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Adherence to application technique of inhaled corticosteroid in patients with asthma and COVID-19 improves outcomes

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ABSTRACT

Background Inhaled corticosteroids have been widely reported as a preventive measure against the development of severe forms of COVID-19 not only in patients with asthma.

Methods In 654 Czech and Slovak patients with asthma who developed COVID-19, we investigated whether the correct use of inhaler containing corticosteroids was associated with a less severe course of COVID-19 and whether this had an impact on the need for hospitalisation, measurable lung functions and quality of life (QoL).

Results Of the studied cohort 51.4% had moderate persistent, 29.9% mild persistent and 7.2% severe persistent asthma. We found a significant adverse effect of poor inhaler adherence on COVID-19 severity (p=0.049). We also observed a lower hospitalisation rate in patients adequately taking the inhaler with OR of 0.83. Vital capacity and forced expiratory lung volume deterioration caused by COVID-19 were significantly reversed, by approximately twofold to threefold, in individuals who inhaled correctly.

Conclusion Higher quality of inhalation technique of corticosteroids measured by adherence to an inhaled medication application technique (A-AppIT) score had a significant positive effect on reversal of the vital capacity and forced expiratory lung volume in 1 s worsening (p=0.027 and p<0.0001, respectively) due to COVID-19. Scoring higher in the A-AppIT was also associated with significantly improved QoL. All measured variables concordantly and without exception showed a positive improvement in response to better adherence. We suggest that corticosteroids provide protection against the worsening of lungs in patients with COVID-19 and that correct and easily assessable adherence to corticosteroids with appropriate inhalation technique play an important role in preventing severe form of COVID-19.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Currently, inhaled corticosteroids stand out as potent anti-inflammatory medications for asthma management, and their potential benefits extend to viral infections, particularly those caused by COVID-19. A challenge lies in the proper inhalation technique when using inhalers.

WHAT THIS STUDY ADDS

⇒ The study suggests that correct adherence to inhaled corticosteroids (ICS) with proper inhalation technique is crucial in preventing severe COVID-19 outcomes among patients with asthma. Failure in correct inhalation technique led to a significant negative impact on lung function due to COVID-19. Adherence to ICS was associated with reduced COVID-19 severity, improved lung function and better quality of life. Age and cognitive ability were potential factors affecting adherence, but adjusting for these factors still indicated the positive impact of ICS. The study highlighted the importance of regular inhaler technique assessment and adherence to optimise COVID-19 outcomes and overall health in patients with asthma .

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As the importance of addressing the needs of the ageing population worldwide continues to grow, potential declines in adherence to inhalation techniques due to factors such as diminished motor skills and cognitive function may present additional challenges. Improper inhaler usage can persist unnoticed in patients over extended periods, eluding physician detection. Hence, the necessity of implementing a straightforward and all-encompassing assessment protocol during regular clinical visits becomes paramount.

INTRODUCTION

Rates of COVID-19 infections and deaths have varied geographically and temporally since the beginning of the pandemic.[1] Considerable research activities have been carried out to understand the immune response triggered on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. To some extent, identifying the drivers of severe and fatal COVID-19 have been understood. Autopsies of deceased patients with COVID-19 have revealed very little active viral infection

and substantial accumulation of activated immune cells, suggesting that organ failure is unlikely to result from extensive viral-induced tissue damage but is instead caused by an overactivated immune system or vascular damage.[2] Hence, multiple efforts were made to establish empirical treatments to prevent COVID-19 symptoms progression, especially among high-risk population.[3] Before the advent of effective antivirals, reducing the activity of the immune system in patients with COVID-19 was one of the first lines of treatment to prevent the development of the severe form of the disease, in which corticosteroids (CS) offered a promising perspective, whereas evidence for budesonide is predominantly encouraging. Even now, this approach is mainly applied where expensive antivirals are not balanced by health and economic benefits such as in lower-risk groups or in developing countries.[4]

The Czech Republic and Slovakia were among the countries mostly affected by COVID-19.

Asthma is a chronic disease of the airways that is caused by inflammation of the airways, which leads to bronchial hyper-reactivity, variable bronchial obstruction and episodes of acute dyspnoea, cough, chest tightness and wheezing. Asthma therapy is based on the anti-inflammatory effect of preventive drugs controlling the airway inflammation and relieving bronchodilators which alleviate the symptoms.[5–8] The most effective anti-inflammatory drugs for the treatment of asthma are currently inhaled CS (ICS), whose effectiveness has been demonstrated in a number of studies and novel monoclonal antibodies indicated for most severe patients who require phenotype-specific therapy because of frequent exacerbation and uncontrolled disease despite maximal therapy. ICS therapy alone or in combination with long-acting beta2-agonists and if needed with other anti-asthma drugs as leukotriene inhibitors are effective in controlling asthma symptoms in nearly 90% of patients with asthma.

