Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Comorbidity defines asthmatic patients' risk of COVID-19 hospitalization: A global perspective

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Background: The global epidemiology of asthma among patients with coronavirus disease 2019 (COVID-19) presents striking geographic differences, defining prevalence zones of high and low co-occurrence of asthma and COVID-19.
Objective: We aimed to compare asthma prevalence among hospitalized patients with COVID-19 in major global hubs across the world by applying common inclusion criteria and definitions.
Methods: We built a network of 6 academic hospitals in Stanford (Stanford University)/the United States; Frankfurt (Goethe University), Giessen (Justus Liebig University), and Marburg (Philipps University)/Germany; and Moscow (Clinical Hospital 52 in collaboration with Sechenov University)/Russia. We collected clinical and laboratory data for patients hospitalized due to COVID-19.
Results: Asthmatic individuals were overrepresented among hospitalized patients with COVID-19 in Stanford and underrepresented in Moscow and Germany as compared with their prevalence among adults in the local community. Asthma prevalence was similar among patients hospitalized in an intensive care unit and patients hospitalized in other than an intensive care unit, which implied that the risk for development of severe COVID-19 was not higher among asthmatic patients. The numbers of males and comorbidities were higher among patients with COVID-19 in the Stanford cohort, and the most frequent comorbidities among these patients with asthma were other chronic inflammatory airway disorders such as chronic obstructive pulmonary disease.
Conclusion: The observed disparity in COVID-19–associated risk among asthmatic patients across countries and continents is connected to the varying prevalence of underlying comorbidities, particularly chronic obstructive pulmonary disease. (J Allergy Clin Immunol 2022;■■■:■■■-■■■.)

Key words: *Chronic airway in inflammation prevalence, chronic obstructive pulmonary disease, COPD, public health, SARS-CoV-2*

The current coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a major burden for the global health care infrastructure. Several comorbidities, such as diabetes, hypertension, coronary heart disease, obesity, and metabolic syndrome, confer an increased risk of SARS-CoV-2 infection and/or severe

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Abbreviations used
COPD: Chronic obstructive pulmonary disease
COVID-19: Coronavirus disease 2019
ICU: Intensive care unit
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
T2: Type 2

COVID-19, including COVID-19–associated mortality.[1] In contrast to seasonal influenza, an early cohort reported that the prevalence of asthma among patients with COVID-19 in the Tongji Hospital (Wuhan, China) was 0.9% lower than that in the general adult population of Wuhan (6.4%).[2-4] We previously published on the global epidemiology of asthma among patients with COVID-19 and found striking geographic differences defining zones with high (eg, the United States, United Kingdom, Ireland, Australia) and low (eg, China, Italy, Spain, Israel, Mexico, Brazil, Saudi Arabia, India) rates of asthma-associated COVID-19.[5] However, why these differences were observed was unclear.

Individuals with asthma are more susceptible to respiratory viral infections, and the majority of acute asthma exacerbations are preceded by a common cold, which is attributed to rhinoviruses, influenza and respiratory syncytial virus among other viruses.[6,7] Furthermore, asthma was consistently recognized as a major risk factor for influenza-associated hospitalization across the several seasons reviewed in Schwarze et al.[8] In regard to COVID-19 infections, the data indicate that SARS-CoV-2 infection is not associated with acute asthma exacerbations; however, the relationship between asthma and severe COVID-19 outcomes is less clear. Early-onset asthma is associated with lower risk of a SARS-CoV-2–positive PCR result.[9] Some studies suggest that nonallergic asthma is associated with a greater risk of severe COVID-19 than the risk among individuals with allergic/type 2 (T2) asthma.[10,11] Indeed, there is evidence that the T2 mediator IL-13 inhibits SARS-CoV-2 infection of the bronchial epithelium[10] and that asthma medication such as inhaled corticosteroids protect against worsening COVID-19 symptoms. Inhaled corticosteroids presumably reduce the expression of angiotensin-converting enzyme-2 (ACE-2) and transmembrane protease serine in the lung.[11] Currently, there is no indication that children with asthma are at higher risk of (severe) COVID-19 than children without asthma.[12]

There is little information on the interrelationship between COVID-19 and chronic inflammatory airway disorders studied by international sites using validated and unified criteria. Such reports often correct for age and sex but very rarely adjust for existing comorbidities, which can vary greatly throughout the world. In this context, the objective of our study was to compare asthma prevalence among hospitalized patients with COVID-19 in major global hubs across continents, as well as associated clinical and laboratory features.

