the combination treatment analysis. Adjusted OR (aOR) and 95%CI for hospitalization due to COVID-19 were calculated, adjusted as per the monotherapy analysis.

Patients reported in the registry from April 1st 2020 to October 31st 2021 were included in this analysis. All analyses were performed using R (Vienna, Austria), version 4.1.1. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies was used.[26]

Results

452 patients with AD and a COVID-19 diagnosis from 27 countries were registered in the SECURE-AD Physician Registry. Ten patients were excluded from further analysis: 3 receiving systemic immunomodulation for conditions other than AD, 3 participating in blinded clinical trials, and 4 who had an unknown COVID-19 outcome. One patient receiving tofacitinib for rheumatoid arthritis, in combination with dupilumab, was retained in the analysis due to presumed similar mechanism of action of JAKi used in AD.

Demographics, clinical characteristics and COVID-19 outcomes

Table 1 provides a summary of demographics and clinical characteristics of the study subjects (n=442), as well as full details of AD therapies used and the observed variation between immunomodulatory treatment groups. All combinations of systemic immunomodulatory treatments are summarized together in Table 1, and the number of patients receiving each specific combination of treatments is listed in the accompanying footnote. Further details of the doses of systemic treatments used are available in Supplementary Table 1 (single agent systemic therapy, i.e. systemic monotherapy) and Supplementary Table 2 (systemic treatments used in combination). Table 2 outlines the overall proportions of patients with pre-defined COVID-19 outcomes. Hospitalization was reported in 26 patients (5.9%). ICU admissions (n=8, 1.8%) and mechanical ventilation were infrequent (n=6, 1.4%) and there were no reported deaths.

COVID-19 outcomes in patients treated with topical or single agent systemic immunomodulatory therapy (monotherapy analysis)

Figure 1 depicts the proportions of patients with pre-specified COVID-19 outcomes, according to their immunomodulatory treatment group. 48 patients in the monotherapy analysis attended the Emergency Department (ED). ED attendance rates differed between treatment groups (p=0.053) and was higher in those treated with topical treatments compared to dupilumab (15.5% vs 8.7%, p=0.075). Overall, hospitalization because of COVID-19 was infrequent (n=21 [5.2%]), but the proportions of hospitalized patients varied between the treatment groups (p=0.068) and was highest in those treated with systemic corticosteroids (14.3%). Patients treated with topical treatments were more likely to be hospitalized than those treated with dupilumab (9.9% vs 2.3%, p=0.004). Compared to dupilumab (14.9%), patients treated with topical treatments (34.4%), ciclosporin (31.8%) and JAKi (36.4%) were more likely to experience a flare (exacerbation) of AD during COVID-19 (p<0.001, p=0.065, p=0.08 respectively). Supplementary Table 3 presents the p-values for between group comparisons for each pre-specified COVID-19 outcome.

Regression analysis of hospitalization rates according to topical or single agent systemic immunomodulatory treatment group

To further explore the differences in hospitalization rates observed between systemic treatments identified in the monotherapy analysis (Figure 1, Supplementary Table 3), a multivariable logistic regression model was fitted, adjusting for confounding variables (age, sex, ethnicity, comorbidity score). No hospitalizations were reported in patients treated with JAKi (n=12), other conventional immunosuppressant treatments (n=6), or other biologic/small molecule treatments (n=4), so these treatment groups were excluded from regression analysis. An additional 41 patients with missing BMI data were excluded, leaving 365 patients to assess the association between hospitalization and topical treatments and systemic monotherapy (Figure 2). Compared to patients prescribed dupilumab,

patients treated with topical treatments had significantly higher rates of hospitalization from COVID-19 (OR 4.65 [95%CI 1.71-14.78]), including after adjusting for age, sex, ethnicity and comorbidity score (aOR 4.99 [95%CI 1.4-20.84]). Compared to dupilumab, hospitalization was more frequently reported in patients receiving systemic corticosteroids (OR 7.03 [95%CI 0.34-53.86], aOR 2.85 [95%CI 0.08-38.11]), or ciclosporin (OR 2.01 [95% 0.1-13.25], aOR 3.02 [95%CI 0.14-25.72]), however, these findings were not statistically significant. After adjustment for confounding variables, patients treated with methotrexate and dupilumab had equivalent odds of hospitalization (OR 1.46 [95%CI 0.07-9.45], aOR 0.98 [95%CI 0.05-7.58]).

Exploring the effects of combination systemic therapy on COVID-19 outcomes in patients with AD (combination treatment analysis)

To evaluate the effects of systemic treatments used in combination, a subgroup analysis including patients treated with systemic monotherapy (n=297) or combination systemic therapy (n=14) was performed. Patients were prescribed systemic corticosteroids as monotherapy (n=7), NSISS as monotherapy (n=290), combination treatments not including systemic corticosteroids (n=6) and combination treatments including systemic corticosteroids (n=8). Figure 3 depicts the proportions of patients in each treatment group with each pre-specified COVID-19 outcome. Patients prescribed combination treatments including systemic corticosteroids had the highest rates of ED attendance, hospitalization, ICU admission, ventilation, AD flares (exacerbations) and persistent COVID-19 symptoms. Statistically significant comparisons between treatment groups are highlighted in Figure 3, and p-values for all comparisons are presented in Supplementary Table 4. The effects of combination systemic therapy on hospitalization from COVID-19 was investigated further using multivariable logistic regression, adjusted for confounding variables (age, sex, ethnicity, comorbidity score (Figure 4)). Compared to patients treated with any NSISS as monotherapy, significantly higher rates of hospitalization from COVID-19 were reported in patients treated with combination therapy including systemic corticosteroids (OR 40.43 [95%CI 8.16-207.49], aOR 45.75 [95%CI 4.54-616.22]), and in patients treated with combination therapy not including systemic corticosteroids (OR 8.09 [95%CI 0.4-59.96], aOR 37.57 [95%CI 1.05-871.11]). Compared to single agent NSISS, systemic corticosteroid monotherapy was associated with higher rates of hospitalization (OR 6.74 [95%CI 0.33-47.64], aOR 1.87 [95%CI 0.03-55.4]), although the difference was not statistically significant.