Patients with asthma were initially considered to be at risk of developing severe COVID-19.[9] Predisposition to morbidity and mortality from COVID-19 was, however, shown to be less straight-forward.[10] A consideration that ICS may confer some degree of protection against SARS-CoV-2 infection and the development of severe disease is justified. Evidence suggests that ICS may be beneficial in viral infections, specifically those due to COVID-19.[11] Other studies have also suggested that ICS reduced cytokines interleukin (IL)-6 and IL-8 responsible for inflammation.[12 13] The routine use of ICS was suggested as an explanation to observed under-representation of chronic obstructive pulmonary disease (COPD) and asthma among patients with COVID-19.[14] Recently, the inhaled budesonide was shown in a phase II clinical trial set-up to reduce the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19.[15]

In management of asthma, all patients (older ≥12 years) should be treated with ICS-containing controller treatment to reduce risk of serious exacerbations and to control symptoms.[5] The critical role of patients' correct use of inhalation aerosol delivery devices has been well acknowledged yet recently shown to pose a persisting challenge.[16–22] It was shown that a patient's adherence to medication delivered via an inhalation device can be as low as 10%—greatly due to various inhalation systems in use and frequent need for combination therapy.[18] There are three main types of inhalers: pressurised metered dose inhaler (pMDI), dry powder inhaler (DPI) and soft mist inhaler. These inhalers differ in the way they are manually operated and, in the inhalation, manoeuvre technique.[16 21]

Vytrisalova *et al* suggested a Five-Steps Assessment tool, which uses five simple steps to determine the adherence to an inhaled medication application technique (A-AppIT). This method is currently being used as an easy-to-use clinical tool for fast and effective evaluation of correctness of inhalation technique.[18] We hypothesise that impaired inhalation not only affects the treatment of underlying asthma but is also associated with increased severity of COVID-19.

MATERIALS AND METHODS

Study design and objectives

A cross-sectional observational retrospective study encompassing an analysis of medical charts, patient interview and visual examination of inhalation technique in Czech and Slovak patients with asthma, who were diagnosed with COVID-19 in the reported period from 1 March 2020 to 31 March 2021 and, at the same time, had asthma diagnosed not later than on 31 January 2019. COVID-19 was confirmed by the patient by submitting a document from the national disease reporting system (COVID-19 pass) or alternatively the patient presented a confirmatory email or short message confirmation with a positive PCR test result. The first and last date of the COVID-19 were assessed by the investigator based on the patient chart, patient narrative and available COVID-19 diagnostics test certificate. The study involved experienced pulmonologist and specialist in immunology and allergology in outpatient settings as investigators. Each specialist was asked to enrol 10–20 patients. Patient data were collected as to the first and last visit charts available before and after the COVID-19. The data was collected to predefined electronic case report forms. In addition, patients' A-AppIT was evaluated during a single face-to-face meeting arranged between investigator and patient based on a training video manual for investigators. The date of the first visit after patient's recovery from COVID-19 was herein considered the index date facilitating head-to-head description of various strata of the cohort and the comparison of the disease course between groups with varying A-AppIT.

The primary objective of the study was to confirm or disprove the hypothesis that A-AppIT is negatively associated with the COVID-19 severity, presumably because of incomplete or absent protective effect of ICS. The

primary objective was tested by means of inferential statistics with the response variable—COVID-19 severity classified into three levels (mild, moderate and severe).

Secondary objectives included: assessing the effect of A-AppIT in patients without hospitalisation versus those requiring hospitalisation for COVID-19; comparing the effect of A-AppIT on vital capacity (VC) and forced expiratory lung volume in 1 s (FEV1) before and after COVID-19; and assessing quality of life after COVID-19.

Study population and inclusion criteria

Enrolled patients had to meet the following inclusion criteria being aged 50 years or older (to observe sufficient prevalence of moderate and severe form of COVID-19), being diagnosed with asthma not later than on 31 January 2019, irrespective of treatment used and who contracted COVID-19 during period from 1 March 2020 until 31 March 2021 and who provided their consent to use of their retrospective medical chart data. To be included in the ICS-treated cohort, a patient must have had at least one inhaler containing ICS as a monotherapy or as a fixed combination of two or more active ingredients at the time of COVID-19. The inhalers employed were of either pMDI or DPI type. In cases where a patient used both pMDI and DPI inhalers concurrently, the superior A-AppIT score between the two was selected for that individual. Furthermore, an analysis cohort was formed, consisting of all patients from the ICS-treated group with complete key data, including the unequivocal A-AppIT score.