METHODS

We built a network of 6 academic hospitals in California (Stanford University)/the United States; Frankfurt (Goethe University), Giessen (Justus Liebig University) and Marburg (Philipps University)/Germany; and Moscow (Clinical Hospital 52 in collaboration with Sechenov University)/Russia. The German and US participating centers collected clinical and laboratory data for all patients because of COVID-19 from the beginning of the pandemic until the end of 2020 and in September 2020, respectively. Moscow delivered case-control–type data and included patients hospitalized during the period from March 23 to May 16, 2020. Comorbidities reported in the present study were based on the *2020 International Classification of Diseases, 10th Revision,* codes, as described in Table E1 (available in the Online Repository at www.jacionline.org). Whenever applicable, laboratory values were calculated and expressed in the same units for direct comparison.

TABLE I. Age and sex distribution of hospitalized patients with COVID-19, stratified by presence of asthma across the study sites

Patient age and sex categories by location	Patients with asthma	Patients without asthma
Germany, no.	33	1125
Age (y), no. (%)		
0-14	0 (0%)	21 (1.9%)
15-49	6 (18.2%)	274 (24.4%)
50-64	18 (54.5%)	294 (26.1%)
>65	9 (27.3%)	536 (47.6%)
Sex, no. (%)		
Female	15 (45.5%)	451 (40.1%)
Male	18 (54.5%)	674 (59.9%)
Moscow, no.	32	624
Age (y), no. (%)		
0-14	0 (0%)	0 (0%)
15-49	9 (28.1%)	175 (28.0%)
50-64	14 (43.8%)	250 (40.1%)
>65	9 (28.1%)	199 (31.9%)
Sex, no. (%)		
Female	12 (37.5%)	305 (48.9%)
Male	20 (62.5%)	319 (51.1%)
Stanford, no.	89	396
Age (y), no. (%)		
0-14	4 (4.5%)	17 (4.3%)
15-49	34 (38.2%)	149 (37.6%)
50-64	19 (21.3%)	108 (27.3)
>65	32 (36%)	122 (30.8%)
Sex, no. (%)		
Female	36 (40.4%)	211 (53.3%)
Male	53 (59.6%)	185 (46.7%)

Statistical analysis

All statistical analyses were conducted in R software (R Core Team [2021]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/; version 4.1.2).

The prevalence of patients with asthma among hospitalized patients with COVID-19 was calculated from the number of hospitalized patients with asthma divided by the total reported number of hospitalized patients. Although the Germany and Stanford data correspond to a cohort of all hospitalized patients with COVID-19 at these hospitals in the indicated time interval, the Moscow data correspond to all patients with asthma and a set of control individuals without asthma. The prevalence in Moscow was calculated on the basis of all hospitalized patients with COVID-19 in the Moscow hospitals (n = 4549). To compare the prevalence of asthma with the corresponding prevalence in the general population, a binomial test was used. The 95% CI was calculated by the Clopper-Pearson method.[13]

To test whether patients with asthma were overrepresented among the ICU-admitted patients, we used the Fisher exact test; we show the estimated odds ratios and 95% CIs between the odds of ICU|asthma and ICU|no asthma determined by using the R-function Fisher test.