Discussion

In this global registry study of AD patients from 27 countries, we found important differences in COVID-19 outcomes between different treatment modalities, even if hospitalization rates overall (5.9% of all SECURE-AD patients) did not appear higher than would be expected in the general population.[27] Compared to other IMID registries, hospitalization rates in SECURE-AD patients were lower than reported in patients with inflammatory bowel disease (IBD, 31%), rheumatic diseases (46%) or psoriasis (21%). Fatality rates were also higher in the comparable studies (3%, 10.5% and 2% respectively, vs 0% in the SECURE-AD physician registry).[22-24, 28]

Among those treated with systemic monotherapy, the highest rates of hospitalization were seen in those receiving systemic corticosteroids (14.3%). This finding is consistent with results reported for patients with rheumatic diseases, where ≥10mg prednisolone/day (or equivalent) was associated with higher COVID-19-related mortality, compared to patients prescribed methotrexate.[28]

Compared to dupilumab, topical treatments were associated with significantly higher rates of hospitalization from COVID-19, even after adjusting for confounding variables (aOR 4.99 [95%CI 1.4-20.84]). Compared to dupilumab, patients on methotrexate had equivalent odds of hospitalization, and dupilumab was associated with lower odds of hospitalization than ciclosporin, or systemic corticosteroids, although these findings did not reach statistical significance.

Dupilumab targets interleukin (IL)-4 and IL-13 which are not activated for viral infections, therefore inhibition is not expected to significantly affect rates of SARS-CoV-2 infection. COVID-19 is characterized by an exaggerated Th1/Th17 immune response and can be associated with a cytokine storm in severe disease.[29] Emerging evidence suggests that expression of Th2 cytokines, including IL-4 and IL-13, may also be increased during COVID-19.[30-34] Our data reinforces the established safety profile of dupilumab from clinical trials and case series during the COVID-19 pandemic.[35-38] In an electronic health record analysis, dupilumab exposure (for any indication) was associated with a lower risk of ventilation and death from COVID-19 (risk of death in dupilumab-treated cohort: 0% vs 1.98% in those not receiving dupilumab [95%CI 1.94-2.03%]).[33] Using the COVID-19 Research Database, Wu et al. compared the risk of contracting SARS-CoV-2 in patients prescribed different AD treatments.[15, 39] Patients on dupilumab were at lower risk of infection, compared to patients on prednisone, ciclosporin, azathioprine and patients not on systemic medication. In contrast to our work, this study did not examine the severity of COVID-19 in relation to AD treatments. Ungar et al. reported a prospective, single-center case series of patients with moderate-severe AD (n=1237), of whom 87 experienced a COVID-19 episode, and reported no deaths or ICU admissions, and only 4 hospitalizations due to COVID-19.[16] In contrast to our study, which used hospitalization as the primary outcome of severe COVID-19, Ungar et al. created a custom COVID-19 symptom severity score and found that patients treated with dupilumab experienced fewer and less severe COVID-19 symptoms, compared to patients on other systemic treatments (including phototherapy), and topical or no treatments. While their study provides useful insights into COVID-19 symptoms in patients with AD treated with systemic therapies, the generalizability of this study's findings is limited by low rates of laboratory-confirmed COVID-19 (7%, compared to 69% in our study) and the use of a COVID-19 symptom score, rather than more objective measures of COVID-19 severity, such as hospitalization or ICU admission.

Our subgroup analysis including patients treated with either a single systemic agent or combination systemic therapy showed that patients treated with combination therapy including systemic

corticosteroids had the highest rates of ED attendance, hospitalization, ICU admission, ventilation, AD flares (exacerbations) and persistent COVID-19 symptoms. Compared to patients on NSISS monotherapy, patients on combination treatment with or without systemic corticosteroids had significantly higher odds of hospitalization, after adjusting for confounding variables (aOR 45.75 [95%CI 4.54-616.22]) and aOR 37.57 [95%CI 1.05-871.11]) respectively). The numbers of patients receiving combination systemic therapy was small, reflected in wide confidence intervals, and further research is warranted to validate these findings in a larger sample.

Risk of COVID-19 in patients treated with combination systemic therapy has previously been evaluated in other IMID registries.[40] In a pooled analysis of 6077 patients with IMIDs (IBD, inflammatory arthritis, psoriasis) and COVID-19, TNFi in combination with thiopurines (azathioprine/6-mercaptopurine) was associated with significantly higher odds of hospitalization or death compared with TNFi monotherapy (aOR 1.74 [95%CI 1.17-2.58]), whereas TNFi combined with methotrexate was not associated with significantly higher odds of severe COVID-19 (defined as hospitalization or death) (aOR 1.18 [95%CI 0.85-1.63]). Interestingly, the use of both methotrexate and thiopurines as monotherapy was associated with higher odds of severe COVID-19 than TNFi monotherapy, highlighting the importance of evaluating the risks of specific combinations of treatments. This study adjusted for systemic corticosteroid use, rather than analyzing systemic therapy in combination with corticosteroid use, and found a dose-dependent relationship with corticosteroid use (aOR per 1 mg increase prednisolone-equivalent, 1.07 [95%CI 1.05-1.08]). While systemic corticosteroids are sometimes used in severe or refractory AD, they are immunosuppressive and can cause hyperglycemia, a strong risk factor for severe COVID-19 and mortality, independent of pre-morbid diabetic status.[41] In contrast to poorer outcomes in those on systemic corticosteroids prior to contracting COVID-19, the RECOVERY trial demonstrated that dexamethasone significantly improves survival in hospitalized patients with severe COVID-19 requiring supplemental oxygen or ventilation.[42] The benefit was not seen across all COVID-19 severity strata, and in hospitalized patients not requiring supplemental oxygen, dexamethasone was associated with numerically higher rates of death than usual care (17.8% vs 14.0%), although the finding was not statistically significant (rate ratio 1.19 [95%CI 0.92- 1.55]). Thus, it is likely that pre-existing treatment with systemic corticosteroids increases the risk of COVID-19, whereas the hyper-inflammatory state seen in severe COVID-19 can be attenuated by systemic corticosteroids when they are administered during the course of severe illness.

Strengths and limitations

Strengths of our study include the geographically and ethnically diverse sample of patients, and a detailed description of the COVID-19 disease course in patients with AD. We included cases from 27 countries, making our findings more generalizable than single-centre, regional or national studies. Utilization of physician-reported data on AD treatments and comorbidity status reinforce the validity of the SECURE-AD data.

Our data are drawn from mostly secondary and tertiary care dermatology centres, and the sample is mostly adults. Therefore, this cohort is unlikely to be representative of the whole population of people with AD, the majority of whom are children and at overall lower risk of severe COVID-19. Thus, our conclusions should only be applied in the appropriate context.

