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ORIGINAL RESEARCH

Uncontrolled Asthma and Severe COVID-19: A Prospective Bidirectional Risk Analysis

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Purpose: Asthma control is multifaceted, involving symptoms and risk of adverse outcomes. Emerging evidence suggests a bidirectional link between poor asthma control and severe COVID-19, but large studies addressing all components of asthma control in this context are lacking. Our aims were to evaluate if 1) uncontrolled asthma was a risk factor for COVID-19 hospitalization and death, 2) asthma control changed during the pandemic and 3) COVID-19 hospitalization was a risk factor for future uncontrolled asthma.

Methods: Patients with asthma (n = 125,362) were identified in the Swedish National Airway Register from January 2014 to 2020, whereof n = 2377 were hospitalized and n = 305 died due to COVID-19 during follow-up until December 2022. Asthma control was evaluated by symptoms (Asthma Control Test (ACT) ≥ 20: well controlled, ACT 16–19 not well-controlled and ACT < 16 very poorly controlled asthma), lung function (FEV_1% predicted (pp)) and frequent and/or severe exacerbations (dispensed oral corticosteroids and asthma inpatient care).

Results: ACT 16–19 (RR 1.57, 95% CI 1.34–1.84), ACT < 16 (1.72, 1.46–2.02), FEV_1 < 80pp (1.29, 1.13–1.48), frequent (1.99, 1.79–2.21) and severe exacerbations (2.54, 2.09–3.08) were associated with a higher risk for COVID-19 hospitalization. COVID-19 death was associated with ACT < 16, frequent and severe exacerbations. Overall, at follow-up, proportions of ACT < 20 (36.1%) and FEV_1 < 80pp (48.3%) were stable, while exacerbations decreased (frequent; 7.9% to 6.8%, severe; 1.3% to 0.4%). COVID-19 hospitalization was a risk factor for frequent (1.35, 1.22–1.51) and severe (3.42, 1.22–1.51) future asthma exacerbations.

Conclusion: All dimensions of poor asthma control were associated with an increased risk of severe COVID-19. In contrast, only exacerbation risk was elevated following COVID-19.

Plain Language Summary: Poor asthma control may increase the risk of severe COVID-19, and severe COVID-19 may also affect asthma afterwards. This has not been studied in a large group before. We analyzed data from over 125,000 patients with asthma in Sweden. We found that patients who, at the start of the study, had poor symptom control, reduced lung function, or had experienced asthma flare-ups in the past were more likely to develop severe COVID-19 later on. During the pandemic, symptom control and lung function stayed stable, while flare-ups decreased. However, patients who had been hospitalized for COVID-19 experienced more flare-ups afterwards, compared to those who had not been hospitalized.

Keywords: asthma control, asthma control test, ACT, COVID-19, exacerbation, lung function

Introduction

Asthma is a chronic inflammatory airway disease characterized by respiratory symptoms that fluctuate in intensity and frequency over time, accompanied by variable expiratory airflow. The main target of asthma management is to attain asthma control, as uncontrolled asthma is associated with increased morbidity and mortality.[1,2] Overall, asthma control involves achieving good symptom control and reducing the risk of impaired lung function and exacerbations, where the

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latter may be caused by viral infections.[2] Therefore, there was a significant concern that the coronavirus (SARS-CoV-2) could increase the risk of asthma exacerbations, and more severe COVID-19 outcomes.[3,4]

During the first wave of the pandemic, several studies showed that uncontrolled asthma was a risk factor for a more severe COVID-19.[5–7] However, other studies reported that asthma exacerbations decreased, and possible explanations were the reduced spread of viruses due to isolation and social distancing, and improved self-care with better adherence to asthma treatment.[1,8] However, reduced care availability during the pandemic, ie patients not receiving care, complicated the assessment of exacerbation frequency.[9] Thus, the conditions during the pandemic continued to change, and uncontrolled asthma as a risk factor beyond the first wave of the COVID-19 pandemic has been less extensively investigated.