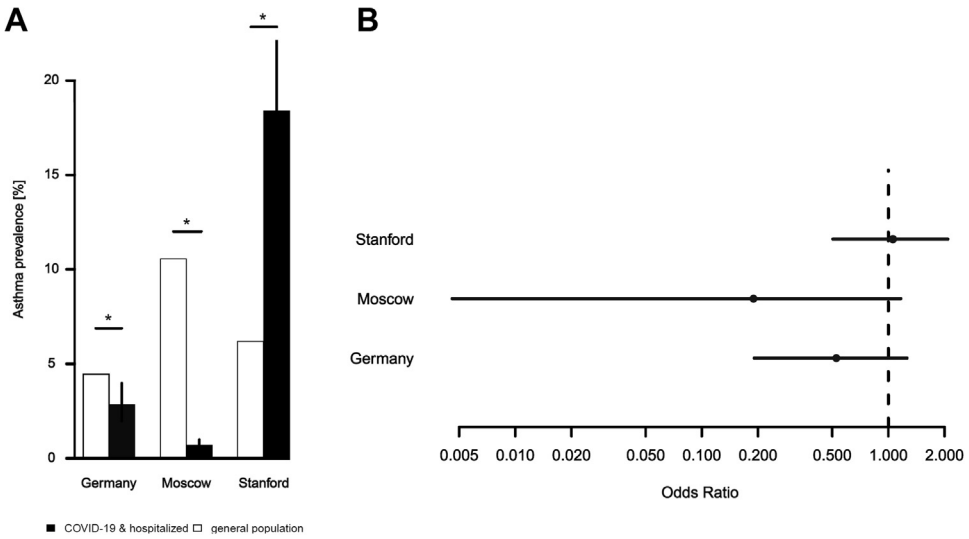

FIG 1. Asthma prevalence and ICU admission for hospitalized patients with COVID-19. **A,** Prevalence of asthma in hospitalized patients with COVID-19. Y-axis denotes the prevalence of the precondition asthma in hospitalized patients with COVID-19 as a percentage. Filled bars correspond to the prevalence of the precondition asthma in hospitalized patients with COVID-19 in Germany (Frankfurt, Giessen, and Marburg), Moscow, and Stanford. Open bars indicate the prevalence of asthma in the general populations in the corresponding areas. Vertical lines indicate the 95% Clopper-Pearson CI. **B,** Odds ratios for asthma and ICU admission. X-axis denotes the odds ratio between Odds (ICU|asthma) and Odds (ICU|no asthma). Dots indicate the value of the point estimate for Germany (Frankfurt, Giessen, and Marburg), Moscow, and Stanford. Horizontal lines indicate the 95% CI. Dotted vertical line denotes an odds ratio of 1 (ie, no association).

To test whether any of the additional preconditions are overrepresented in the patients with asthma versus in the patients without asthma, we used the Fisher exact test. We corrected for multiple testing by using the Benjamin-Hochberg method[14] and report significant differences at a false discovery rate of 10%.

To test whether the number of additional preconditions differs between patients with asthma and patients without asthma, we used a Wilcoxon rank sum test. To adjust for confounders explaining the overrepresentation of asthmatic patients in Stanford, we performed logistic regression using the center, age group, sex, and 11 comorbidities to predict whether a patient was asthmatic. This analysis was restricted to the centers in Moscow and Stanford, for which we had microdata available. From the so-fitted model, we calculated the odds of being asthmatic given that the patient was from Stanford, was female, and had no comorbidity over the different age groups.

To identify possible confounders for the laboratory measurements, a linear regression model was fitted with the predictors age group, sex, and preconditions (including asthma). These analyses revealed a strong and significant effect of the precondition chronic obstructive pulmonary disease (COPD) and the eosinophil count at admission, during the hospital stay, and at discharge. Thus, we removed patients who had a precondition of COPD and recalculated averages and SEs.

Data sharing

All data requests should be submitted to the corresponding author via e-mail for consideration. Access to anonymized data may be granted after review of each study site's principal investigator(s) and signing of bilateral data transfer agreements as applicable.

RESULTS

Age and sex distributions for all included hospitalized COVID-19 cohorts stratified for the presence of asthma are shown in Table I. The participating German centers included asthmatic patients who were significantly younger than those in the nonasthmatic patient group, whereas the Stanford group of patients with asthma had significantly more male patients (Table I [$P = .0343$]). The vast majority of patients included in the German and Russian cohorts (>90%) were White individuals, although we could not collect precise data on ethnicity for these cohorts. The US cohort included 246 Hispanic individuals (50.7%) and 18 African American individuals (3.7%). In all of the studied countries with the exception of the United States (as represented by the Stanford cohort), asthma was significantly underrepresented in the cohorts of hospitalized patients with COVID-19 versus among adults in the respective local community. In the Stanford cohort, the prevalence of asthma was 18.35%, as compared with a prevalence of 10.56% in the broader California area.[15] (Fig 1, *A*). We assessed the prevalence of asthma among intensive care unit (ICU) patients and found that it did not differ significantly from the prevalence among patients in non-ICU care for any of the participating centers (Fig 1, *B*).

