Comorbidity defines risk of asthmatics for COVID-19 hospitalization: a global perspective

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Abstract

Background: The global epidemiology of asthma among COVID-19 patients presents striking geographic differences defining high and low [asthma and COVID-19] co-occurrence prevalence zones (1). The objective of the present study was to compare asthma prevalence among hospitalized COVID-19 patients in major global hubs across the world with the application of common inclusion criteria and definitions. **Methods:** We built a network of six academic hospitals in Stanford (Stanford University)/USA, 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. Comorbidities reported were based on the 2020 International Classification of Diseases-10th Revision codes. **Results:** Asthmatics were overrepresented among hospitalized COVID-19 patients in Stanford and underrepresented in Moscow and Germany as compared to the prevalence among adults in the local community. Asthma prevalence was similar among ICU and hospital non-ICU patients, which implied that the risk for developing severe COVID-19 was not higher among asthmatics. The number of males and comorbidities was higher among COVID-19 patients in the Stanford cohort, and the most frequent comorbidities among these asthma patients were other chronic inflammatory airway disorders such as chronic obstructive pulmonary disease (COPD). **Conclusion:** Observed disparity in COVID-19-associated risk among asthmatics across countries and continents is connected to varying prevalence of underlying comorbidities, particularly COPD. Public health policies in the future will need to consider comorbidities with an emphasis on COPD for prioritization of vaccination and preemptive treatment.

Introduction

The current coronavirus-induced disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a major burden for the global healthcare infrastructure. Several comorbidities such as diabetes, hypertension, coronary heart disease, obesity and metabolic syndrome confer an increased the risk for SARS-CoV-2 infection and/or severe COVID-19, including COVID-19-associated mortality . In contrast to seasonal influenza, an early cohort reported that the prevalence

of asthma among COVID-19 patients in the Tongji Hospital (Wuhan) was 0.9%, lower than that in the adult population of Wuhan (6.4%) . We previously published on the global epidemiology of asthma among COVID-19 patients and found striking geographic differences defining high (eg USA, UK, Ireland and Australia) and low (eg China, Italy, Spain, Israel, Mexico, Brazil, Saudi Arabia, India) asthma COVID-19 zones . 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 (RSV) among other viruses . Furthermore, asthma has been consistently recognized as a major risk factor for influenza-associated hospitalization across several seasons reviewed in . In regards to COVID-19 infections, data indicate that SARS-CoV-2 infection is not associated with acute asthma exacerbations but the relationship between asthma and severe COVID-19 outcomes is less clear. Early onset asthma is associated with a lower risk of SARS-CoV-2 positive PCR test . Some studies suggest that non-allergic asthma is associated with a greater risk for severe COVID-19 as compared to individuals with allergic/type 2 asthma . Indeed, there is evidence that type 2 mediator IL-13 inhibits SARS-CoV-2 infection of bronchial epithelium and that asthma medication such as inhaled corticosteroids protect from worsening COVID-19 symptoms. Inhaled corticosteroids presumably reduce the expression of angiotensin converting enzyme-2 (ACE-2) and transmembrane protease serine in the lung . Currently, there is no indication that children with asthma are at higher risk for (severe) COVID-19 than children without asthma .

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 COVID-19 patients in major global hubs across continents as well as associated clinical and laboratory features.

Methods

We built a network of six academic hospitals in California (Stanford University)/USA, 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 hospitalized due to COVID-19 since the beginning of the pandemic until end of 2020 and September 2020 respectively. Moscow delivered case-control type of data and included patients hospitalized during 23.03.-16.05.2020. Reported comorbidities reported in the present study were based on the 2020 International Classification of Diseases-10$^{\text{th}}$ Revision codes as described in Supplementary Table 1. Laboratory values were calculated and expressed in the same units for direct comparison whenever applicable.

Statistical Analysis

All statistical analyses were conducted in R (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 asthma patients among the hospitalized COVID-19 patients was calculated from the number of hospitalized asthma patients divided by the reported number of total hospitalized patients. While Germany and Stanford data correspond to a cohort of all hospitalized COVID-19 patients at these hospitals in the indicated time interval, Moscow data corresponds to all asthma cases and a set of control cases without asthma. The prevalence in Moscow was calculated based on all hospitalized COVID-19 cases in the Moscow hospitals (4,549). To compare the prevalence of asthma to the corresponding prevalences in the general population, a binomial test was used. The 95% confidence interval was calculated by the method of Clopper-Pearson .