The impact of COVID-19 on asthma patients is complex and varies by multiple factors such as asthma phenotype, severity, medication response, and other known risk factors such as male sex, older age, obesity, cardiovascular disease and diabetes.[10–13] Some studies have reported impaired asthma control following COVID-19 infection, whereas others have found no deterioration in asthma control in relation to COVID-19 infection.[11,12,14–16] However, these studies include relatively small study samples, and to better understand the relationship between asthma and rapidly evolving communicable diseases such as COVID-19, population-based registries containing real-world information are of great importance.[17] Therefore, we used the Swedish National Airway Register (SNAR), which includes clinical data on more than 100,000 patients with asthma and has been previously utilized in similar studies.[6,18] Our aims were to evaluate 1) if uncontrolled asthma assessed by Asthma Control Test (ACT), lung function and asthma exacerbations was a risk factor for COVID-19 hospitalization and death, 2) if asthma control changed during the pandemic and 3) if COVID-19 hospitalization was a risk factor for future uncontrolled asthma.

Materials and Methods

Study Design and Data Collection

This is a prospective cohort study with individuals from the SNAR, a national quality register that includes patients in primary and secondary care with a physician diagnosed asthma (International Classification of Diseases, version 10; ICD-10 J45) or chronic obstructive pulmonary disease (COPD) (ICD-10 J44). A flowchart of the study design is shown in Figure 1. The study sample consists of adult patients with asthma, identified in the SNAR between 1 January 2017 and 24 January 2020 (n = 125,362). Patients younger than 18 years, and patients with concomitant COPD were excluded. Baseline data: sex, age, Body Mass Index (BMI), smoking status, allergy diagnosis, ACT scores and lung function values, were extracted from SNAR during the same period, ie before the first case of COVID-19 was registered in Sweden. Follow-up data on ACT and lung function were retrieved during the period from 24 January 2020 to 31 December 2022. If hospitalized due to COVID-19, only the ACT score and lung function value after the first admission due to COVID-19 were extracted. For variables with repeated measurements, only the most recent value was extracted.

The SNAR database was linked to other Swedish mandatory national registers using the unique Swedish identity number as a key. COVID-19 hospitalization was identified in n = 2377 patients as primary discharge diagnosis in the National Patient Register (NPR) and COVID-19 deaths in n = 305 patients as primary cause of death in the National Cause of Death Register (NCDR) until 31 December 2022 based on the ICD-10 codes U07.1 or U07.2, respectively. Data on dispensed medication according to Anatomical Therapeutic Chemical (ATC) codes were linked from the National Prescribed Drug Register (NPDR), and information on inpatient care due to asthma with a primary ICD-10 code J45 or J46 from the NPR. The time window for the extracted baseline data was 23 January 2019 to 23 January 2020 and for follow-up data 31 December 2021 to 31 December 2022.

The study complied with the Declaration of Helsinki. After approval by the Swedish Ethical Review Authority (reference number 2019-04915 and 2020-02777), the SNAR data were extracted from the Centre of Registers Västra Götaland and linked with register data provided by the National Board of Health and Welfare (NPR, NCDR and NPDR). The pseudonymized research database is held and managed by Region Norrbotten, Sweden. Informed consent is not required in Sweden when quality register data is used for research and was therefore not obtained.