We next examined the presence of comorbidities among hospitalized patients with COVID-19 across our centers and found that the Stanford cohort exhibits an overrepresentation of patients with asthma and COPD versus patients without asthma and COPD (Fig 2, *A* [$P = .0046$]). We observed a similar trend for other comorbidities (concurrent or past) such as cancer and chronic renal disease for patients hospitalized in Stanford; however, these differences between patients with asthma and without asthma who were hospitalized for COVID-19 did not reach statistical significance (Fig 2, *A*). Furthermore, the patients in Stanford had more (total) comorbidities than the patients in Germany and Moscow did (Fig 2, *A*). Importantly, the asthma group in Stanford had more additional preconditions than the group without asthma, with more than 85% of asthmatic patients having an additional comorbidity (Fig 2, *B* [$P = .0346$]). This was not the case with the German and Moscow centers, in which asthmatic patients and nonasthmatic patients showed a similar pattern in terms of frequency of additional comorbidities (Germany, $P = .216$; Moscow,

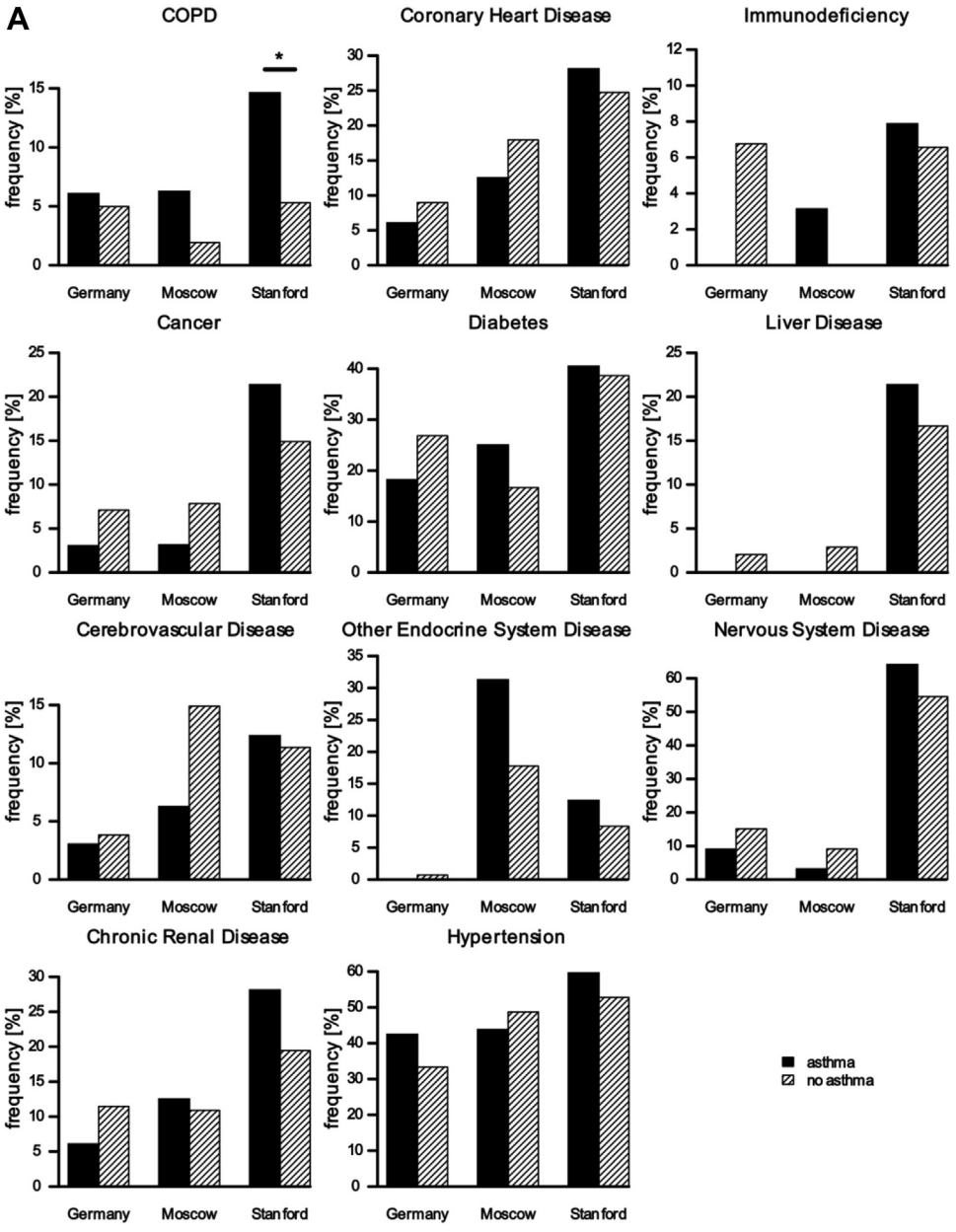

FIG 2. Additional preconditions for hospitalized patients with COVID-19 with or without asthma. **A,** Prevalence of additional preconditions in patients with and without asthma. Y-axes denote the prevalence of the respective precondition. The filled bars correspond to the prevalence of the respective precondition among