Patient and public involvement

Patients were enrolled in the study based on selection according to the above criteria listed in the medical records and informed consent. Patients' active participation consisted only of a one-time personal interview and demonstration of inhalation technique.

Data collection, transformation and classification

Data were collected using an electronic data capture system (eCRF). All data collected via the eCRF were reviewed by remote data managers for clarity and completeness. Patients initially filled paper version of the EuroQol-5 Dimension (EQ-5D) form which were then entered in eCRF during visit. After the database was locked, a data completeness check was performed and three data cohorts were defined: a complete cohort of all patients with a diagnosis of asthma and COVID-19 reported at the given time intervals; a cohort of ICS subjects taking at least one inhaler containing ICS and lung function assessed before and after COVID-19; and an analytic cohort with available COVID-19 severity and A-AppIT scores, which allowed testing of the primary hypothesis.

In addition, demographics data such as year of birth, gender, weight, height; medical history such as diagnosis of comorbidities, the asthma grade (as mild persistent, moderate persistent and severe persistent asthma), asthma-specific medication; VC and FEV1 and their change (difference between before and after COVID-19); COVID-19 diagnosis with onset and recovery date, severity grade of COVID-19, outpatient treatment; asthma management during COVID-19; hospitalisation due to COVID-19 and COVID-19 symptoms; quality of life by EQ-5D questionnaire including the Visual Analogue Scale (VAS); and the A-AppIT score according to Vytrisalova *et al*[18] were collected.

Severity of COVID-19 infection was classified as mild if patient was treated at home, as moderate if patient was admitted to hospital and had an oxygen support and as severe if patient was admitted to hospital and had been treated on Intensive Care Unit(ICU) and/or was treated by oxygen delivered via mask and/or high-flow oxygen nasal therapy and/or non-invasive/invasive ventilatory support. In a second exploratory subanalysis of the primary objective, the three severity grades of COVID-19 were binned to dichotomous values as without hospitalisation versus requiring hospitalisation. The reported mild intermittent asthma grade was classified as mild persistent.

Visual inspection and scoring of patients' inhalation technique regarding A-AppIT was performed by the investigators at a dedicated face-to-face visit. Each step was rated in a simple dichotomous manner: performed correctly (=1) or incorrectly (=0), which was the reverse of the rating as described in Vytrisalova.[18] The use of reverse scoring allowed us to sum the dichotomous scores of each step and assign each patient an A-AppIT score that covers the patient's adherence to inhalation in all five steps simultaneously. Ratings of 1 and 0 were made with respect to the different types of inhalers according to the respective manufacturer's based on summaries of product characteristics (SPC) in the following categories corresponding to the sequence of steps in their correct use: preparing the inhaler for use, handling the inhaler before use, immediately before inhalation, actual inhalation, immediately after inhalation. An instructional video describing the correct execution of all steps was made available to the investigators to facilitate proper evaluation of the inhaler types studied. Thus, a patient who correctly performed all the steps scored five A-AppIT points. For each incorrect step, the patient lost one point. A-AppIT scores of less than two points were assigned to one group referred to as '<=2', which was considered the lowest A-AppIT score.

Doses of administered observed types of ICS were recalculated into equivalent doses of dry powdered budesonide by means of conversion tables presented in the on the Global Initiative for Asthma[8] and the National Institute for Health and Care Excellence on their website.[23] The tables did not offer precise conversions for ICS types observed, but rather categorised them into 'Low', 'Medium' and 'High' dose classifications as well as neither of the tables provided conversion for all the ICS

observed in our study; therefore, we amalgamated both tables. Based on the ranges indicated in the tables, each ICS was assigned to the appropriate 'Low', 'Medium' or 'High' dose category. Where any of the tables provided an exact dose (as opposed to a dose range), the range boundaries were set at the median between the given doses. Subsequently, a median dose (or the already provided dose value) was established for each category and ICS and its ratio to the dose of budesonide in the corresponding category was determined. This ratio was then applied to the respective ICS dose observed.

Quality of life

The generic health/related quality of life EQ-5D questionnaire was used in the study and presented on the index date visit (after COVID-19).[24] In each of the five dimensions of the questionnaire (mobility, self-care, usual activities, pain and discomfort and anxiety and depression), patients rate the degree of their problems from none[1] to the maximum possible.[5] Each response indicating a certain extent of problem is associated with a defined disutility value. Here, the UK disutility value set was used.[25] The disutility values for all five dimensions are then added and subtracted from 1, indicating some impairment in otherwise full health with a value of 1. Further the VAS was administered to patients recording their self-rated health on a vertical VAS from 0 to 100, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

Data analysis

Descriptive and inferential statistical analysis was carried out using SAS V.9.4 for Windows.

