Timberlake et al. World Allergy Organization Journal (2021) 14:100508
http://doi.org/10.1016/j.waojou.2021.100508

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Severity of COVID-19 in hospitalized patients with and without atopic disease

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ABSTRACT

Background: Data from the 2009 influenza pandemic suggested asthma might protect from severe disease in hospitalized patients. Asthma does not appear to increase risk for hospitalization or mortality with COVID-19.

Objective: This study was undertaken to see if atopy actually protected those hospitalized with COVID-19.

Methods: 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. Charts were evaluated for history of atopic disease, as were the need for ICU admission, requirement for supplemental oxygen and/or intubation, and in hospital mortality.

Results: 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% ($p = 0.19$). More patients with atopic disease had COPD listed as a diagnosis in their chart (38.8% versus 17.3%, $p < 0.001$). COPD was associated with an increased rate of ICU admission (aOR = 2.22 (1.15, 4.30) $p = 0.02$) and intubation (aOR = 2.05 (1.07, 3.92) $p = 0.03$). After adjusting for COPD, patients with atopic disease had a trend for reduced mortality (aOR 0.55 (0.23, 1.28), $p = 0.16$), but those with asthma did not ($p > 0.2$).

Conclusion: Severity of COVID-19 in hospitalized patients does not differ based on atopic status. However, adjusting for presence of COPD led to a suggestion of possible reduced severity in patients with atopy but not asthma.

Keywords: COVID-19, Atopy, Asthma, SARS-CoV-2, Hospitalization, Severity

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Full list of author information is available at the end of the article https://doi.org/10.1016/j.waojou.2021.100508

http://doi.org/10.1016/j.waojou.2021.100508

Received 3 September 2020; Received in revised from 7 December 2020; Accepted 3 January 2021
Online publication date xxx

INTRODUCTION

With the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic there has been concern that patients with asthma might develop more severe disease. Indeed, asthma was listed by the U.S. Centers for Disease Control and Prevention (CDC) as a potential risk factor early in the pandemic.[1] Further, non-SARS coronaviruses have been reported to drive pulmonary symptoms including asthma exacerbations.[2] However, the initial case series of patients with Coronavirus Disease 2019 (COVID-19) from Wuhan, China, did not list asthma as a coexisting disorder.[3] A subsequent case series of 24 critically ill patients in Seattle, Washington, found asthma as a coexisting disorder in 14% of patients[4] which is similar to the 13.6% prevalence of patients reporting ever having asthma in the 2018 Summary Health Statistics: National Health Interview Survey.[5] More recently, data from Chicago, Illinois, found no increased risk of hospitalization due to SARS-CoV-2 in patients with asthma[6] and additional data from New York did not find increased mortality in those with asthma who were hospitalized with COVID-19.[7] A retrospective chart review of Korean patients showed a risk of more severe disease with COVID-19 in patients with atopic disease, but this risk was small with an adjusted odds ratio of 1.29 and 95% confidence interval of 1.02–1.66. In this study, asthma was not found to be a risk factor for severe disease, but when stratified into allergic asthma (defined as asthma plus allergic rhinitis or atopic dermatitis) versus non-allergic asthma, non-allergic asthma was found to have a greater risk for severe outcomes, with allergic asthma having no increased risk.[8]

While the data overall suggest no increased risk of severity or mortality associated with SARS-CoV-2 infections in asthma patients, there are reasons to believe asthma or atopic disease might be protective – a recent study of Italian patients found decreased risk of severe COVID-19 disease in patients with atopic disease.[9] Further, during the H1N1 influenza pandemic, patients with asthma who were hospitalized with influenza had lower mortality, decreased risk of intensive care unit (ICU) stay, and need for mechanical ventilation.[10] Other than the Italian study, whether a similar level of protection could be seen with the current pandemic respiratory virus, SARS-CoV-2, is not known. With conflicting current data, this study was undertaken to better determine the relationship between atopic disease (including asthma) and severity of COVID-19 in hospitalized patients.