hospitalized patients with COVID-19 with asthma in Germany (Frankfurt, Giessen, and Marburg), Moscow, and Stanford. Striped bars denote the prevalence of the respective precondition among hospitalized patients with COVID-19 without asthma. Horizontal line indicates significant differences in the prevalence of the respective precondition between patients with asthma and without asthma. **B,** Frequency of patients with 0 to 11 additional preconditions (except asthma). X-axis denotes the number of additional preconditions per patient. Y-axis denotes the frequency of patients as a percentage.

$P = .8256$ [Fig 2, *B*]). Furthermore, a second "wave" of comorbidity frequency was recorded with a second peak after 3 comorbidities on top of asthma and COVID-19 (Fig 2, *B*). The overrepresentation of asthmatic patients among hospitalized patients with COVID-19 in Stanford can be explained by confounders such as age, sex, and comorbidities. To mitigate the effect of these confounders, we performed logistic regression to predict asthma by using the center (Moscow or Stanford, where microdata were available), sex, and the 11 comorbities. This resulted in a decrease in the odds of being asthmatic given that the center was Stanford, the sex was female, and no comorbidity was present in any of the 4 age groups (Fig 3). The 95% CIs of the

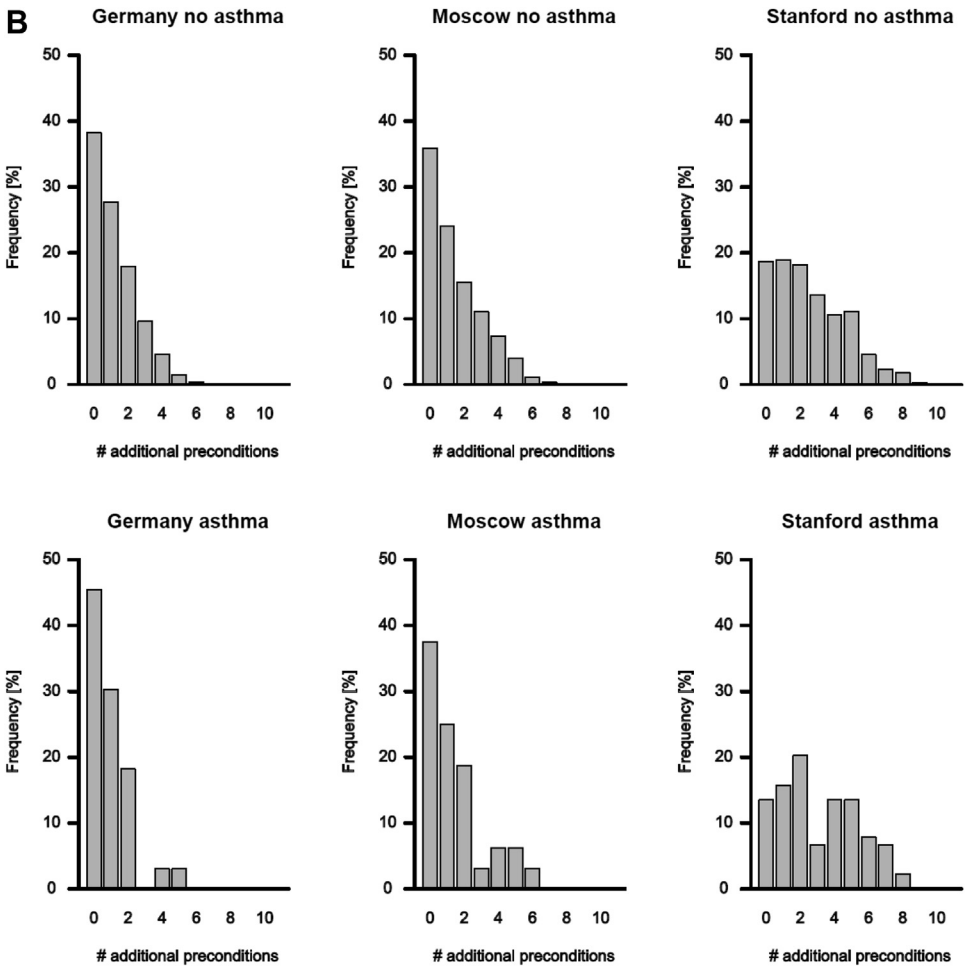

FIG 2. *(Continued).*

so-adjusted odds reach the population level, and lower odds than the population level are not excluded.