Our study also has weaknesses. An important limitation is the absence of vaccination status of the included patients. We considered utilizing a binary timepoint cut-off, to identify patients, before and after which time, were likely to have received COVID-19 vaccination. A significant limitation of

this approach would be the multitude of approaches to vaccination prioritization, provision/administration and up-take across different jurisdictions, and we felt that there was no accurate way to define a binary time-point for such a sensitivity analysis. However, one aspect of our analysis which reassures us of the validity of our findings, despite inability to control for vaccination status, is that our adjusted analysis controlled for age, sex, BMI and comorbidity status, which in many jurisdictions, were the variables used to prioritize patients for vaccination. Therefore, it is likely that we have already (at least partially) adjusted for likelihood of vaccination by proxy, in our adjusted analysis.

A further limitation, is the selection bias inherent in registry studies. Physicians may be more likely to report patients on systemic therapy, or with more severe COVID-19 infections. The absence of any reported deaths is therefore reassuring. Patients receiving systemic immunomodulatory medications may be more likely to access testing, report COVID-19 to their clinician, or come to the attention of SECURE-AD collaborating clinicians whilst hospitalized due to perceived risks associated with immunomodulation.

Because of the relatively small numbers of patients on some individual treatments, some analyses were at aggregate level. This is particularly important when interpreting findings from the combination therapy analysis, where numbers are small and the groups contain a variety of combination treatments. Data collection is ongoing and larger patient numbers will provide more power to detect differences in COVID-19 outcomes between immunomodulatory treatments. Although we have adjusted for variables such as age, gender, comorbidities and BMI, unmeasured confounding remains a possibility. Despite our global sample, numbers of patients from individual countries varied widely (median n=4, range 1-139). With infrequent hospitalization, and in some countries no hospitalizations, we were thus unable to adjust for country-level differences in hospitalization rates, or country-level factors such as socioeconomic factors, background rates of COVID-19 or availability and frequency of use of systemic treatments for AD. Due to the size of our cohort, we were unable to adjust for dosage of systemic immunomodulatory treatments, including corticosteroids, or changes in the management of COVID-19 over the course of the pandemic, including vaccination.

Future perspectives

As the global COVID-19 pandemic goes on, we continue to collect data to investigate the determinants of COVID-19 outcomes in patients with AD using our web-based SECURE-AD registry. To help us better understand the effects on patients with AD, we set up a second self-report registry platform, the SECURE-AD Patient Registry, launched globally in June 2020. Co-operation with patient organizations and the involvement of all patients is crucial,[43] and will support further data analyses, including the impact of COVID-19 vaccination on patients with AD. Beyond our own initiatives, we strongly advocate for collaboration with and harmonization of data across COVID-19 registries to facilitate comparative analyses to gain a broad understanding of the impact of COVID-19 on patients treated with various immunomodulatory therapies. Consensus on harmonization has been reached among the leaders of the COVID-19 dermatology registries.[44] Collaboration between registries, including non-dermatological diseases, has been crucial for the rapid generation of knowledge and can serve as an example for the prospective harmonization of data collection in the future.[45]

Conclusions

The overall risk of COVID-19 complications appears to be low in patients with AD treated with immunomodulatory treatments. Compared to topical treatment, patients on dupilumab monotherapy were less likely to be hospitalized. Systemic monotherapy with either dupilumab or methotrexate was associated with similar odds of hospitalization. An increased rate of hospitalization was seen in patients treated with combination systemic therapy, particularly patients treated with combinations including systemic corticosteroids. Risks and benefits need to be considered by physicians who treat patients with AD using systemic therapies. We will examine the risk associated with individual immunomodulatory treatments in more detail in future analyses.

Acknowledgements

We are very grateful to all healthcare professionals who have reported cases to the SECURE-AD Physician Registry. We would also like to acknowledge our partner organizations and related registries who supported or promoted the SECURE-AD registry. We are particularly grateful to the following:

- Members of the SECURE-AD International Scientific Advisory Committee: Sebastien Barbarot MD PhD, Esther Freeman MD PhD, Emma Guttman MD PhD, USA (IEC), Jo Lambert MD PhD, Tamar Nijsten MD PhD, Amy Paller MD, Carle Paul MD PhD, Alain Taieb MD PhD, Andreas Wollenberg MD PhD, Christian Vestergaard MD PhD, Andrea Chiricozzi MD, Ketty Peris MD;
- All healthcare professionals who have submitted one or more cases in the SECURE-AD registry: Eleni Anthony, Valeria Aoki, Esther Baldrich, Alberto Barea, Paula Beattie, Anthony Bewley, Andrew Blauvelt, Andrea Carugno, Cécile Morice, Petra Cetkovska, Aisling Clery, Katerina Damevska, Vincent Descamps, Jitske Dijkstra, Roni Dodiuk-Gad, Marta Elosua-González, Felicity Ferguson, Susannah George, Tina Haase, Mariana Hernandez Flores, Ai Shuen Hew, Philipp Hinteregger, Manrip Hunjan, Jing Husaini, Ariënna Hyseni, Karina Jackson, Erin Kamp, Jasbinder Kaur, Dimitra Kiritsi, Emek Kocatürk, Sinead Langan, Yael Leshem, Peter Lio, Clodagh Loftus, Paula Luna, Teena Mackenzie, Satveer Mahil, Alexander Marsland, Valeria Mateeva, Zeljko Mijuskovic, Nicola Milanesi, Lucy Moorhead, Esra Musbahi, John Newsham, Jane O'Connor, Swetlina Pradhan, Amy Paller, Bibiana Pérez García, Anke Piekar, Nadia Raison-Peyron, Giulia Rech, Pawinee Rerknimitr, Rosalind Simpson, Sahana Srinivas, Katarzyna Stankiewicz-Sojka, Ting Seng Tang, Efstratios Vakirlis, Richard Weller, Richard Woolf, Zenas Yiu;
- Our partner organisations: British Association of Dermatologists (BAD), European Society for Dermatological Research (ESDR), International League of Dermatological Societies (ILDS), European Task Force on Atopic Dermatitis (ETFAD), International Eczema Council (IEC), Skin Inflammation & Psoriasis International Network (SPIN), European Dermato-Epidemiology Network (EDEN), European Academy of Dermatology and Venereology (EADV), International Society of Atopic Dermatitis (ISAD), TREatment of ATopic eczema (TREAT) Registry Taskforce, TREatment of ATopic eczema – The Netherlands (TREAT NL) Registry, The UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR), Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV), Japanese Dermatological Association (JDA), National Eczema Association (NES);
- National and International Skin Registry Solutions (NISR) CLG for their support and expertise which enabled rapid development, deployment and maintenance of the registry platform and harmonisation effort;
- The related COVID-registries: SECURE-AD Patient Survey, AAD COVID-19 registry, DA-COVID-19 registry, SECURE-Alopecia, PsoProtect, SECURE-Psoriasis, SECURE-IBD, COVID-19 Global Rheumatology Alliance.