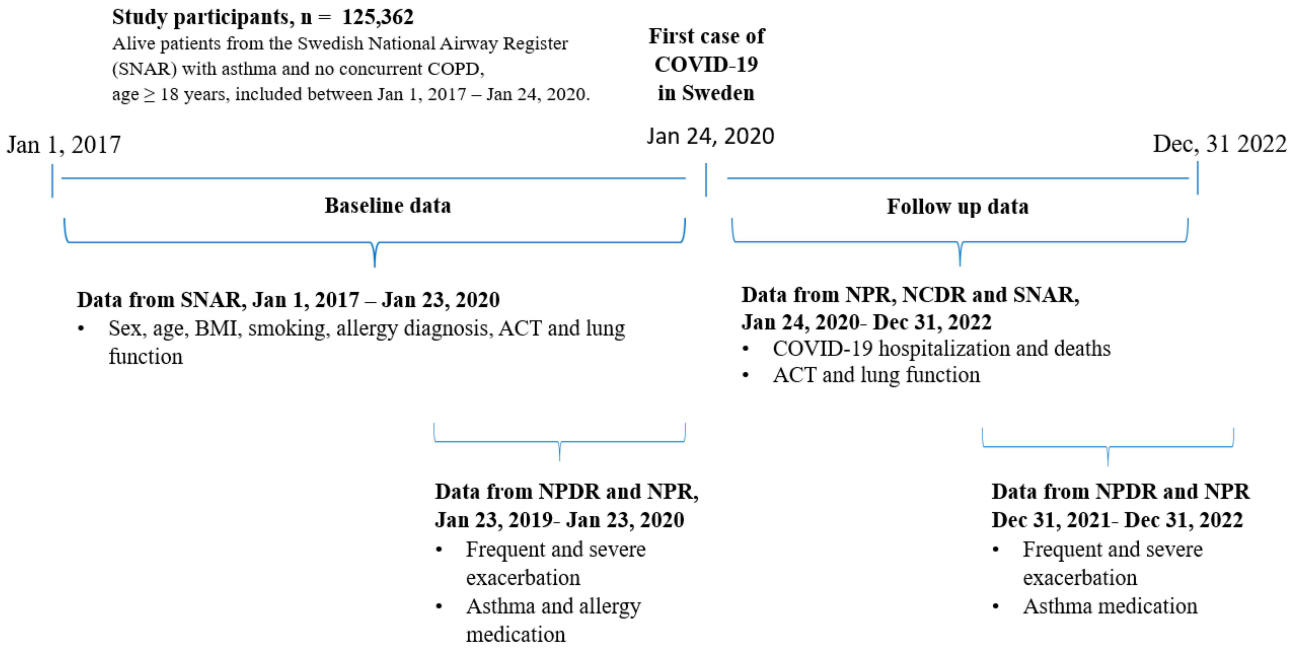

Figure 1 Flowchart of the study design and included study participants.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; BMI, Body Mass Index; ACT, Asthma Control Test; NPDR, National Prescribed Drug register; NPR, National Patient Register.

Definitions

Obesity was defined as BMI ≥ 30.0 kg/m^2.

Smoking status was divided into current smokers, former smokers (including those who quit smoking during the last 6 months) and non-smokers.

Allergy was defined as from a physician-reported, affirmative response to the following question in SNAR: Does the patient have an allergy diagnosis? And/or dispensed medication of antihistamines (R06AE07, R06AX).

Asthma control test (ACT) score 5–25 was used as a continuous variable and dichotomized as ACT ≥ 20 (controlled asthma) and ACT < 20 (uncontrolled asthma), and furthermore into subgroups, ACT 16–19 (not well-controlled asthma) and ACT < 16 (very poorly controlled asthma).[2]

Lung function was assessed based on pre bronchodilator Forced Expiratory Volume in one second in liters (FEV_1), and percent of predicted value (FEV_1pp) and Swedish reference values were used.[19,20] Pre FEV_1pp was further categorized as FEV_1 < 80pp to identify patients with lower lung function.[21]

Frequent exacerbations were defined as ≥2 dispensed oral corticosteroid (OCS) during one year using the ATC code H02AB.[2]

Severe exacerbations were defined as ≥1 hospitalization due to asthma with a primary ICD-10 code J45 (asthma) or J46 (status asthmaticus) during one year.[2]

Asthma medications were categorized according to ATC codes into only short-acting beta-agonists (SABA) and any inhaled corticosteroids (ICS). Any ICS included single ICS, and/or combinations of ICS/long-acting beta-agonists (LABA) and/or ICS/LABA/long-acting muscarinic antagonists (LAMA).

Statistics

All statistical analyses were conducted using IBM SPSS Statistics (version 29). Chi-square tests, and independent-sample t-tests, were used to assess differences in means and proportions between groups. A p-value less than .05 was considered statistically significant. The association between asthma control and COVID-19 was analyzed by adjusted Poisson regression and the results are presented as risk ratios (RR) with 95% confidence intervals (CI). For the first aim, the dependent variables were COVID-19 hospitalization and death, respectively. The independent variables were ACT 16–19

and ACT < 16, FEV_1 < 80pp, frequent, and severe exacerbations at baseline, all analyzed in separate models and adjusted for sex, age and BMI at baseline. For the second aim, paired sample *t*-test and McNemar's test was used. For the third aim, similar analyses were conducted as in the first aim, but with ACT < 20, FEV_1 < 80pp, frequent, and severe exacerbations at follow-up respectively, as the dependent variables, and COVID-19 hospitalization as independent variable with additional adjustment for baseline ACT < 20, FEV_1 < 80pp, frequent and severe exacerbations as appropriate. To maintain statistical power in the adjusted models, internal missing values on BMI ACT and FEV_1pp were handled as separate categories.