METHODS

Chart review methods

This study was approved by the Institutional Review Board (IRB) of both hospitals. A retrospective chart review of all patients admitted from 3/1/20 (prior to any COVID-19 admissions) through 5/5/20 to Ohio State University Wexner Medical Center (OSUWMC) and Nationwide Children's Hospital (NCH) in Columbus, Ohio was performed. We included all patients admitted to either hospital who had a positive SARS-CoV-2 test at any point during their admission. Both OSUWMC and NCH initially only tested patients who were symptomatic or had known contacts with confirmed COVID-19. On 4/9/20 NCH began testing all admitted patients, while OSUWMC continued testing only those with symptoms or known COVID-19 contacts during the study period. Testing at both institutions was performed by real time polymerase chain reaction (RT-PCR) in the clinical laboratories of each institution. Patients were included if they were admitted for any reason and subsequently were found to have positive testing during their hospitalization. Patients were excluded if they did not have SARS-CoV-2 testing, had negative SARS-CoV-2 testing, or were still admitted on 5/5/20 ($n = 20$). A total of 275 subjects met inclusion criteria, and their charts were evaluated for any history of atopic disease (defined as asthma, allergic rhinitis, atopic dermatitis/eczema, or food allergy) and subsequent hospital course. Allergic rhinitis and food allergy were classified as confirmed or reported based on the presence of confirmatory radioallergosorbent test (RAST) or skin prick testing. When possible, asthma was stratified by disease severity. The primary endpoint was ICU admission, used as a surrogate marker of disease severity. Secondary endpoints included length of stay, supplemental oxygen requirement, ICU length of stay, and whether intubation was required. Laboratory values of

interleukin-6 (IL-6) and C-reactive protein (CRP), as markers of disease severity, were evaluated for correlation with atopic disease.

Statistical analysis

Patient characteristics were compared between patients with and without atopic disease by *t*-test or chi-square test. Outcomes were compared between atopic disease (and specific atopic disease) by chi-square tests for binary outcomes and Wilcoxon rank-sum tests for continuous outcomes. Unadjusted comparison of primary outcomes was performed with both confirmed and reported atopic disease. Results were similar between patients with confirmed and reported atopic disease (data not shown); therefore, subsequent statistical analyses were performed using confirmed atopic disease. Multivariable logistic regression was used to compare outcomes (ICU admission, supplemental oxygen, intubation, and mortality) between patients with and without atopic disease adjusting for age, sex, race, admission diagnosis, obesity, and chronic obstructive pulmonary disease (COPD) status. An additional exploratory analysis was done in the subset of patients who did not have COPD, and their outcomes compared with those of subjects with or without confirmed atopic disease.

RESULTS

Demographics

Based on our inclusion and exclusion criteria, 295 subjects were identified across both hospitals; however, due to a lack of outcome data, 20 subjects who were not discharged by the time of data analysis were excluded from our analysis. The characteristics of the remaining 275 subjects are shown in Table I. Thirteen pediatric patients were from NCH, while 262 adults were hospitalized at the OSUWMC.

As shown in Table I, there were no differences in the age, sex, and race of those subjects with or without atopic disease. However, those with atopic disease had COVID-19 listed as their admission diagnosis more frequently (91%) than those hospitalized without atopic disease (78.9%, $p = 0.02$). Also, subjects with atopic disease were more likely to have a diagnosis of COPD (38.8%) than those without atopic disease (17.3%, $p < 0.001$; overall prevalence of COPD in our cohort was 22.5%). No difference was seen in the frequency of congestive heart failure, chronic kidney disease, hypertension, obesity, or type-2 diabetes between those with and without atopic disease (Table I). Although there was a trend toward increased frequency in the atopic subjects, coronary artery disease was not significantly different between the two groups (20.9% versus 12.5%, atopic versus non-atopic, $p = 0.09$).