We next analyzed the basic laboratory values of all included patients across study centers and observed a peripheral blood eosinopenia at admission in all centers except the Stanford center, followed by a recovery close to discharge (Fig 4 and see Fig E1 in the Online Repository at www.jacionline.org). The Stanford group showed higher levels at admission and overlapping values until discharge (ie, no significant change throughout their hospitalization). Platelet counts showed a somewhat similar pattern; however, both the patients with asthma and those without asthma at Stanford had relatively stable counts throughout. The values of all other studied laboratory parameters did not deviate significantly between the centers of our network (see Fig E1).

DISCUSSION

The global epidemiology of asthma among patients with COVID-19 has been described by a number of contradictory reports. We aimed at investigating potential reasons underlying the published discrepancies by joining forces with key academic institutions across 3 countries and 3 continents with varying local allergy and asthma epidemiology. Our study has contributed important findings in the field: first, we showed that when the same inclusion criteria were used, a male sex bias characterized asthmatic populations when they were overrepresented among hospitalized patients with COVID-19. Second, we tested the hypothesis that patients with COVID-19 with asthma have a more severe disease trajectory but found similar asthma prevalence among patients who received care in the ICU and patients not admitted to the ICU . Third, we showed that the number of comorbidities was higher among patients with COVID-19 in the Stanford cohort, which showed a higher prevalence of asthma than in the other centers (spectrum bias). The most frequent comorbidities among these patients with asthma were other chronic inflammatory airway disorders such as COPD, which has been long recognized as a risk factor for COVID-19 hospitalization.

The prevalences of asthma among hospitalized patients with COVID-19 in our German (2.85%) and Moscow (0.70%) centers are in accordance with those in previously published reports (as high as 1.8%-2.6% in Sweden[16] and 1.8% in Russia[17]). Our Stanford data (18.39%) showed a similar trend but an even higher asthma prevalence than in previous reports (up to 14%).[18,19] Clinical outcome was not adverse for asthmatic patients because there was no overrepresentation among patients in the ICU versus among patients not in the ICU. This finding is in accordance with the findings of prior studies looking into severe COVID-19 outcomes, including mortality, among patients with asthma.[2] Male sex bias