Results

Pre-Pandemic Characteristics

At baseline, patients later hospitalized due to COVID-19 (n = 2377) were older and more frequently male and obese than those without COVID-19 hospitalization (n = 122,985). Hospitalized patients had also significantly lower mean ACT scores, lower FEV_1pp, more frequent and severe exacerbations and more dispensions of asthma medications (Table 1).

Table 1 Pre-Pandemic Characteristics at Baseline of Adult Asthma Patients with COVID-19 Hospitalization versus No COVID-19 Hospitalization

	COVID-19 Hospitalization n = 2377	**No COVID-19 Hospitalization n = 122,985**	**p-value**
Age, mean (± SD)	63.5 (16.1)	51.5 (18.5)	<0.001
Men, n (%)	993 (41.8)	46,796 (38.1)	<0.001
BMI			
BMI, kg/m^2, mean (± SD)	30.45 (6.2)	27.9 (5.8)	<0.001
Obesity, BMI ≥ 30, n (%)	829 (46.6)	25,928 (30.4)	<0.001
Smoking status, n (%)			
Current smoker	133 (7.4)	11,040 (12.0)	<0.001
Former smoker	507 (28.1)	19,971 (21.6)	
Non-smoker	1166 (64.6)	61,350 (66.4)	
Allergy, n (%)	1013 (42.6)	55,032 (44.7)	0.039
ACT			
ACT score, mean (± SD)	18.7 (4.9)	19.9 (4.4)	<0.001
ACT ≥ 20, n (%)	459 (50.7)	19,214 (37.4)	<0.001
ACT 16–19, n (%)	234 (25.9)	10,485 (20.4)	<0.001
ACT < 16, n (%)	225 (24.9)	8729 (17.0)	<0.001
Lung function			
FEV_1 in Liters, mean (± SD)	2.3 (0.8)	2.7 (0.9)	<0.001
FEV_1pp, mean (± SD)	74.6 (17.7)	80.5 (16.1)	<0.001
FEV_1 < 80pp, n (%)	567 (60.1)	24,219 (45.2)	<0.001
Exacerbations, n (%)			
Frequent exacerbations	427 (18.0)	9511 (7.7)	<0.001
Severe exacerbations	108 (4.5)	1562 (1.3)	<0.001
Asthma Medication			
Dispensed SABA[1], mean (± SD)	1.7 (2.7)	1.3 (2.2)	<0.001
Only SABA[1], n (%)	124 (5.2)	9810 (8.0)	<0.001
Any ICS[2], n (%)	1850 (77.8)	85,750 (69.7)	<0.001

Notes: [1]Number of dispensations during the year 2019. [2]Any Inhaled corticosteroids (ICS) includes single ICS, and/or ICS/long-acting beta-agonists (LABA), and/or ICS/LABA/long-acting muscarinic antagonists (LAMA) during the year 2019. Missing data n (%): BMI, 38,324 (30.6), Smoking status, 31,195 (24.9), ACT, 73,075 (58.3), FEV_1pp 70,828 (56.5); percentages calculated for those with complete data.

Abbreviations: ACT, Asthma Control Test; FEV_1pp, FEV_1% predicted (pp); SABA, short-acting beta-agonists.

Asthma Control in Association with COVID-19 Hospitalization and Death

There was a significantly higher risk for COVID-19 hospitalization for patients with ACT 16–19 (not well-controlled asthma), RR 1.57 (95% CI 1.34–1.84), ACT < 16 (very poorly controlled asthma), RR 1.72 (95% CI 1.46–2.02), FEV_1 < 80pp, RR 1.29 (95% CI 1.13–1.48) frequent, RR 1.99 (95% CI 1.79–2.21) and severe exacerbations RR 2.54 (95% CI 2.09–3.08). There was also a significantly higher risk for COVID-19 death for patients with ACT < 16, RR 2.33 (95% CI 1.37–3.97), frequent exacerbations, RR 2.61 (95% CI 1.95–3.49) and severe exacerbations, RR 3.21 (95% CI 1.84–5.59). Adjustments for sex, age, and obesity were applied in both models (Figure 2).