Patient medications

A total of 5 subjects with asthma without COPD were on inhaled corticosteroid (ICS) therapy and 7 were on ICS and long-acting beta agonist (ICS-LABA) therapy, while 2 subjects with asthma and COPD were on ICS therapy and 12 were on ICS-LABA therapy, and 0 subjects with COPD without asthma were on ICS and 14 were on ICS-LABA therapy (eTable IV). There were no significant differences between ICS usage between groups ($p = 0.07$). No subjects were on anti-allergic biologic therapies, defined as omalizumab, benralizumab, mepolizumab, or dupilumab. Inpatient usage of systemic steroids, convalescent plasma, remdesivir, and tocilizumab were similar among both the subjects with atopic disease and those without (steroids: 37.3% with atopic disease versus 30.7% without; convalescent plasma: 7.5% with versus 3.4% without; remdesivir: 1.5% with versus 1% without; tocilizumab 9% with versus 12.5% without).

Atopic disease and COVID-19 severity

The frequency of atopic disease in all subjects ranged from 24.4% to 33.1% (confirmed disease versus reported disease) in subjects hospitalized with COVID-19. Interestingly, this is lower than the reported frequency of atopic disease (approximately 40%) in the United States.[11] In our pediatric cohort, 53% had reported atopic disease (23% with confirmed atopic disease) with 7.6% having asthma; however, due to the small sample size, we analyzed the pediatric and adult data together. As shown in Table 2, asthma was the most prevalent atopic disease in our population and was present in 21.8% of the patients hospitalized with COVID-19. This is higher than the current expected prevalence of asthma, which

Variable	Any Confirmed Atopic Disease (n = 67)	No Confirmed Atopic Disease (n = 208)	p-value
Age, mean (SD)	57.7 (18.2)	58.0 (18.5)	0.92
Sex, male	50 (74.6%)	162 (77.9%)	0.58
Race			0.41
White	36 (53.7%)	108 (51.9%)	
Black/African-American	27 (40.3%)	76 (36.5%)	
Other	4 (6.0%)	24 (11.5%)	
Admission Diagnosis			**0.02**
COVID-19[a]	61 (91.0%)	164 (78.9%)	
Other	6 (9.0%)	44 (21.2%)	
Coronary artery disease	14 (20.9%)	26 (12.5%)	0.09
Congestive heart failure	10 (14.9%)	20 (9.6%)	0.23
Chronic kidney disease	9 (13.4%)	27 (13.0%)	0.92
COPD[b]	26 (38.8%)	36 (17.3%)	<**0.001**
Hypertension	42 (62.7%)	119 (57.2%)	0.43
Type 2 diabetes mellitus	22 (32.8%)	63 (30.3%)	0.69
Obesity	29 (43.3%)	73 (35.1%)	0.23

Table 1. Demographics of subjects admitted with COVID-19 *Significance to emphasize statistical significance (p<0.05). a. COVID-19, coronavirus disease 2019 b. COPD, chronic obstructive pulmonary disease*

in Ohio is 9.4%.[12] Allergic rhinitis was found in 11.3% of subjects, which is similar to the national prevalence of this disease; food allergy was seen in 5.5%, slightly less than the 8% prevalence in the United States.[11] While not designed to assess the risk of SARS-CoV-2 infection in subjects with or without asthma/atopy, these data would suggest that patients with asthma were more likely to

Atopic Disease Category	n (%)
Any confirmed atopic disease[a]	67 (24.4%)
Any reported atopic disease[b]	91 (33.1%)
Asthma	60 (21.8%)
Confirmed allergic rhinitis	2 (0.7%)
Reported allergic rhinitis	31 (11.3%)
Dermatitis/eczema	8 (2.9%)
Confirmed food allergy	3 (1.1%)
Reported food allergy	15 (5.5%)

Table 2. Prevalence of atopic disease in study subjects *a. One or more of asthma, confirmed allergic rhinitis, dermatitis/eczema, or confirmed food allergy b. One or more of asthma, reported allergic rhinitis, dermatitis/eczema, or reported food allergy*