Figure legends

Figure 1. Barchart demonstrating the proportions of patients and their pre-specified COVID-19 outcomes, according to the immunomodulatory treatment groups. Patients receiving topical therapy (n=131) or a single systemic therapy for atopic dermatitis (n=297) were included. 95% confidence intervals around the percentage of each outcome were calculated using the Pearson-Klopper method. P-values were calculated using Fisher's exact test for differences across all groups (boxed P-values). Asterix notation shows statistically significant differences between bracketed pairs of treatments (P-values>0.1 are not shown but are available in ***Supplementary Table 3***). AD = atopic dermatitis, ICU = intensive care unit, JAK inhibitor = Janus Kinase inhibitor.

Figure 2. Forest plot demonstrating adjusted odds ratios (aOR) and associated 95% confidence intervals (95%CI) for hospitalization from COVID-19, in patients with atopic dermatitis (AD) treated with topical therapies or a single systemic therapy, compared to those patients receiving dupilumab for their AD. OR were adjusted for age, sex, ethnicity and comorbidity score. aORs less than 1 are in blue, while aORs greater than 1 are in red.

Figure 3. Barchart demonstrating the proportions of patients and their pre-specified COVID-19 outcomes, according to systemic treatment groups. Patients receiving topical therapy (n=131) were excluded to allow comparison of single agent vs combination systemic therapy for atopic dermatitis. 95% confidence intervals around the percentage of each outcome were calculated using the Pearson-Klopper method. P-values were calculated using Fisher's exact test for differences across all groups (boxed P-values). Asterix notation identifies statistically significant differences between bracketed pairs of treatments (P-values >0.1 are not shown but are available in ***Supplementary Table 4***). AD = atopic dermatitis, ICU = intensive care unit, NSISS = non-steroidal immunosuppressive systemic treatment.

Figure 4. Forest plot demonstrating adjusted odds ratios (aOR) and associated 95% confidence intervals (95%CI) for hospitalization from COVID-19, in patients with atopic dermatitis (AD) treated with systemic corticosteroids (as monotherapy), combination therapy not including systemic corticosteroids, and combination therapy including systemic corticosteroids, compared to those patients receiving a non-steroidal immunosuppressive systemic treatment (NSISS) for AD. OR were adjusted for age, sex, ethnicity and comorbidity score. aORs greater than 1 are in red.

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Table 1. Demographics and clinical characteristics

	Overall	Topical treatments only	Dupilumab	Methotrexate	Ciclosporin	Systemic corticosteroids	Other conventional immuno-suppressants	JAK inhibitors	Other biologic/small molecule treatments	Combination treatments	P-value
COVID-19 cases	442	131	216	30	22	7	6	12	4	14	
Sex (%)											0.661
Female	213 (48.2)	58 (44.3)	108 (50.0)	15 (50.0)	8 (36.4)	3 (42.9)	5 (83.3)	6 (50.0)	2 (50.0)	8 (57.1)	
Male	229 (51.8)	73 (55.7)	108 (50.0)	15 (50.0)	14 (63.6)	4 (57.1)	1 (16.7)	6 (50.0)	2 (50.0)	6 (42.9)	
Age, mean (SD)	35.93 (18.00)	28.58 (18.10)	40.38 (16.92)	38.73 (19.78)	29.95 (13.15)	63.43 (18.31)	30.00 (9.94)	37.00 (22.79)	40.75 (17.80)	41.64 (15.79)	<0.001
Age category (%)											<0.001
<2 years	5 (1.1)	5 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
2-9 years	20 (4.5)	17 (13.0)	1 (0.5)	0 (0.0)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
10-19 years	60 (13.6)	24 (18.3)	19 (8.8)	7 (23.3)	2 (9.1)	1 (14.3)	1 (16.7)	3 (25.0)	1 (25.0)	2 (14.3)	
20-39 years	168 (38.0)	47 (35.9)	86 (39.8)	10 (33.3)	12 (54.5)	4 (57.1)	4 (66.7)	3 (25.0)	0 (0.0)	2 (14.3)	
40-59 years	145 (32.8)	32 (24.4)	79 (36.6)	9 (30.0)	6 (27.3)	1 (14.3)	1 (16.7)	5 (41.7)	3 (75.0)	9 (64.3)	
60-79 years	40 (9.0)	6 (4.6)	30 (13.9)	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)	
≥80 years	4 (0.9)	0 (0.0)	1 (0.5)	2 (6.7)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Ethnicity (%)											<0.001
White	286 (64.7)	54 (41.2)	175 (81.0)	17 (56.7)	11 (50.0)	2 (28.6)	3 (50.0)	9 (75.0)	3 (75.0)	12 (85.7)	
South Asian	60 (13.6)	36 (27.5)	8 (3.7)	5 (16.7)	7 (31.8)	2 (28.6)	0 (0.0)	1 (8.3)	1 (25.0)	0 (0.0)	
Asian - Chinese	2 (0.5)	1 (0.8)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asian - other	4 (0.9)	4 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hispanic or Latino	14 (3.2)	4 (3.1)	4 (1.9)	1 (3.3)	1 (4.5)	1 (14.3)	1 (16.7)	1 (8.3)	0 (0.0)	1 (7.1)	
Afro Caribbean	8 (1.8)	2 (1.5)	5 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Black-African	5 (1.1)	2 (1.5)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Other	6 (1.4)	2 (1.5)	0 (0.0)	2 (6.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	