Change in ACT Scores, Lung Function and Exacerbations

Follow-up data on ACT was available for n = 155 (6.5%) of those with a COVID-19 hospitalization and n = 14,829 (12.1%) among those without. The mean value of ACT increased by less than one point, and the proportion of patients with ACT 16–19 and ACT < 16 decreased in both groups. Lung function follow-up data was available for n = 150 (6.3%) of those who had been hospitalized, and n = 13,744 (11.2%) among non-hospitalized patients. FEV_1pp remained on a similar level among hospitalized patients and decreased among non-hospitalized patients. There was no significant change in the proportion of patients with FEV_1 < 80pp. In both those hospitalized and not hospitalized for COVID-19, the proportion of frequent and severe exacerbations decreased significantly (Table 2). When comparing baseline characteristics between patients with and without follow up data on ACT and lung function, only small differences were found. Patients with follow-up on ACT had higher mean ACT at baseline than those without follow-up, 20.0 vs 19.8 while patients with lung function follow-up data had lower mean FEV_1pp at baseline than those without, 79.5 vs 80.6. Of the patients who received a follow-up assessment of ACT, 91.3% also underwent a spirometry follow-up (Supplementary Table 1).

COVID-19 Hospitalization and Associations with Future Asthma Control

In the adjusted analysis, COVID-19 hospitalization was not a risk factor for future uncontrolled asthma as measured by ACT < 20 or FEV_1 < 80pp (Figure 3). The strongest risk factors for ACT < 20 and FEV_1 < 80pp at follow-up, were low values on ACT and FEV_1 at baseline, RR 2.48 (95% CI 2.34–2.63) and RR 4.94 (95% CI 4.62–5.29), respectively. When adjusted for exacerbations at baseline, COVID-19 hospitalization was a risk factor for future asthma exacerbations; frequent exacerbations, RR 1.35 (95% CI 1.22–1.51), and severe exacerbations, RR 3.42 (95% CI 2.60–4.49) (Figure 3). Moreover, previous exacerbations were the strongest risk factor for future exacerbations at follow up: frequent, RR 7.83 (95% CI 7.50–8.18) and severe, RR 17.30 (95% CI 14.12–21.19).

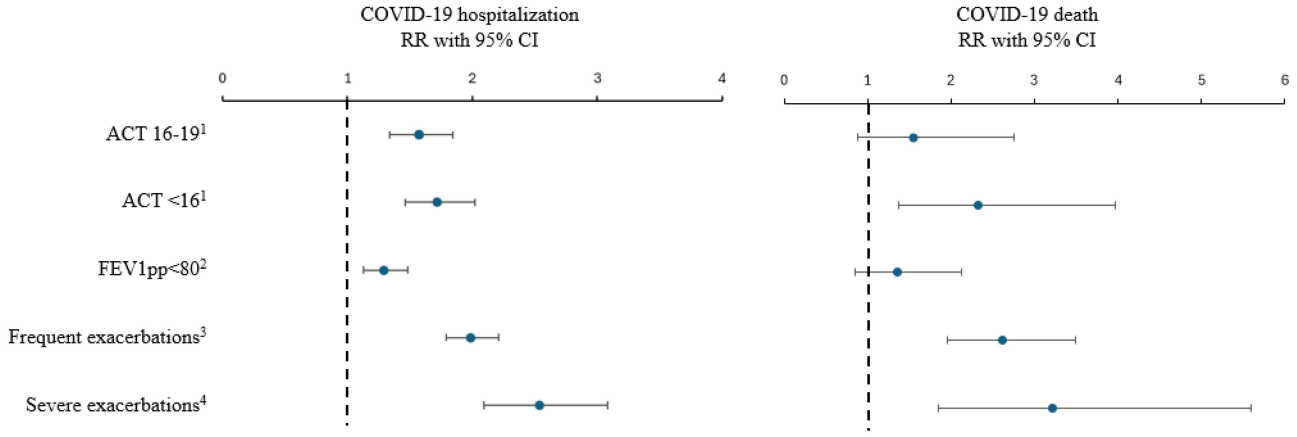

Figure 2 Association between asthma control assessed by Asthma Control Test (ACT), FEV_1< 80pp and exacerbations respectively, and COVID-19 hospitalization and death.

Notes: [1]ACT ≥ 20 as reference, [2]FEV_1 ≥ 80pp as reference, [3]no frequent exacerbations and [4]no severe exacerbations as reference. All models were also adjusted for sex, age and BMI. Results presented as risk ratio (RR) with 95% confidence interval (CI).