A χ^2 test was used to test to determine whether there was a significant association between two categorical variables such as in gender and anamnesis in table 1.

To measure the effect of A-AppIT score (≤2, 3, 4, 5) on the COVID-19 severity, a probit model regression with three ordered response categories (mild, moderate, severe) and a logit regression model with two response categories (hospitalised, not hospitalised) were used.

The effect of the A-AppIT score on continuous variables such as the change of pulmonary parameters VC or FEV1 and quality of life variables (EQ-5D utility and VAS)

Table 1 Characteristics of the cohort of patients who used ICS and the analysis cohort

	Mild COVID-19	Moderate COVID-19	Severe COVID-19	Unadjusted p value
Gender	522 (80.06%)	104 (15.95%)	26 (3.99%)	0.051
Males	202 (82.11%)	34 (13.82%)	10 (4.07%)	
Females	320 (78.82%)	70 (17.24%)	16 (3.94%)	
Age (years) mean (SD)	59.93 (8.30)	61.86 (8.76)	60.65 (8.60)	0.096
Body mass index mean (SD)	**28.63 (4.81)**	**30.42 (5.49)**	**32.68 (6.76)**	**<0.001**
Anamnesis				
Diabetes mellitus I/II	**107 (16.41%)**	**32 (4.91%)**	**8 (1.23%)**	**0.047**
Ischaemic heart disease	89 (13.65%)	25 (3.83%)	5 (0.77%)	0.255
Arterial hypertension	**336 (51.53%)**	**72 (11.04%)**	**23 (3.53%)**	**0.030**
Heart failure	19 (2.91%)	5 (0.77%)	1 (0.15%)	0.086
Chronic kidney disease	21 (3.22%)	9 (1.38%)	1 (0.15%)	0.131
Solid/haematology organ transplantation	0 (0.00%)	0 (0.00%)	0 (0.00%)	–
Cancer in active therapy	4 (0.61%)	1 (0.15%)	0 (0.00%)	0.883
Active cigarette smoking	38 (5.83%)	9 (1.38%)	0 (0.00%)	0.316
Severity of asthma				**0.004**
Mild persistent	211 (32.36%)	26 (3.99%)	8 (1.23%)	
Moderate persistent	281 (43.10%)	63 (9.66%)	14 (2.15%)	
Severe persistent	30 (4.60%)	15 (2.30%)	4 (0.61%)	
Quality of life by EQ-5D^{AS}	**0.82 (0.17)**	**0.72 (0.19)**	**0.61 (0.25)**	**<0.001**
Median (IQR) ICS daily dose equivalent before COVID-19^{E}	700 (400–875)	800 (429–1280)	800 (400–1288)	11^{K}
median (IQR) ICS daily dose equivalent during COVID-19^{E}	800 (523–1288)	875 (644–1625)	800 (640–1600)	0.136^{K}

Statistically significant differences between groups are denoted in **bold**.
AS, analysis cohort, that is, patients with COVID-19 severity assessed (N=652); E, calculated as an equivalent of dry budesonide powder; EQ-5D, EuroQol-5 Dimension; ICS, inhaled corticosteroids; K, Kruskal-Wallis test.

was analysed using general linearised model adjusted for the effect of age and the underlying asthma grade and a baseline value of the studied variable, if available. Kruskal-Wallis test was used where the response variable was obtained by rather grouping into more or less precise ranks such as the calculated equivalent of dry budesonide powder explained above.[8 23]

If any of the adjusting variables did not reach the minimum alpha level of 0.1 in the model, they were excluded and the model was recalculated. When analysing changes in the VC and FEV1, the respective value measured before COVID-19 (baseline value) was taken as additional adjusting covariate.

RESULTS

Patient disposition, demographics and epidemiology

A total of 63 centres participated in the study and 833 patients were enrolled from February to June 2022, comprising the full cohort. As ICS use was not an inclusion criterion, some patients were excluded as they used no ICS. Hence, in total 654 subjects constituted the ICS-treated cohort. Two more patients from the group undergoing ICS treatment (ICS-treated cohort) had to be excluded due to incomplete data in the COVID-19 severity assessment and/or the A-AppIT scores. This led to the formation of the final analysis cohort.