Outcome: Supplemental Oxygen		
Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Any Confirmed Atopic Disease	1.25 (0.58, 2.68)	0.57
Age	1.04 (1.02, 1.06)	<0.001
Male Sex	2.61 (1.28, 5.34)	0.01
Race		
White	Reference	
African-American	1.14 (0.59, 2.22)	0.70
Other	1.03 (0.37, 2.82)	0.96
Admission for COVID-19 vs. Other Reason	2.18 (1.04, 4.55)	0.04
COPD	1.95 (0.78, 4.84)	0.15
CAD	0.33 (0.14, 0.79)	0.01
Obesity	1.82 (0.92, 3.61)	0.09
Outcome: ICU Admission		
Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Any Confirmed Atopic Disease	0.72 (0.38, 1.35)	0.30
Age	1.02 (1.01, 1.04)	0.01
Male Sex	2.46 (1.27, 4.77)	0.01
Race		
White	Reference	
African-American	0.99 (0.57, 1.73)	0.98
Other	0.52 (0.19, 1.46)	0.21
Admission for COVID-19 vs. Other Reason	1.45 (0.72, 2.92)	0.30
COPD	2.33 (1.19, 4.55)	0.01
CAD	0.97 (0.47, 2.02)	0.94
Obesity	1.78 (1.01, 3.14)	0.05
Outcome: Mortality		
Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Any Confirmed Atopic Disease	0.55 (0.23, 1.28)	0.16
Age	1.05 (1.02, 1.08)	<0.001
Male Sex	2.36 (0.94, 5.92)	0.07
Race		
White	Reference	
African-American	1.12 (0.56, 2.23)	0.75
Other	0.54 (0.11, 2.59)	0.44
Admission for COVID-19 vs. Other Reason	1.10 (0.45, 2.67)	0.84

(continued)

Outcome: Mortality		
Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
COPD	1.37 (0.65, 2.90)	0.41
CAD	0.94 (0.41, 2.16)	0.89
Obesity	1.07 (0.53, 2.14)	0.86
Outcome: Intubation		
Variable	**Adjusted Odds Ratio (95% CI)**	**p-value**
Any Confirmed Atopic Disease	0.77 (0.40, 1.47)	0.43
Age	1.03 (1.01, 1.05)	0.01
Male Sex	2.74 (1.35, 5.58)	0.01
Race		
White	Reference	
African-American	0.96 (0.54, 1.69)	0.88
Other	0.61 (0.21, 1.83)	0.38
Admission for COVID-19 vs. Other Reason	1.31 (0.63, 2.72)	0.47
COPD	2.14 (1.11, 4.14)	0.02
CAD	0.95 (0.45, 1.97)	0.88
Obesity	1.90 (1.07, 3.38)	0.03

Table 3. (Continued) Multivariable analysis of risk for severe COVID-19 *All multivariable models adjusted for age, sex, race, admission diagnosis (COVID-19 vs. other), COPD, CAD, and obesity. Atopic disease refers to any confirmed atopic disease. a Coronavirus Disease 2019, b Chronic Obstructive Pulmonary Disease, c Coronary Artery Disease*

be hospitalized with COVID-19 than would normally be expected from the general population, while food allergy may have reduced the likelihood of hospitalization with COVID-19 in our population. It is important to stress, however, that these are retrospective data and this study was not designed to assess risk of infection, but rather severity of disease in those already infected (and hospitalized).

In our initial unadjusted comparison, no significant differences in any of our primary or secondary outcomes for patients stratified by atopic disease (or any specific atopic disease) were noted (eTable I). Specifically, there were no differences in the frequency of subjects who were admitted to the ICU, required oxygen or intubation, or died between those with confirmed or reported atopic disease and those without. No differences were seen between the atopic and non-atopic groups in terms of total length of hospitalization or length of ICU stay for those admitted to the ICU. In those subjects in whom IL-6 and CRP levels were available, there was no difference in peak IL-6 or CRP levels between the atopic and non-atopic groups. Altogether, these data suggest that atopy and asthma provide no increased or decreased risk of severe disease when hospitalized with COVID-19.