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Table 2 Changes in Asthma Control as Assessed by Asthma Control Test (ACT), Lung Function and Exacerbations Among Adult Asthma Patients with and without COVID-19 Hospitalization

	Baseline	Follow-Up	p-value	Baseline	Follow-Up	p-value
	COVID-19 hospitalization n=2377 (1.9%)			**No COVID-19 hospitalization n=122,985 (98.1%)**		
ACT assessments, n (%)	905 (38.1)	255 (10.7)	<0.001	51,382 (41.8)	22,727 (18.5)	<0.001
Lung function assessments, n (%)	970 (40.8)	241 (10.1)	<0.001	55,819 (45.4)	20,596 (16.7)	<0.001
Exacerbations, n (%)						
Frequent exacerbations	427 (18.0)	360 (15.1)	<0.001	9511 (7.7)	8202 (6.7)	<0.001
Severe exacerbations	108 (4.5)	62 (2.6)	<0.001	1562 (1.3)	483 (0.4)	<0.001
ACT, available values	**COVID-19 hospitalization n=155 (6.5%)**			**No COVID-19 hospitalization n=14,829 (12.1%)**		
ACT score, mean (± SD)	18.6 (4.9)	19.0 (5.0)	0.439	20.1 (4.3)	20.5 (4.3)	<0.001
ACT < 20, n (%)	80 (51.1)	66 (42.6)	0.103	5331 (35.9)	4741 (32.0)	<0.001
ACT < 16, n (%)	37 (23.9)	34 (21.9)	0.761	2317 (15.6)	2015 (13.6)	<0.001
Lung function, available values	**COVID-19 hospitalization n=150 (6.3%)**			**No COVID-19 hospitalization n=13,744 (11.2%)**		
FEV_1, mean (± SD)	2.3 (0.8)	2.2 (0.8)	0.005	2.7 (0.9)	2.6 (0.9)	<0.001
FEV_1pp, mean (± SD)	76.4 (16.7)	75.8 (18.5)	0.512	79.5 (15.2)	78.8 (17.5)	<0.001
FEV_1 < 80pp, n (%)	75 (54.3)	76 (55.1)	1.000	6106 (48.4)	6048 (48.0)	0.214

Abbreviations: ACT, Asthma Control Test; FEV_1pp, FEV_1% predicted.

Discussion

In this large nationwide study of 125,362 patients with asthma, the result showed a higher risk of severe COVID-19 among patients with lower ACT scores, particularly those with ACT < 16. Reduced lung function was identified as a risk factor for COVID-19 hospitalization, but not for COVID-19 death. In contrast, pre-pandemic asthma exacerbations were