Unknown	57 (12.9)	26 (19.8)	20 (9.3)	5 (16.7)	3 (13.6)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	
Country of residence (%)											<0.001
Italy	138 (31.2)	9 (6.9)	112 (51.9)	1 (3.3)	4 (18.2)	2 (28.6)	0 (0.0)	3 (25.0)	2 (50.0)	5 (35.7)	
India	64 (14.5)	41 (31.3)	2 (0.9)	8 (26.7)	10 (45.5)	2 (28.6)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	
United Kingdom	61 (13.8)	7 (5.3)	26 (12.0)	13 (43.3)	2 (9.1)	0 (0.0)	2 (33.3)	4 (33.3)	1 (25.0)	6 (42.9)	
France	36 (8.1)	17 (13.0)	16 (7.4)	2 (6.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	
The Netherlands	31 (7.0)	7 (5.3)	21 (9.7)	1 (3.3)	1 (4.5)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	
United States	20 (4.5)	14 (10.7)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	1 (7.1)	
Europe (other)	61 (13.8)	20 (15.3)	26 (12.0)	4 (13.3)	4 (18.2)	2 (28.6)	2 (33.3)	2 (16.7)	0 (0.0)	1 (7.1)	
South America	16 (3.6)	5 (3.8)	6 (2.8)	1 (3.3)	1 (4.5)	1 (14.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (7.1)	
Asia (other)	9 (2.0)	9 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Middle East	4 (0.9)	0 (0.0)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
North America (other)	2 (0.5)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Dose of systemic treatment, median (IQR)	NA	NA	See sTable 1	12.5mg (10 - 15mg) per week*	100mg (100mg - 150mg) per day**	See sTable 1	See sTable 1	See sTable 1	See sTable 1	See sTable 2	
Dose by weight, median (IQR)	NA	NA	NA	0.18mg/kg (0.16 - 0.23mg/kg) per week*	2.86mg/kg (2.22 - 3.15mg/kg) per day**	NA	NA	NA	NA	NA	
Method of COVID-19 diagnosis (%)											0.008
Positive test	305 (69.0)	103 (78.6)	137 (63.4)	20 (66.7)	20 (90.9)	5 (71.4)	4 (66.7)	4 (33.3)	3 (75.0)	9 (64.3)	
Presumptive diagnosis based	135 (30.5)	28 (21.4)	77 (35.6)	10 (33.3)	2 (9.1)	2 (28.6)	2 (33.3)	8 (66.7)	1 (25.0)	5 (35.7)	

on typical features											
Unknown	2 (0.5)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
BMI (median (IQR)) - patients aged 16+ only	24.05 (21.92, 26.51)	23.15 (21.63, 25.31)	24.54 (22.22, 26.83)	23.84 (22.04, 26.47)	22.49 (21.08, 24.24)	23.77 (21.32, 26.07)	25.44 (23.83, 29.26)	22.95 (21.71, 24.98)	24.73 (22.74, 27.57)	25.9 7(23.51, 31.20)	0.059
BMI categories (%) - patients aged 16+ only											0.239
BMI < 19	11 (2.8)	2 (2.2)	7 (3.4)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	
BMI 19 - 25	206 (53.4)	54 (58.7)	104 (50.0)	15 (55.6)	12 (63.2)	3 (50.0)	2 (40.0)	8 (66.7)	2 (50.0)	6 (46.2)	
BMI 25 - 30	100 (25.9)	17 (18.5)	64 (30.8)	6 (22.2)	4 (21.1)	3 (50.0)	1 (20.0)	2 (16.7)	1 (25.0)	2 (15.4)	
BMI > 30	38 (9.8)	4 (4.3)	22 (10.6)	4 (14.8)	0 (0.0)	0 (0.0)	1 (20.0)	1 (8.3)	1 (25.0)	5 (38.5)	
Unknown	31 (8.0)	15 (16.3)	11 (5.3)	2 (7.4)	2 (10.5)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	
AD activity prior to COVID-19 infection (%)											<0.001
Remission	211 (47.7)	38 (29.0)	63 (29.2)	6 (20.0)	1 (4.5)	1 (14.3)	2 (33.3)	5 (41.7)	1 (25.0)	1 (7.1)	
Mild	76 (17.2)	62 (47.3)	113 (52.3)	10 (33.3)	5 (22.7)	1 (14.3)	4 (66.7)	6 (50.0)	3 (75.0)	7 (50.0)	
Moderate	118 (26.7)	20 (15.3)	25 (11.6)	13 (43.3)	11 (50.0)	5 (71.4)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)	
Severe	29 (6.6)	7 (5.3)	11 (5.1)	1 (3.3)	5 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (35.7)	
Unknown	8 (1.8)	4 (3.1)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Comorbidities (%)											
Asthma	143 (32.4)	35 (26.7)	71 (32.9)	11 (36.7)	8 (36.4)	3 (42.9)	1 (16.7)	5 (41.7)	3 (75.0)	6 (42.9)	0.446
COPD or other lung disease	14 (3.2)	5 (3.8)	6 (2.8)	2 (6.7)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.624
Allergic rhinitis	52 (11.8)	3 (2.3)	37 (17.1)	4 (13.3)	1 (4.5)	1 (14.3)	1 (16.7)	1 (8.3)	1 (25.0)	3 (21.4)	0.008
Cardiovascular disease	19 (4.3)	3 (2.3)	11 (5.1)	2 (6.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	1 (7.1)	0.593
Hypertension	40 (9.0)	9 (6.9)	25 (11.6)	3 (10.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (14.3)	0.45
Stroke	4 (0.9)	0 (0.0)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.836

Diabetes	22 (5.0)	8 (6.1)	11 (5.1)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	0.645
Chronic liver disease	7 (1.6)	3 (2.3)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	0.032
Chronic kidney disease	5 (1.1)	1 (0.8)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.972
Cancer	2 (0.5)	0 (0.0)	1 (0.5)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.6
Other	66 (14.9)	8 (6.1)	44 (20.4)	5 (16.7)	0 (0.0)	1 (14.3)	2 (33.3)	0 (0.0)	0 (0.0)	6 (42.9)	<0.001
None	174 (39.4)	77 (58.8)	62 (28.7)	12 (40.0)	12 (54.5)	2 (28.6)	1 (16.7)	6 (50.0)	0 (0.0)	2 (14.3)	<0.001
Smoking status (%)											0.39
Current smoker	63 (14.3)	15 (11.5)	39 (18.1)	2 (6.7)	2 (9.1)	1 (14.3)	0 (0.0)	2 (16.7)	1 (25.0)	1 (7.1)	
Former smoker	44 (10.0)	8 (6.1)	29 (13.4)	2 (6.7)	2 (9.1)	1 (14.3)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)	
Never smoked	314 (71.0)	102 (77.9)	139 (64.4)	25 (83.3)	16 (72.7)	4 (57.1)	5 (83.3)	9 (75.0)	2 (50.0)	12 (85.7)	
Unknown	21 (4.8)	6 (4.6)	9 (4.2)	1 (3.3)	2 (9.1)	1 (14.3)	1 (16.7)	0 (0.0)	1 (25.0)	0 (0.0)	

The category 'other conventional immuno-suppressants' includes patients on azathioprine (n=4), and mycophenolate mofetil (n=2). The category 'JAK inhibitors' includes patients on upadacitinib (n=7), abrocitinib (n=4), and an unspecified JAK inhibitor (n=1). The category 'other biologic/small molecule treatments' includes patients on omalizumab (n=2), tralokinumab (n=1), and apremilast (n= 1). The category 'combination treatments' includes patients on dupilumab + systemic corticosteroids (n=6), dupilumab + ciclosporin (n=2), dupilumab + methotrexate (n=1), dupilumab + tofacitinib (n=1), azathioprine + systemic corticosteroids (n=1), ciclosporin + systemic corticosteroids (n=1), ciclosporin + methotrexate (n=1), and mycophenolate mofetil + omalizumab (n=1).