Race and COVID-19 severity

In our population 37% of the admitted subjects were Black. Since non-White race has been reported as a risk factor for more severe COVID-19 disease,[13] we examined our data for supplemental oxygen use, ICU admission, and mortality stratified by race. As can be seen in eTable II, when stratifying by race, there were no significant differences in any of these outcomes between Black and White subjects.

Adjusted outcomes of COVID-19 severity

Because age, sex, obesity, and race have been reported to increase risk for severe COVID-19

disease, we performed multivariable regression analysis to adjust for these variables.[13,14] We also included COPD and coronary artery disease (CAD) in our adjusted models due to the increased prevalence of these diseases in our atopic population, and their reported association with more severe COVID-19 disease.[14] As shown in Table 3, when adjusting for variables, having atopic disease led to an adjusted odds ratio (aOR) for ICU admission of 1.02 (95% CI: 1.01–1.04) for age, 2.14 (1.13, 4.07) for male sex, and 2.22 (1.15, 4.30) for COPD. No other variables in the model were associated with ICU admission. Odds of intubation or supplemental oxygen requirement were similarly increased with age, male sex, and COPD in those with atopic disease. Obesity was found to be associated with an increased aOR for intubation of 1.90 (95% CI: 1.07, 3.38) and increased aOR for ICU admission of 1.78 (95% CI: 1.01, 3.14). Coronary artery disease was found to be protective of supplemental oxygen need in our study (aOR 0.32 [0.13, 0.77], p = 0.01), although why coronary artery disease would be protective in this case is unclear.

Death during the hospitalization was significantly increased only for age (aOR 1.05 [1.02, 1.08]), although there was a trend for male sex (aOR 2.32 [0.93, 5.77], p = 0.07). Neither COPD nor any of the other the variables in our analysis were associated with increased mortality in our cohort. Interestingly, there was a slight trend for protection from mortality in those with any confirmed atopic disease (aOR 0.55 [0.23, 1.28], p = 0.16).

There was a high prevalence of COPD among both the general cohort and among asthmatic patients. In order to evaluate if the data was skewed by these subjects (ie, those with non-atopic lung disease), we performed a sub-group analysis excluding COPD patients and compared primary outcomes for subjects with atopic disease versus those without atopic disease (eTable III). There were no differences between any primary outcomes; however, there were trends towards decreased ICU admission (26.8% versus 41.3%, p = 0.09) and intubation (22% versus 33.1%, p = 0.16) in the subjects with atopic disease.

DISCUSSION

Previous studies have suggested no increased risk of severe disease in patients with asthma. Our data would support these findings, and we further found no difference in severity of disease in those with atopic disease beyond just asthma. We did find that age, sex, obesity, and presence of COPD as a diagnosis were associated with more severe disease in atopic patients hospitalized with COVID-19. These are risk factors that have been identified in other studies, as well.[14]

Interestingly, the patients admitted with COVID-19 had a much higher rate of asthma (21.8%) than what is expected in Ohio (9.4%). This could suggest that patients with asthma are more likely to be hospitalized if they are infected with SARS-CoV-2 or even that they are more susceptible to the infection. However, an even more likely explanation is that having a history of asthma made it more likely that the patient was hospitalized – especially since the CDC listed asthma as a significant risk factor for severe disease early in the pandemic. In order to truly know if asthma is a risk factor for infection, prospective studies would have to be undertaken.

Our study is somewhat limited by differences in patient population compared to other publications and public health data. We demonstrated a much higher prevalence of COPD (22.5%) in our whole cohort compared to what the Ohio Department of Health has reported for our region of Ohio (5.4%).[15] This suggests, like asthma, that the presence of COPD could be a risk factor for becoming infected with SARS-CoV-2 and/or being hospitalized once infected. Again, as discussed above, an alternative explanation would be that having COPD increased the likelihood of a physician wanting the patient admitted. Again, a prospective study would be required to better address this issue. Regardless of the increased prevalence of COPD in our hospitalized patients, our data demonstrate that having COPD as a diagnosis significantly increased the risk of being intubated and requiring an ICU admission.