To test whether asthma patients were over-represented among the ICU admitted patients we used Fisher's exact test and show the estimated odds ratios and 95% confidence intervals between Odds (ICU|asthma)

and Odds (ICU|no asthma) reported by the R-function fisher test.

To test whether any of the additional preconditions are over-represented in the asthma compared to the non-asthma patients we used Fisher's exact test. We corrected for multiple testing using the method of Benjamin-Hochberg and report significant differences at a false discovery rate of 10%.

To test whether the number of additional preconditions is different between patients with asthma and without asthma we used a Wilcoxon rank sum test. To adjust for confounders explaining the overrepresentation of asthmatics in Stanford, we performed logistic regression using the center, age group, sex and the 11 comorbidities to predict whether a patient was asthmatic. This analysis was restricted to the centers Moscow and Stanford, for which we had microdata available. From the so-fitted model, we calculated the Odds to be asthmatic given that the patient was from Stanford, 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, preconditions (including asthma). These analyses revealed a strong and significant effect of the precondition COPD and the eosinophil count at admission, during the hospital stay, and at discharge. Thus, we removed patients that had a precondition of COPD and recalculated averages and standard errors.

Results

Age and gender distribution for all included hospitalized COVID-19 cohorts stratified for the presence of asthma are shown in Table 1. The participating German centers included asthmatics who were significantly younger than the non-asthmatic group, while Stanford asthma group had significantly more male patients (Table 1, p-value = 0.0343). The vast majority ($> 90\%$) of patients included in the German and Russian cohorts were Caucasian, albeit we could not collect precise data on ethnicity for these cohorts. The US cohort comprised of 246 (50.7%) Hispanics and 18 (3.7%) Afro-Americans. Asthma was significantly underrepresented (vs. prevalence among adults in local community) in hospitalized COVID-19 cohorts of all included countries in our study with the exception of the Stanford cohort. The latter encompassed asthmatics with a prevalence of 18.35% as compared to a 10.56% prevalence of asthma in the broader California area (Figure 1). We assessed the prevalence of asthma among intensive care unit (ICU) patients and found that it did not significantly differ from the prevalence among patients in normal care for any of the participating centers (Supplementary Figure 1).

We next examined the presence of comorbidities among hospitalized COVID-19 patients across our centers and found that the Stanford cohort exhibits an over-representation of asthma & COPD patients versus non-asthma & COPD patients (Figure 2a, p-value = 0.0046). 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 asthma and non-asthma hospitalized COVID-19 patients did not reach statistical significance (Figure 2a). Furthermore, the patients in Stanford had more (total) comorbidities compared to Germany and Moscow (Figure 2a). Importantly, the asthma group in Stanford had more additional preconditions than the non-asthma group with over 85% of asthmatics having an additional comorbidity (Figure 2b, p-value = 0.0346). This was not the case with the German and Moscow centers, where asthmatics and non-asthmatics showed a similar pattern in terms of frequency of additional comorbidities (Figure 2b, Germany: p=0.216, Moscow: p=0.8256). Furthermore, a second 'wave' of comorbidity frequency was recorded with a second peak after 3 comorbidities on top of asthma and COVID-19 (Figure 2b). The overrepresentation of asthmatics among hospitalized COVID-19 patients in Stanford can be explained by confounders, like age, sex, and comorbidities. To mitigate the effect of these confounders we performed logistic regression to predict asthma using the center ("moscow" or "stanford", where microdata was available), sex and the 11 comorbities. This resulted in a decrease in the Odds to be asthmatic given that the center was "stanford", the sex was "female" and no comorbidity was present in all four age groups (Figure 3). The 95% confidence intervals of so-adjusted Odds reach the population level and lower Odds than the population level are not excluded.

We next analyzed basic lab values of all included patients across study centers and observed a peripheral blood eosinopenia at admission in all centers except Stanford, followed by a recovery close to discharge (Figure 4, Supplementary Figure 2). The Stanford group showed higher levels at admission and overlapping values until discharge i.e., no significant change throughout their hospitalization. Platelet counts showed a somewhat similar pattern; however, both asthma and non-asthma patients at Stanford had relatively stable counts throughout. Values of all other studied laboratory parameters did not significantly deviate between centers of our network (Supplementary Figure 2).