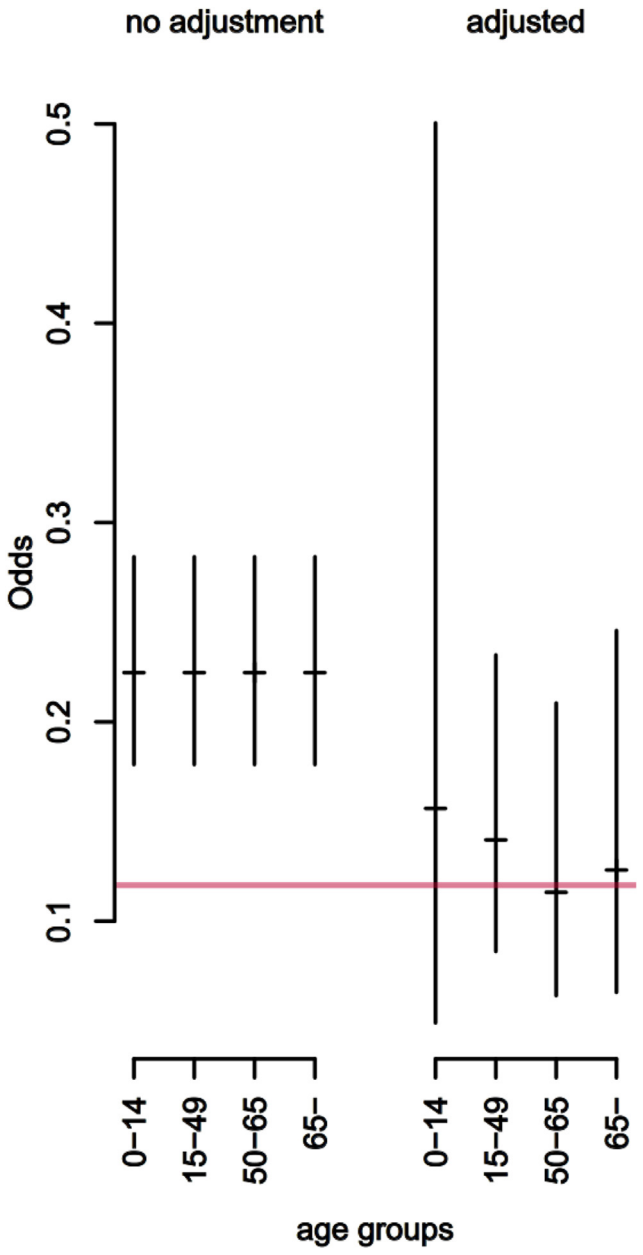

FIG 3. Confounder analysis. Odds of a patient having asthma given that he or she was from Stanford are shown on the left (no adjustment) for the indicated age groups. Odds of a patient having asthma given that he or she was from Stanford, female, and had no comorbidity are shown on the right (adjusted) for the indicated age groups. Vertical lines indicate the 95% CI. Red horizontal line indicates the odds of asthma in the general population.

is expected in childhood asthma, and although the vast majority of participants were adults (Table I), males were overrepresented among patients with asthma in the Stanford cohort. Given the fact that male sex is also associated with more severe COVID-19 outcomes, this may somehow be associated with the higher prevalence of asthmatic patients among hospitalized patients in Stanford.[20]

Patients with underlying comorbidities are at risk for development of severe COVID-19, and the association is closer with particular comorbidities such as diabetes and hypertension. The overrepresentation of asthmatic patients in the hospitalized COVID-19 cohort in Stanford may thus be due to the copresence of a number of other comorbidities that exist in this population and shape their actual risk of hospitalization. Moreover, COPD stood out as a significantly more prevalent condition among asthmatic patients in Stanford. Indeed, COPD increases the risk for development of severe COVID-19 outcomes, including mortality. This may explain the epidemiologic finding of a high asthma prevalence in the Stanford cohort.[21] More than 50% of patients with asthma and COVID-19 in Stanford (vs ~5% in Germany and 20% in Moscow) had 3 or more additional comorbidities, which underlines the fact that this population differed significantly in terms of risk factors.

We have assessed basic hematologic, biochemical, coagulation, and inflammatory biomarkers of COVID-19 across patient groups and centers. The difference in terms of eosinophil counts at admission and trend during hospitalization between the Stanford and other centers could have several potential explanations. Peripheral blood eosinophil counts are associated with disease endotype, and higher numbers could be indicative of a high-T2 endotype among asthmatic patients in the United States. In addition, SARS-CoV-2 is associated with peripheral blood eosinopenia, and a difference in this regard could reflect different timing of admission following infection with the virus, differences in underlying pathomechanisms, or differences in treatment regimens. Quite importantly, the guidelines regarding reasons for hospital admission in individual countries differ. Therefore, asthma comorbidity as a potential risk factor for severe disease could potentially drive enhanced hospitalization in the US cohort as opposed to in the other included cohorts, and this may be further reflected by the absence of eosinophil suppression in the former (collider bias).

Our study has several limitations. We could not address differences in COVID-19 severity as per the World Health Organization or National Institutes of Health criteria across cohorts because the necessary information was not accessible by all centers. Moreover, 1 participating center (Moscow) delivered data in a case-control rather than cohort manner, whereas data on individual patients were available for only the Moscow and Stanford cohorts, thus excluding additional biostatistical analyses for the other centers. To determine overall risk of hospitalization we needed data on all patients being tested in the participating centers, which was not possible for the index study. In addition, data on disease phenotype could not be collected for asthmatic patients included in the study. Precise data on the ethnicity of patients included in the German and Russian cohorts were not available, and we therefore could not test the hypothesis of an ethnicity bias with the Stanford cohort. Indeed, ethnicity may play an important role in susceptibility to and severity of COVID-19.[22] Finally, we were also unable to compare socioeconomic status and access to health care across study sites.