We did not see evidence of a differential effect of severity based on subject's race. This is in contrast to early reports that Black patients had increased mortality; however, this is in line with a recent publication that demonstrated that the risk

for in hospital mortality was actually associated with sociodemographic and clinical characteristics, not race.[16] The Ohio census estimations for 2019 record people of Hispanic origin at 4% of the Ohio population,[17] which is mirrored in our data with 3% of patients being of Hispanic origin (included within the "Other" category in Table I). This contrasts to the census data for the United States showing 18.5% of the U.S. population is of Hispanic origin.[18] Similar to data from Louisiana, our study found that African American patients made up a larger proportion of admitted COVID patients than would be expected in the community (37% of admissions, 13.1% of Ohio population),[17] while disease severity and in-hospital mortality was similar between Black and White patients.[16]

Compared to other states, our study found a higher rate in all subjects of ICU admission (44% versus 34% [Louisiana], 14% [New York]) and intubation (36% versus 26% [Louisiana], 12% [New York]) but similar in-hospital mortality (19% versus 23.5% [Louisiana], 21% [New York]).[16,19] This increased risk of ICU admission and intubation may be explained by the increased prevalence of COPD in our study, which was noted to be a risk factor for both ICU admission and intubation. Despite these differences, our study demonstrates no significant difference between severe outcomes for patients with or without atopic disease or asthma.

This retrospective review of patients admitted to OSUWMC and NCH in Columbus, Ohio demonstrated no increased rate of severity or mortality for patients with pre-existing atopic disease, including asthma. Similarly, we did not see any statistically significant protection from COVID-19 disease severity in patients with atopic disease or asthma. COPD, age, obesity, and male sex demonstrated the greatest risk of severe disease in our adjusted models. Additional prospective studies will need to be undertaken to determine whether asthma and/or COPD increase the risk of hospitalization and/or SARS-CoV-2 infection. Nonetheless, this study adds to the mounting data that asthma and atopy are not risk factors for severe COVID-19 disease, something that should be reassuring to patients with these diseases.

Abbreviations

CDC: Centers for Disease Control and Prevention; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease 2019; CRP: C Reactive Peptide; ICS: Inhaled corticosteroid; ICU: Intensive Care Unit; Il-6: Interleukin 6; LABA: Long acting beta agonist; NHANES: National Health and Nutrition Examination Survey; RAST: Radioallergosorbent test; RT-PCR: Real time polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Financial support

The project described was supported by Award Number UL1TR002733 from the National Center for Advancing Translational Sciences, National Institutes of Health, United States of America. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

Author contributions

DTT, PUO, RR, RS, BP, and MG contributed to conception. DTT, DN, RR, and PUO contributed to data collection. KP contributed to statistical analysis. All authors contributed to manuscript preparation and review.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to HIPAA requirements and requirement for IRB approval for data release.

Consent for publications

All authors give consent for the article Severity of COVID-19 in Hospitalized Patients With and Without Atopic Disease to be published in the World Allergy Organization Journal.

Ethics approval

This study was approved by the Institutional Review Board (IRB) of Nationwide Children's Hospital (NCH) and The Ohio State University Wexner Medical Center (OSUWMC).

Declaration of competing interest

Mitchell Grayson: Medical advisory board participant for Aimmune, DBV, GlaxoSmithKline, and Genzyme; Director and Treasurer of the ABAI; Associate Editor of the Annals of Allergy, Asthma, and Immunology; Chair of the Medical Scientific Council of the Asthma and Allergy Foundation of America; Member of the Scientific Advisory Committee of the American Lung Association; Member

of the American Academy of Allergy, Asthma, and Immunology COVID-19 Task Force.

Princess Ogbogu: Advisory board member for AstraZeneca and GlaxoSmithKline; Medical consultant for AstraZeneca; Member of the Board of Directors of the ABAI.

All other authors have no conflicts of interest to disclose.

Acknowledgements
The authors would like to thank Eric McLaughlin, MS for his contribution of statistical analysis for the manuscript revision.

Appendix ASupplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2021.100508.

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