** Median weekly dose, and median weekly dose by weight of methotrexate calculated from n=29 patients receiving MTX weekly, and excluding n=1 receiving methotrexate on alternate weeks.*

*** O*ne patient was reported to be taking ciclosporin 100mg twice per week, but this was likely to be a typographical error and the median daily dose, and median dose by weight were calculated under the assumption this dose was 100mg twice per day.

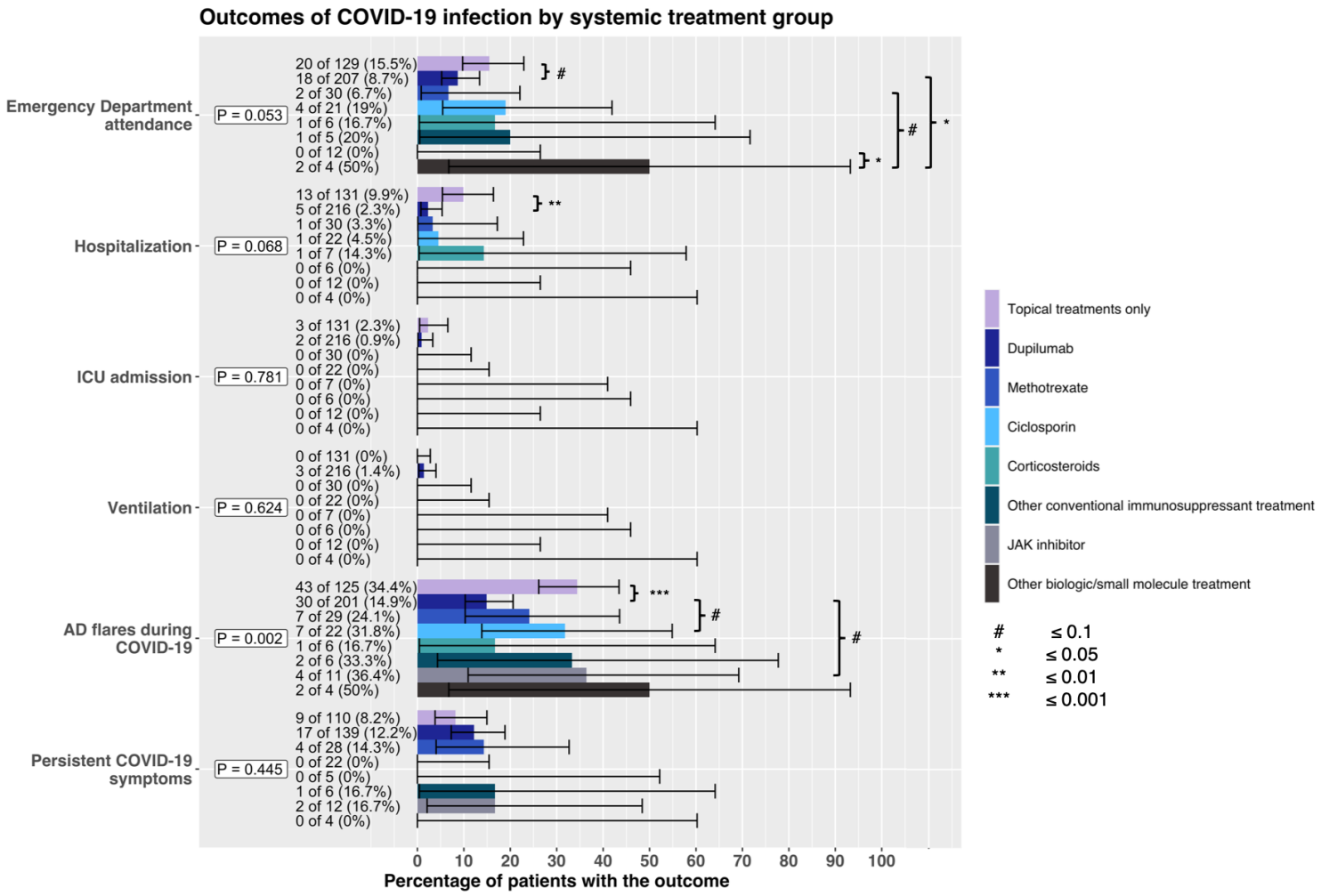
SD = Standard Deviation; IQR = Interquartile range; sTable 1 = Supplementary Table 1; sTable 2 = Supplementary Table 2.

Table 2. **COVID-19 outcomes**

	Overall	Topical treatments only	Dupilumab	Methotrexate	Ciclosporin	Systemic corticosteroids	Other conventional immuno-suppressants	JAK inhibitors	Other biologic/small molecule treatments	Combination treatments
Cases of COVID-19	442	131	216	30	22	7	6	12	4	14
Duration of COVID-19 symptoms in days (median (IQR))	7.0 (3.0, 14.0)	6.0 (0.0, 11.0)	7. 0 (4.0, 14.0)	10.0 (3.0, 15.5)	12.0 (6.0, 15.0)	14.0 (3.0, 14.0)	6.0 (5.0, 24.25)	8.0 (7.0, 13.0)	10.0 (8.25, 11.75)	19.0 (11.0, 42.0)
Complete resolution of COVID-19 (%)										
YES	302 (68.3)	101 (77.1)	122 (56.5)	24 (80.0)	22 (100.0)	5 (71.4)	5 (83.3)	10 (83.3)	4 (100.0)	9 (64.3)
NO	34 (7.7)	9 (6.9)	17 (7.9)	4 (13.3)	0 (0.0)	0 (0.0)	1 (16.7)	2 (16.7)	0 (0.0)	1 (7.1)
Unknown	106 (24.0)	21 (16.0)	77 (35.6)	2 (6.7)	0 (0.0)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (28.6)
Died of COVID-19 (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ED attendance (%)										
YES	55 (12.4)	20 (15.3)	18 (8.3)	2 (6.7)	4 (18.2)	1 (14.3)	1 (16.7)	0 (0.0)	2 (50.0)	7 (50.0)
NO	373 (84.4)	109 (83.2)	189 (87.5)	28 (93.3)	17 (77.3)	5 (71.4)	4 (66.7)	12 (100.0)	2 (50.0)	7 (50.0)
Unknown	14 (3.2)	2 (1.5)	9 (4.2)	0 (0.0)	1 (4.5)	1 (14.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalized (%)	26 (5.9)	13 (9.9)	5 (2.3)	1 (3.3)	1 (4.5)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (35.7)
Median length of hospital stay in days (IQR)	8.0 (4.0, 11.0)	6.0 (4.0, 10.0)	11.0 (9.0, 12.0)	2.0 (2.0, 2.0)	10.0 (10.0, 10.0)	4.0 (4.0, 4.0)	NA	NA	NA	33.0 (5.0, 42.0)
Admitted to ICU (%)	8 (1.8)	3 (2.3)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)