On the other hand, our study is characterized by a number of strengths, including the intercontinental collection of both clinical and laboratory data, the stringent definition of comorbidities including asthma, and the harmonized inclusion criterion in terms of hospitalization due to COVID-19 rather than to SARS-CoV-2 testing positivity alone. Our findings suggest that pathogenetic mechanisms involving eosinophils and the T2 disease endotype as factors protective against COVID-19 are less important than associated comorbidities, which seem to dictate the hospitalization risk of asthmatic patients. Future research is required to address pending questions such as overall risk of hospitalization for people with asthma.

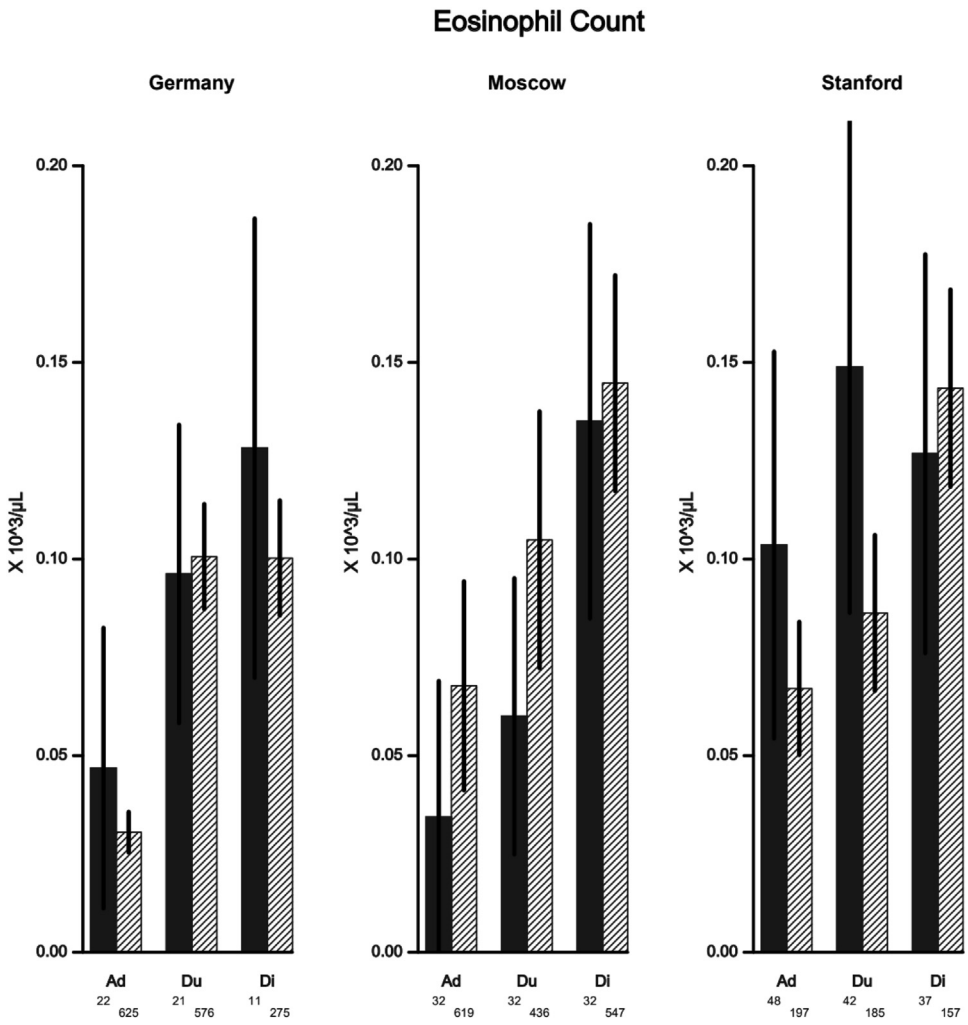

FIG 4. Peripheral blood eosinopenia for hospitalized patients with COVID-19 with or without asthma. Average eosinophil counts at admission (Ad), during the hospital stay (Du), and at discharge (Di) for patients with asthma (*solid bars*) and without asthma (*striped bars*). Y-axis denotes the eosinophil count ($\times 10^3/\mu L$). Vertical lines denote the 95% CI. Numbers below the bars indicate the number of patients.

Clinical implications: In the future, public health policies will need to consider comorbidities with an emphasis on COPD for prioritization of vaccination and preemptive treatment.

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