The following demographic and epidemiology characteristic of the full cohort refer to the index date (the first visit after COVID-19). In total 518 (62.16%) women and 315 (37.84%) men were included in the study. The mean age in years of all patients was 61.8 (SD: 8.2), 60.8 (SD: 7.7) for men and 62.4 (SD: 8.4) for women. A total of 390 (46.83%) patients were in the age group 50–59 years. The mean body mass index (BMI) in kg/m was 29.01 (SD: 5.15) for all patients, 28.68 (SD: 4.11) for men and 29.22 (SD: 5.69) for women. Of the 833 patients, 310 (37.3%) were overweight with BMI 25–30 and 326 (39.4%) were obese with BMI>30. For details on the ICS and analysis cohort refer to table 1. Of the total 833 patients, 428 (51.4%) had moderate persistent, 345 (29.9%) mild persistent and 60 (7.2%) severe persistent asthma. The two most frequent comorbidities among all patients were arterial hypertension (N=531, 63.7%) and diabetes mellitus I/II (N=177, 21.2%). In the subset of patients with severity of COVID-19 assessed, in total 660 (79.2%) had mild, 143 (17.2%) moderate and 30 (3.6%) severe COVID-19. The most common symptoms in patients with mild COVID-19 were fatigue (87%), fever and chills (85%), cough (85%) and muscle or body pain (78%). While shortness of breath or difficulty of breathing was present in only 59% of patients with mild COVID-19, it was present in 92% and 100% of patients with moderate and severe COVID-19, respectively. Similarly, chest pain was present in only 42% of patients with mild COVID-19 and in 67% and 77% patients with moderate and severe COVID-19, respectively. Memory loss/memory impairment occurred in an overwhelming 50% of patients with the severe form of COVID-19 and in only 6% and 15% of patients with the mild and moderate forms, respectively.

The demographic and epidemiological characteristics of the ICS cohort and the analysis cohort (for the COVID-19 severity) including key comorbidities are specified in table 1.

The majority (92%) of all patients used chronic inhalation treatment prior COVID-19, the second most used therapy was asthma reliever inhalation therapy (78%). After diagnosis of COVID-19, 43% of patients had changed their pharmacotherapy. The biggest increase in the prescription was observed

in the systemic oral corticoids (14% vs 29%). The most frequently used inhalation systems before COVID-19 were pMDI (46%) and the remaining 43% of patients used both types.

Quality of life

Quality of life as utility by EQ-5D differed by up to 0.21 between patients with mild and severe COVID-19 as shown in table 1 and between those requiring hospitalisation and without it. There was also a substantial difference between those with mild persistent (0.84, SD: 0.16), moderate persistent (0.78, SD: 0.18) and severe persistent (0.68, SD: 0.23) grade of asthma. The VAS score showed the same downward trend in those with more severe asthma with mean values and SD (0.82, SD: 0.16), (0.74, SD: 0.16) and (0.68, SD: 0.19), respectively.

Effect of adherence on COVID-19 severity

Among those 652 patients of the analysis cohort using inhaler containing ICS with known COVID-19 severity, 522 (80%) patients had mild, 104 (16%) moderate and 26 (4%) severe COVID-19. For example, 87% of patients with mild COVID-19 scored at least four on the inhalation adherence assessment, while only 73% of patients with severe COVID-19 achieved the same score. In contrast, only 12% of patients with mild COVID-19 scored less than four points, while 27% of patients with severe COVID-19 scored less than four points.

The A-AppIT (score from ≤2 to 5) and the asthma grade were found to be predictors of COVID-19 severity (p=0.049 and <0.001; adjusted for age p=0.078 and <0.001), whereas age alone was not significant in the model (p=0.23). An increase in A-AppIT score, indicating better inhalation technique, was associated with a lower COVID-19 severity score (mild<moderate<severe) by an OR of 0.89 (95% CI 0.79 to 1.01). The trend is shown in figures 1 and 2. An increase in the A-AppIT score was associated with a lower, however not significant (p=0.11), OR 0.86 of hospitalisation for COVID-19 (figure 2). Comorbidities, including smoking, and the ICS dose equivalent before and during COVID-19, were introduced as factors and covariates into the above model, but they did not emerge as significant predictors of either COVID-19 severity or hospitalisation.