Required ventilation (%)	6 (1.4)	0 (0.0)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)
AD flare during COVID-19 (%)										
YES	100 (22.6)	43 (32.8)	30 (13.9)	7 (23.3)	7 (31.8)	1 (14.3)	2 (33.3)	4 (33.3)	2 (50.0)	4 (28.6)
NO	317 (71.7)	82 (62.6)	171 (79.2)	22 (73.3)	15 (68.2)	5 (71.4)	4 (66.7)	7 (58.3)	2 (50.0)	9 (64.3)
UNKNOWN	25 (5.7)	6 (4.6)	15 (6.9)	1 (3.3)	0 (0.0)	1 (14.3)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)

The category 'other conventional immuno-suppressants' includes patients on azathioprine (n=4), and mycophenolate mofetil (n=2). The category 'JAK inhibitors' includes patients on upadacitinib (n=7), abrocitinib (n=4), and an unspecified JAK inhibitor (n=1). The category 'other biologic/small molecule treatments' includes patients on omalizumab (n=2), tralokinumab (n=1), and apremilast (n= 1). The category 'combination treatments' includes patients on dupilumab + systemic corticosteroids (n=6), dupilumab + ciclosporin (n=2), dupilumab + methotrexate (n=1), dupilumab + tofacitinib (n=1), azathioprine + systemic corticosteroids (n=1), ciclosporin + systemic corticosteroids (n=1), ciclosporin + methotrexate (n=1), and mycophenolate mofetil + omalizumab (n=1). Median length of stay calculated amongst hospitalized patients only.



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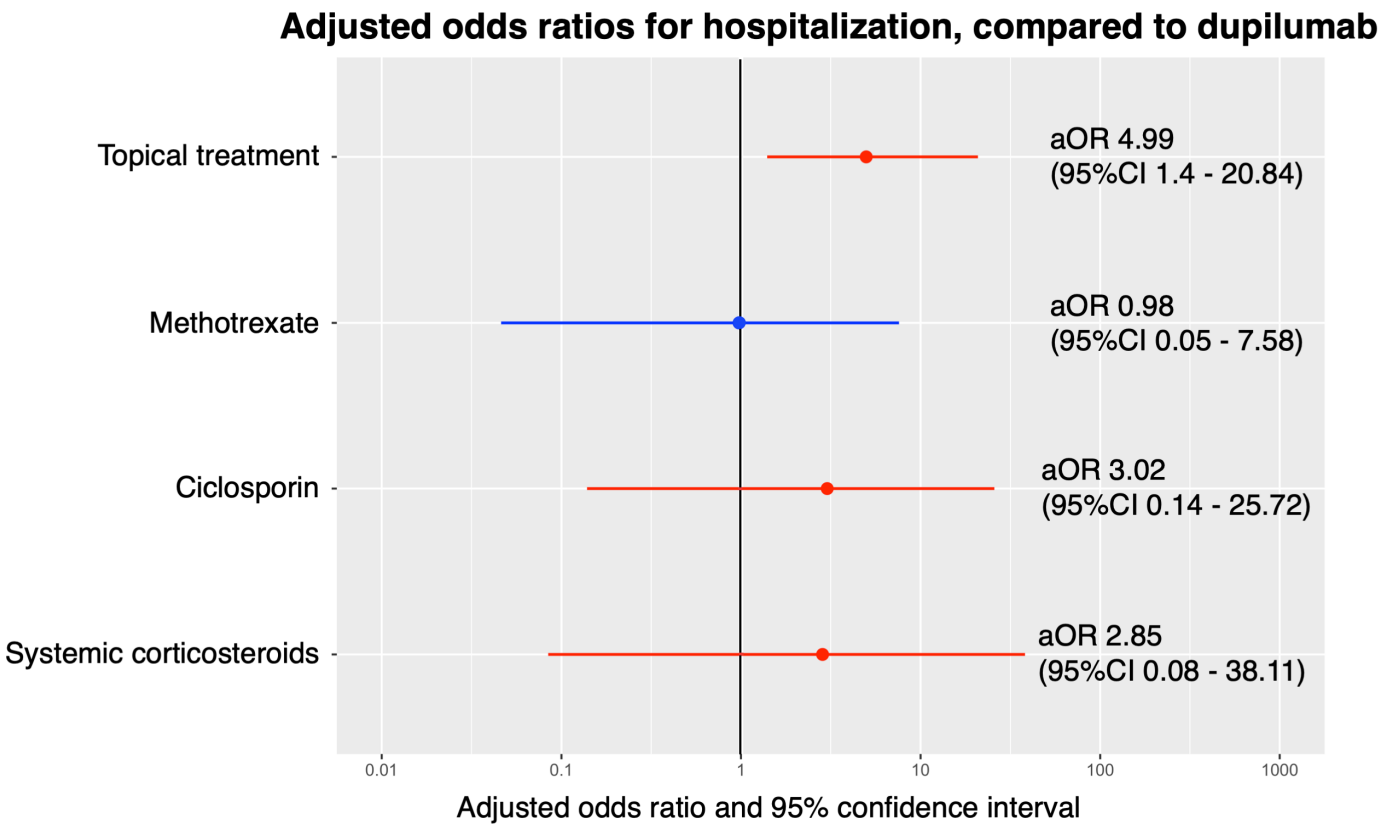