Discussion

Global epidemiology of asthma among COVID-19 patients has been described by a number of contradictory reports. We aimed at investigating potential reasons underlying published discrepancies by joining forces with key academic institutions across three countries and three continents with varying local allergy and asthma epidemiology. Our study has contributed with important findings in the field: first, we showed that using the same inclusion criteria, a male gender bias characterized asthmatic populations, when they were overrepresented among hospitalized COVID-19 patients. Second, we tested the hypothesis whether COVID-19 patients with asthma have a more severe disease trajectory but found similar asthma prevalence among ICU and normal care patients. Third, we showed that the number of comorbidities is higher among COVID-19 patients in the Stanford cohort, which showed a higher prevalence of asthma as compared to the other centers (spectrum bias). The most frequent comorbidities among these asthma patients were other chronic inflammatory airway disorders such as COPD. The latter has been long recognized as a risk factor for COVID-19 hospitalization.

The prevalence of asthma among hospitalized COVID-19 patients in our German (2.85%) and Moscow (0.70%) centers is in accordance to previously published reports of up to 1-8-2.6% in Sweden and 1.8% in Russia . Our Stanford data (18.39%) show a similar trend but an even higher asthma prevalence as compared to previous reports of up to 14% . Clinical outcome was not adverse for asthmatics since there was no overrepresentation among ICU vs standard care patients. This finding is in accordance with prior studies looking into severe COVID-19 outcomes, including mortality, among asthma patients . Male sex bias is expected in childhood asthma and although the vast majority of participants were adults (Table 1), males were overrepresented among asthma patients in the Stanford cohort. Given the fact that male gender is also associated with more severe COVID-19 outcomes, this may somehow be associated with the higher prevalence of asthmatics among hospitalized patients in Stanford .

Patients with underlying comorbidities are at risk for developing severe COVID-19 and the association is closer with particular comorbidities such as diabetes and hypertension. The overrepresentation of asthmatics in the hospitalized COVID-19 cohort in Stanford may thus be due to the co-presence of a number of other comorbidities in this population, which shape their actual risk for hospitalization. Moreover, COPD stood out as a significantly more prevalent condition among asthmatics in Stanford. Indeed, COPD increases the risk for development of severe COVID-19 outcomes, including mortality. This may explain the epidemiological finding of high asthma prevalence in the Stanford cohort . Over 50% of asthma COVID-19 patients in Stanford (versus approx. 5% in Germany and 20% in Moscow) suffered from [?]3 additional comorbidities, which underlines the fact that this population significantly differed in terms of risk factors.

We have assessed basic hematological, 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 US asthmatics. In addition, SARS-CoV-2 is associated with peripheral blood eosinopenia and a difference in this regard could reflect different timing of admission since infection with the virus, differences in underlying pathomechanisms or differences in treatment regimens. Quite importantly, 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 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 WHO or NIH criteria across cohorts since the necessary information was not accessible by all centers. Moreover, one of of the participating centers (Moscow) delivered data in a case-control rather than cohort manner, while individual patients' data were available for only the Moscow and the Stanford cohort thus excluding additional biostatistical analyses for the other centers. In order to determine overall risk for hospitalization we needed data on all patients being tested in 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 was not available and we therefore cannot 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 . Finally, socioeconomic status and access to health care could also not be compared 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 as well as the harmonized inclusion criterium in terms of hospitalization due to COVID-19 rather than SARS-CoV-2 testing positivity alone. Our findings suggest that pathogenetic mechanisms involving eosinophils and T2 disease endotype as protective factors for COVID-19 are less important compared to associated comorbidities, which seem to dictate hospitalization risk of asthmatics. Future research is required to address pending questions such as overall risk for hospitalization for people with asthma.

Contributors

CS and HR conceived the idea and developed the study design. CS, SC, DF, GR, CSe, SS, AG, AV collected clinical and laboratory data. HRC conducted data analysis. CS, AnK, DF, AlK, MX and HR reviewed the literature. CS wrote the initial draft, and all authors were involved in commenting on subsequent revisions. All authors are the guarantors. All authors had full access to all relevant data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

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IgGenix; Consultancy, Excellergy, Red tree ventures, Phylaxis; National Scientific Committee member, Immune Tolerance Network, National Institutes of Health (NIH) clinical research centers; holds patents for, Mixed allergen composition and methods for using the same, Granulocyte-based methods for detecting and monitoring immune system disorders, Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders, Methods of isolating allergen-specific antibodies from humans and uses thereof

Data sharing

All data requests should be submitted to the corresponding author via email 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.