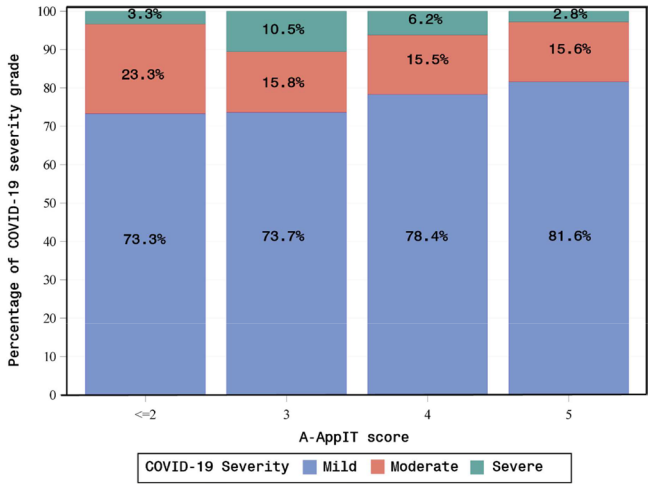

Figure 1 Relative frequencies of patients with given COVID-19 severity grades by the adherence score (A-AppIT). A-AppIT, adherence to an inhaled medication application technique.

Effect of adherence on lung parameters and quality of life

Overall, unadjusted mean VC and the associated CIs (88.2; 95% CI 86.8 to 89.5) and FEV1 (82.8; 95% CI 81.3 to 84.3) were lower after COVID-19 compared with unadjusted mean VC (91.3; 95% CI 89.8 to 92.5) and FEV1 (86.0; 95% CI 84.6 to 87.5) before COVID-19. The same trend was present in the three subcohorts defined by asthma grades. Regarding the subcohort with mild persistent asthma, the unadjusted mean VC (93.9; 95% CI 91.9 to 95.9) and FEV1 (90.3; 95% CI 88.2 to 92.4) were lower after COVID-19 compared with unadjusted mean VC (96.1; 95% CI 94.1 to 97.9) and FEV1

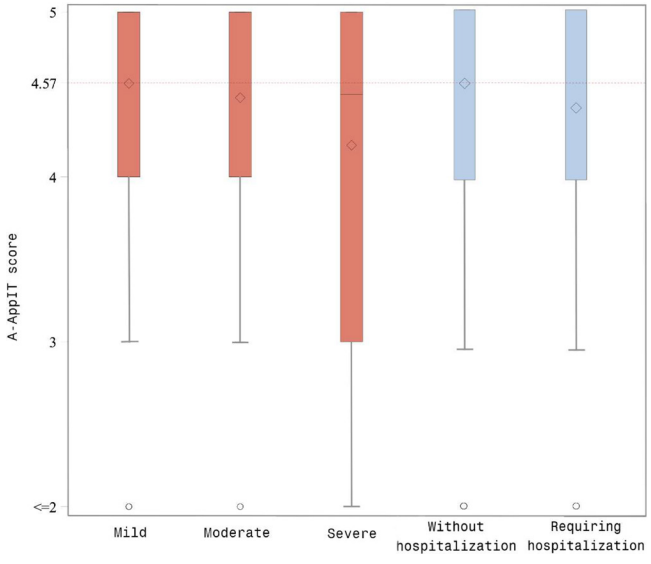

Figure 2 Adherence score (A-AppIT) by COVID-19 severity and hospitalisation status. The A-AppIT (score from ≤2 to 5) and the asthma grade were found to be predictors of COVID-19 severity (p=0.049 and <0.001; adjusted for age p=0.078 and <0.001). A-AppIT, adherence to an inhaled medication application technique.

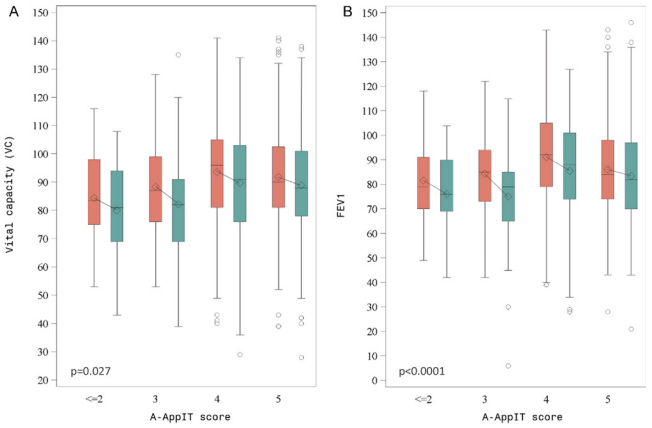

Figure 3 (A) Unadjusted vital capacity (VC, %) prior (red) and after (green) COVID-19 by the A-AppIT score. (B) Unadjusted forced expiratory volume in 1 s (FEV1, %) prior (red) and after (green) COVID-19 by the A-AppIT score. Higher A-AppIT scores had a significant reversal effect on both VC (up to 1.7-fold; p=0.027) and FEV1 (up to 3.4-fold; p<0.0001) deterioration. A-AppIT, adherence to an inhaled medication application technique.