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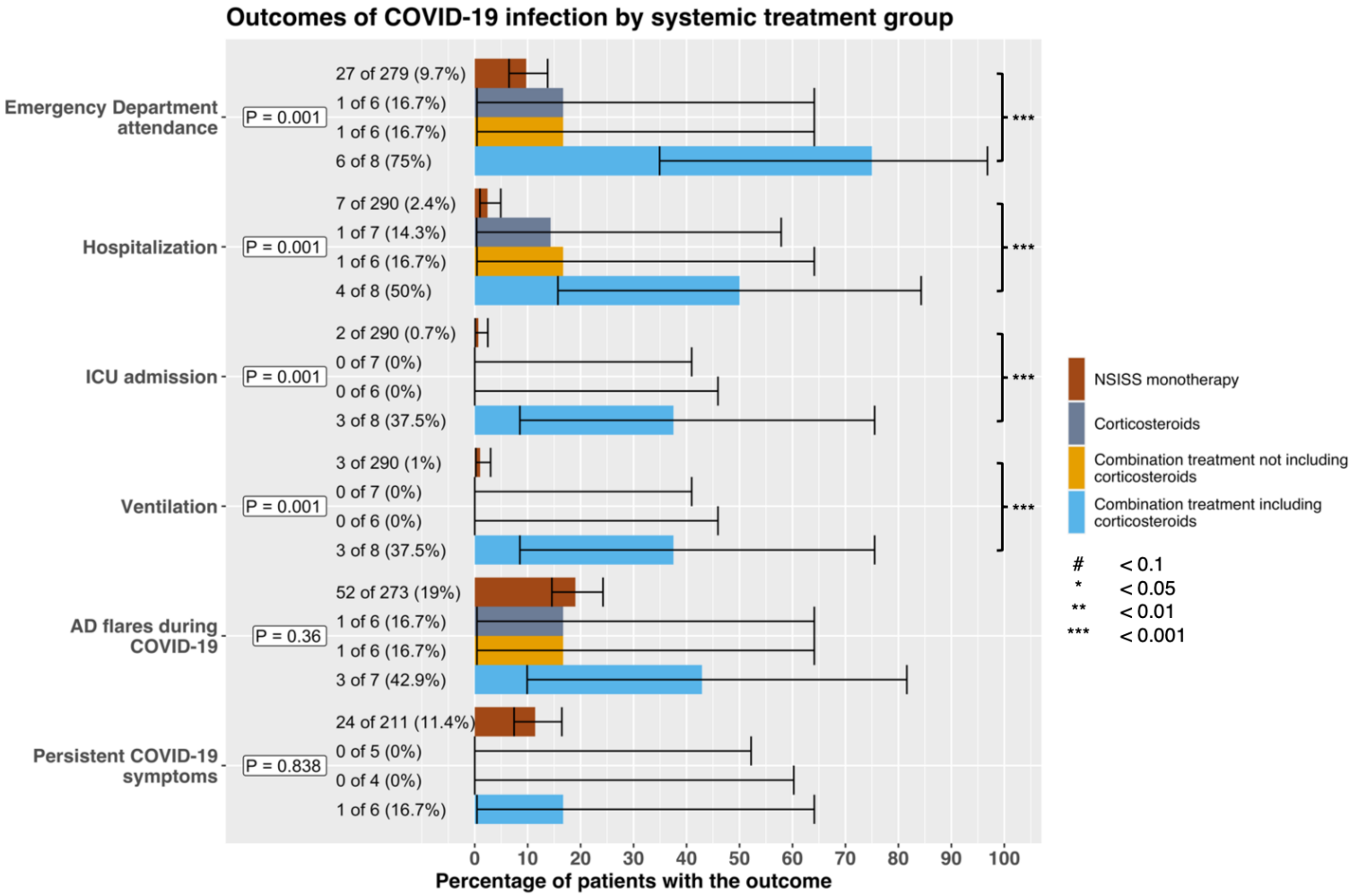

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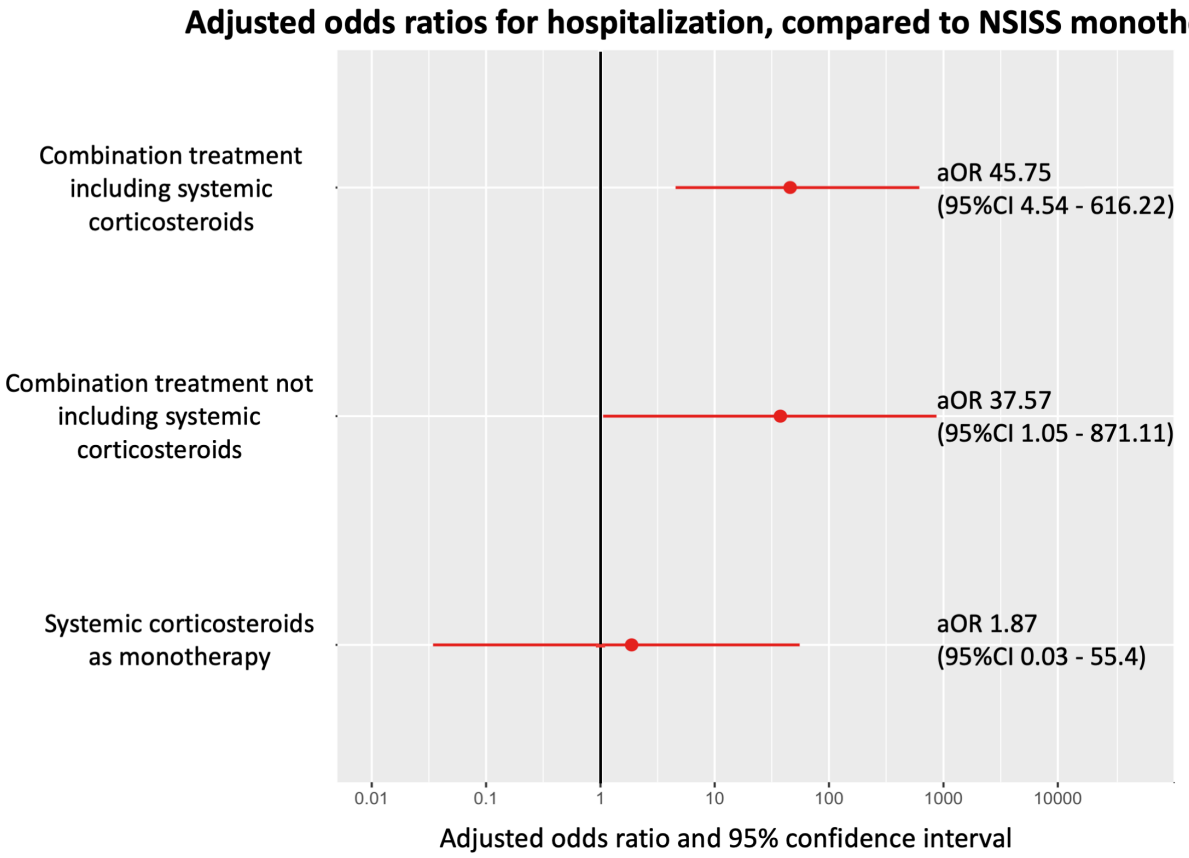

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