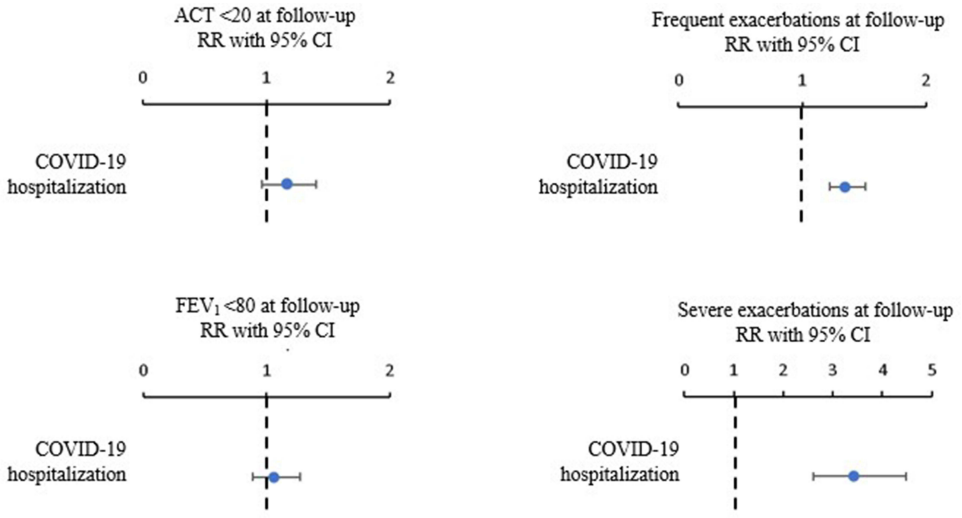

Figure 3 Association between COVID-19 hospitalization and Asthma Control Test (ACT) < 20, FEV_1< 80pp, frequent exacerbations and severe exacerbations at follow-up. **Notes**: [1]ACT ≥ 20 as reference, adjusted for ACT < 20 at baseline. Included in analysis: n = 22,982, whereof n = 255 COVID-19 hospitalizations. [2]FEV_1 ≥ 80pp as reference, adjusted for FEV_1< 80pp at baseline. Included in analysis: n = 19,694, whereof n = 227 COVID-19 hospitalizations. [3,4]No frequent and severe exacerbations as reference, adjusted for frequent and severe exacerbations, respectively, at baseline. Included in the analysis: n = 125,362 whereof, n = 2377 COVID-19 hospitalizations. All models were also adjusted for sex, age and BMI. Results presented as risk ratio (RR) with 95% confidence interval (CI).

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associated with both hospitalization and death. COVID-19 hospitalization was a risk factor for future asthma exacerbations, despite a clear reduction in exacerbations during the pandemic.

Our study showed that poorer symptom control as measured by ACT was a risk factor for COVID-19 hospitalization. Patients with ACT 16–19 or ACT < 16 had an increased risk of hospitalization, with the risk being even higher in the latter group and these patients also had a higher risk of COVID-19 death. These findings are consistent with previous research,[10,12] though the ACT < 16 group has not previously been analyzed separately, as in our study. By stratifying ACT scores in subgroups, the result enabled a more precise evaluation of the relationship between severe symptom burden and the risk of developing severe COVID-19.

This study demonstrated that reduced lung function, measured by FEV_1 < 80pp, was identified as a risk factor for COVID-19 hospitalization, but not for COVID-19 death. In the context of asthma control, there are a relatively few studies examining reduced lung function as a risk factor for COVID-19. However, previous research has provided substantial evidence that FEV_1 is a clinically important marker, where lower values can predict increased risk for various adverse health outcomes,[22] this aligns with the findings of the present study. In our study, frequent and severe asthma exacerbations were associated both with hospitalization and death due to COVID-19, with severe exacerbations emerging as the strongest risk factor among all evaluated indicators of asthma control. The results are consistent with a previous study that identified severe asthma, assessed based on prior exacerbations, as a risk factor for COVID-19.[23]

During the pandemic, ACT scores seem to have improved slightly, however without clinical significance since the minimal important difference of ACT is 3 points.[24] COVID-19 hospitalization was not identified as a risk factor for uncontrolled asthma, as measured by an ACT score of less than 20. These results are consistent with previous findings,[11] but opposed to another study involving 221 asthma patients that reported a significant decline in ACT scores among those with mild-to-moderate COVID-19.[14] However, in the latter study, the follow-up period was considerably shorter, and patients had a less severe course of COVID-19 compared to our study. Consequently, it is plausible that over time, with adequate asthma management and intervention, there may be an improvement in symptom control, or at the very least, no further deterioration, even among patients who experienced more severe manifestations of COVID-19. Our results also showed that patients with a history of poorer symptom control were not prioritized as recommended,[4] as they were less likely to have completed an ACT assessment during the pandemic. Not prioritizing patients with low ACT scores for follow-up is concerning, particularly since we demonstrate that low ACT scores were a strong risk factor for COVID-19 hospitalization and death.

In this study, we observed only minimal changes in lung function, likely too small to be of clinical relevance. These findings remained consistent irrespective of COVID-19 hospitalization status and are also supported by findings from another Swedish study.[25] Furthermore, our results demonstrated that COVID-19 hospitalization was not associated with an increased risk of impaired lung function, as defined by FEV_1 < 80pp. Still, previous studies have demonstrated restrictive lung function impairment in hospitalized COVID-19 patients, but these abnormalities tend to improve in the months after recovery,[26,27] which may also explain this study's findings.

Moreover, our findings showed a significant reduction in asthma exacerbations, which is consistent with previous studies during the pandemic.[8,9] However, our data clearly demonstrated that COVID-19 infection requiring hospitalization was a risk factor for future asthma exacerbations, especially severe exacerbations, even after adjusting for pre-pandemic exacerbations. Similar findings have been reported in previous research,[28] although without the same level of stratification by severity as demonstrated in the present study. The results from this study also support a bidirectional relationship between asthma exacerbations and COVID-19 as patients with frequent and severe exacerbations are more susceptible to adverse COVID-19 outcomes, while the infection itself may trigger further exacerbations. Unlike previous studies,[6,12,14,15,28] which have shown this association in one direction, our results provide evidence of a reciprocal interaction. This finding underscores the importance of implementing evidence-based asthma management strategies to mitigate the burden of exacerbations, as outlined in the GINA guidelines.[2]