(93.0; 95% CI 91.0 to 95.0) before COVID-19. Regarding the subcohort with moderate persistent asthma, unadjusted mean VC (85.3; 95% CI 83.5 to 87.1) and FEV1 (79.3; 95% CI 77.4 to 81.3) were lower after COVID-19 compared with unadjusted mean VC (89.1; 95% CI 87.3 to 90.9) and FEV1 (83.1; 95% CI 81.2 to 84.9) before COVID-19. And similarly in the subcohort with severe persistent asthma, unadjusted mean VC (77.7; 95% CI 71.4 to 84.1) and FEV1 (68.1; 95% CI 61.6 to 74.7) were lower after COVID-19 compared with unadjusted mean VC (78.9; 95% CI 72.6 to 85.3) and FEV1 (70.2; 95% CI 64.3 to 76.1) before COVID-19.

High A-AppIT scores showed a significant reversal effect on VC and FEV1 (+1.14, p=0.027 and +2.33, p<0.001, respectively) deterioration due to COVID-19, calculated as post-COVID-19 values minus pre-COVID-19 values in a model adjusted for age (p=0.54 and p=0.02, respectively), the baseline value (p<0.0001 and p<0.0001, respectively) and the asthma grade (p=0.02 and p<0.08, respectively). Figure 3A,B show the unadjusted VC and FEV1 means, respectively, by the A-AppIT. Scoring higher in the A-AppIT was also associated with significantly improved EQ-5D utility and the VAS score (both p<0.0001) in a model adjusted for age (p=0.004 and p<0.10, respectively) and the asthma grade (both p<0.0001). Figure 4 shows the unadjusted EQ-5D utility by the A-AppIT.

DISCUSSION

Failure in two steps of inhalation already leads to a relatively substantial change in lung function due to COVID-19. Correct and easily assessable adherence to CS with appropriate inhalation technique play an important role in preventing severe form of COVID-19. Errors in inhalation technique led to risk of higher COVID-19 severity and it negatively impacts patients' quality of life. This

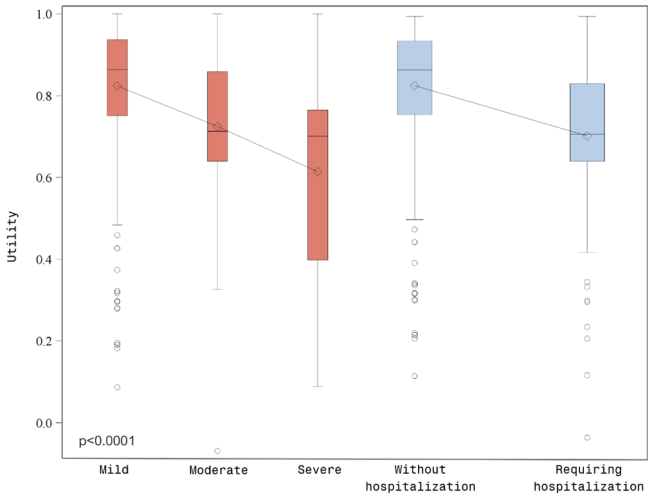

Figure 4 Quality of life expressed as unadjusted utility value based on the EQ-5D by COVID-19 severity and hospitalisation status. Scoring higher in the adherence to an inhaled medication application technique was associated with significantly improved EQ-5D utility (p<0.0001). EQ-5D, EuroQol-5 Dimension.

holds true irrespective of the indicated ICS daily dose, as demonstrated by the overlapping IQR in table 1 across various COVID-19 outcomes, ranging from mild-to-more severe cases.

During the COVID-19 pandemic, researchers focused on asthma as both diseases primarily affect the lungs. CS have been shown to affect the course of COVID-19 and were among the drugs used early in the pandemic.[11 22 26–29] Patients with asthma were reported to be less likely than patients without asthma experiencing severe outcomes of influenza, a possible effect of a premorbidly used ICS therapy in patients with asthma.[30] The proportion of patients with asthma hospitalised with COVID-19 was shown to be lower compared with the underlying background population.[31 32] These findings suggested that behavioural, pharmacological and immunopathological mechanisms in patients with asthma are associated with reduced susceptibility to severe COVID-19.[33 34] Matsuyama *et al*[28] reported that ciclesonide suppressed SARS-CoV-2 replication in cultured cells and inhibits SARS-CoV-2 cytopathic activity. In an analysis of gene expression for ACE2 and TMPRSS2 in sputum cells from 330 patients with well-defined asthma. Peters *et al* found a significantly lower expression of ACE2 and TMPRSS2 in patients treated with ICS.[35] We speculate that age may be a shared covariate although we find no direct support in this study.