Tables

Table 1. Age and gender distribution of hospitalized COVID-19 patients, stratified based on the presence of asthma, across study sites.

			asthma	non-asthma
Germany			33	1125
	Age			
		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%)
	Gender			
		female	15 (45,5%)	451 (40,1%)
		male	18 (54,5%)	674 (59,9%)
Moscow			32	624
	Age			
		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%)
	Gender			
		female	12 (37,5%)	305 (48,9%)
		male	20 (62,5%)	319 (51,1%)
Stanford			89	396
	Age			
		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%)
	Gender			
		female	36 (40,4%)	211 (53,3%)
		male	53 (59,6%)	185 (46,7%)

SUPPLEMENTARY TABLES

Supplementary Table 1. ICD codes included under each studied comorbidity as per the 2020 ICD catalogue.

Chronic obstructive pulmonary disease	J44.0*; J44.1*; J44.8*; J44.9*
Cancer II	C*
Cerebrovascular disease	I60*;I61*;I62*;I63*;I64*;I65*;I66*;I67*;I68*;I69*
Chronic renal disease	N18.2*; N18.3*; N18.4*; N18.5*; N18.89*; N18.9*
Coronary heart disease	I20*;I21*;I22*;I23*;I24*;I25*
Diabetes	E10*;E11*;E12*;E13*;E14*
Other Endocrine system disease	E20*;E21*;E22*;E23*;E24*;E25*;E26*;E27*;E28*;E29*;E31*;E34*
Hypertension	I10*;I11*;I12*;I13*;I14*;I15*
Immunodeficiency	D80*, D81*; D82*; D83*; D84*; D90*; D70*; D71*; B20*;B21*;B22*;B23*;B24*
Liver disease	K70*; K71*; K73*; K74*; K75*; K76*; K77*
Nervous system disease	G*
Other chronic lung disease	E84*; J41*, J42*; J43*, J44*, J47*; J60*;J61*;J62*;J63*;J64*;J65*;J66*;J67*; J84.1*

Figure Legends

Figure 1: Asthma prevalence and ICU admission for hospitalized COVID-19 patients. (a) Prevalence of asthma in hospitalized COVID-19 patients. The y-axis denotes the prevalence of the precondition asthma in hospitalized COVID-19 patients in percent. The filled bars correspond the prevalences of the precondition asthma in hospitalized COVID-19 patients in Germany (Frankfurt, Gießen and Marburg; yellow), Moscow (orange), and Stanford (purple). The open bars indicate the prevalence of asthma in the general population in the corresponding areas. The vertical lines indicate the 95% Clopper-Pearson confidence interval.

(b) Odds ratios for asthma and ICU admission. The 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; yellow), Moscow (orange), and Stanford (purple). The horizontal lines indicate the 95% confidence interval. The dotted vertical line denotes an odds ratio of 1, i.e., no association.

Figure 2: Additional preconditions for hospitalized COVID-19 patients with or without asthma. (a) Prevalences of additional preconditions in patients with and without asthma. The y-axes denote the prevalences of the respective precondition. The filled bars correspond the prevalences of the respective precondition among hospitalized COVID-19 patients with asthma in Germany (Frankfurt, Gießen and Marburg; yellow), Moscow (orange), and Stanford (purple). The striped bars denote the prevalences of the respective precondition among hospitalized COVID-19 patients without asthma. The horizontal line indicates significant differences in the prevalences of the respective precondition between patients with asthma and without asthma. COPD: Chronic Obstructive Pulmonary Disease. (b) Frequency of patients with 0 to 11 additional preconditions (except asthma). The x-axis denotes the number of additional preconditions per patient. The y-axis denotes the frequency of patients in percent.

Figure 3: Confounder analysis. Odds of being asthmatic given that the patient was from Stanford is shown on the left (no adjustment) for the indicated age groups. The odds of being asthmatic given that the patient was from Stanford, female and had no comorbidity is shown on the right (adjusted) for the indicated age groups. The vertical lines indicate the 95% confidence interval. The red horizontal line indicates the Odds of asthma in the general population.

Figure 4: Peripheral blood eosinopenia for hospitalized COVID-19 patients 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). The y-axis denotes the eosinophil count time s103 per µl. The vertical lines denote the 95% confidence interval. The numbers below the bars indicate the number of patients.

Supplementary Figure 2: Laboratory parameters for hospitalized COVID-19 patients with or without asthma. Average laboratory parameters at admission (Ad), during the hospital stay (Du), and at discharge (Di) for patients with asthma (solid bars) and without asthma (striped bars). The y-axis denotes

the value with the indicated unit. The vertical lines denote the 95% confidence interval. The numbers below the bars indicate the number of patients.

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