While recent studies concluded that severe asthma, but not asthma in general was an independent risk factor for adverse COVID-19 outcomes,[5,23] our findings contribute important insights by emphasizing the need to examine different aspects of asthma control, given its heterogeneous nature. Although the acute phase of the COVID-19 pandemic has passed, the virus has entered an endemic stage, further evolution of SARS-CoV-2, along with changes in behavior

and public health policy, continues to play a major role in the endemic burden of disease and mortality.[29] This means that it remains highly relevant to assess asthma control as it is related to COVID-19 severity. It is of great importance to identify individuals who may benefit from targeted interventions, thereby improving overall asthma management and patient care. Additionally, it has been observed that when COVID-19 pandemic restrictions eased, outbreaks of illnesses caused by common viruses exceeded pre-pandemic levels in some countries.[30]

Strengths and Limitations

A major strength of this study is the large number of participants based on real-world data from a national quality registry which covers all aspects of asthma control, ie symptom control, lung function and exacerbations. Another strength was the use of other national registers to define severe COVID-19 and asthma exacerbations, thereby ensuring that no data was missing. Unlike our previous study,[18] that was limited to patients with uncontrolled asthma (ACT < 20), the current study examines both a broader asthma population over a longer follow-up period and asthma control following severe COVID-19 hospitalization. There are also some limitations to this study that should be acknowledged. A limitation of the study is that more than half of the participants lacked baseline data on the asthma control test and lung function prior to the COVID-19 pandemic, and the proportion with follow-up data during the pandemic was even lower, likely due to restricted access to healthcare during this period. However, more than 1000 ACT assessments and lung function measurements were analyzed, which is a large amount of data, and this enhances the generalizability of the study results. The models were not adjusted for other potential respiratory conditions (eg, obstructive sleep apnea[31]) or comorbidities such as cardiovascular disease and diabetes,[13] which may lead to residual confounding. Limited healthcare access during the pandemic also complicated the assessment of exacerbations.[9] Cultural or regulatory differences may further affect uncertainties in identifying and characterizing an exacerbation, thus limiting comparability and generalizability across studies.[32,33] Yet, as our data extends beyond the peak healthcare strain, the assessment of exacerbations is likely less influenced by system capacity. Also, given the widespread societal impact of the pandemic, caution is warranted when attributing observed changes in asthma control solely to the pandemic itself. Still, by stratifying for the severity of COVID-19, we were able to assess how the pandemic could influence asthma control.

Conclusion

In summary, uncontrolled asthma as measured by ACT, lung function and asthma exacerbations were risk factors for COVID-19 hospitalizations. ACT < 16 and asthma exacerbations were also risk factors for COVID-19 death. We observed a reduction in asthma exacerbations during the pandemic, while ACT scores and lung function values remained relatively unchanged. COVID-19 hospitalization was a risk factor for future asthma exacerbations. It was not, however, associated with an increased risk of future uncontrolled asthma as measured by ACT, nor with impaired lung function.

Abbreviations

ACT, Asthma Control Test; ATC, Anatomical Therapeutic Chemical; CI, Confidence Intervals; COPD, Chronic Obstructive Pulmonary Disease; FEV_1, Forced Expiratory Volume in one second in liters; FEV_1pp, Forced Expiratory Volume in one second percent of predicted value; ICS, Inhaled Corticosteroids; ICD-10, International Classification of Diseases, version 10; LABA, Long-Acting Beta-Agonists; LAMA, Long-Acting Muscarinic Antagonists; NCDR, National Cause of Death Register; NPDR, National Prescribed Drug Register; NPR, National Patient Register; OCS, Oral Corticosteroid; RR, Risk Ratio; SABA, Short-Acting Beta-Agonists; SNAR, Swedish National Airway Register.

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Disclosure

S.S. has no conflicts of interest to declare. J.K.S. has no conflicts of interest to declare.

A.L. reports personal fees and/or advisory board fees from AstraZeneca, GSK and Novartis outside the submitted work. J.R.K reports personal fees from Novartis, ALK, and institutional fees from Regeneron Pharmaceuticals and Thermo Fisher Scientific outside the submitted work.

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The authors report no other conflicts of interest in this work.

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