Effective inhalation can be facilitated by a variety of devices, including spacers, nebulisers, breath-actuated metred-dose inhalers, or soft mist inhalers and by repeated and careful education of patient by respiratory nurse or specialist.[16 20] However, in daily practice the use of pMDI and DPI is the most popular way of inhalation therapy.[18 21] Persisting poor adherence to inhalation treatment has a negative effect on the course of disease. It results in an increased incidence of symptoms, increased morbidity, hospitalisation, reduced quality of life and higher healthcare expenses.[22] In most cases, poor adherence is expressed quantitatively, often evaluating, for example, the percentage of doses used. But it is important to realise that non-adherence regarding inhalation of medication can be of two types, quantitative whereas the patient fails in taking medication with prescribed frequency and periodicity and qualitative whereas the patient fails in using the inhalation device correctly and hence suboptimal amount of aerosol is available in lungs.

Most importantly, however, improper inhaler use can persist in a patient for years without being detected by a physician. It is therefore very important to have a simple and comprehensive assessment procedure and use it as a standard tool during routine clinical visit.

Rating adherence associated with the use of inhalers such as by the method proposed by Vytrisalova *et al* has shown throughout this study to be a useful way to consider its impact on its outcomes.[18] Another obvious advantage is that this tool can be used in patients with both asthma and COPD and can be used to evaluate any type of inhaler.

In this study, we further found a significant effect of the adherence score to the CS-containing inhaler on the severity of COVID-19, thus confirming the primary hypothesis of this study. This finding was made when rigorously adjusting for age and asthma burden, which we hypothesise are the most important covariates closely associated with COVID-19 severity. This primary finding was supported by multiple secondary findings. Less deteriorated lung functions and preserved quality of life were found in those with better adherence. Similarly, the effect of correct inhalation on the need for hospitalisation showed a remarkable but non-significant trend. Nevertheless, a higher percentage of hospitalisations was observed in patients with poor adherence.

COVID-19 caused a measurable deterioration of VC an FEV1 in patients and the quality of life differs substantially between patients who experienced mild, moderate or severe COVID-19. This study showed a remarkable difference between adherent and non-adherent patients in deterioration of lung function during COVID-19. Failure in two steps of inhalation already leads to a relatively substantial change in lung function due to COVID-19.

All response variables studied, such as lung functions, COVID-19 severity, quality of life or need for hospitalisation, showed sustained improvement with improved inhalation technique. This can be considered as strong support for the association between proper ICS use and improved COVID-19 outcomes, as well as for the pharmacological effect of CS itself.

In addition, based on the functional spirometric parameters before COVID-19 disease, it is possible to show that the lung function parameters are worse in non-optimally adherent patients. This is not a surprising

finding regarding asthma itself, but some confirmation of the overall study.

For the purposes of a use in the economic model, we assessed the patient's quality of life using the EQ-5D questionnaire. Our results show that the EQ-5D questionnaire can discriminate well by COVID-19 disease burden.

We are aware of some limitations of this study. The design of the study allowed for a temporal gap between the acute phase of COVID-19 infection and the subsequent assessment of inhalation technique. This time interval might have led to alterations in a patient's lung function, physical state and cognitive abilities, consequently influencing their inhaler technique. We assume some collinearity between age and adherence, which in this study is mainly related to cognitive ability and manual dexterity at the same time. This may be largely since older patients have problems with correct inhalation, and at the same time, a more severe course of COVID-19 can be expected. In our study, the age bias was very small and was adjusted for in all statistical models interpreted here, supporting the conclusion of a positive effect of ICS in preventing progression of COVID-19 in patients with asthma and probably also in the general population.

As the global population ages, it is essential to address the management of deteriorating inhalation technique in older individuals, particularly in the context of decreasing cognitive capacity. Ageing is associated with cognitive changes that can impact a person's ability to perform complex tasks, including correctly using inhaler devices. To address these challenges, healthcare providers and researchers should explore strategies to adapt inhaler technique education and assessment to the evolving needs of patients, especially those with age-related cognitive decline. This could involve simplified inhaler devices, caregiver involvement and frequent reassessment of technique to ensure patients continue to receive the full benefits of their medication regimens.

In general, this was an uncontrolled study in real clinical practice, which carries some unspecified risks of bias due to patient selection.

CONCLUSIONS

Impaired inhaler use in patients with asthma suffering from COVID-19 leads to more prominent lung function decline and reversal in comparison to patients who are using their inhalers for asthma properly. Errors in inhalation technique led to risk of higher COVID-19 severity and it negatively impacts patients' quality of life. Our concordant findings on inhaler use indirectly support the notion that ICS most likely provide protection against the development of severe COVID-19 since adequate inhaler use plays a key role in facilitating it.

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