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**Risk of adverse outcomes in patients with underlying respiratory conditions hospitalised with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: a national, multicentre prospective cohort**

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### **Data sharing**

ISARIC4C welcomes applications for data and material access through our Independent Data and Material Access Committee (<https://isaric4c.net>). Data collected for the study, including individual anonymised participant data and a data dictionary defining each field in the set will be available, including the ISARIC WHO CCP-UK study protocol and consent forms. Data will be shared after approval of the proposal and with a signed data access agreement.

## Abstract

### Background

Studies of hospitalised COVID-19 patients have found inconsistencies in mortality associated with underlying respiratory conditions and inhaled corticosteroid (ICS) use. We sought to investigate this relationship using a national, multicentre, prospective cohort.

### Methods

Prospective, multicentre UK cohort of hospitalised COVID-19 patients. Patients with asthma, chronic pulmonary disease (CPD), or both, were identified and stratified by age (years): <16, 16-49 and ≥50. In-hospital mortality was measured using multilevel Cox proportional hazards, adjusting for demographics, comorbidities and medications (ICS, short-acting-beta-agonists (SABA), long-acting-beta-agonists (LABA)). Asthma patients using ICS+LABA+another asthma medication were considered 'severe'.

### Findings

75,463 patients were included: <16 years, 860 patients (8.6% asthma); 16-49 years, 8,950 patients (20.9% asthma), ≥50 years, 65,653 patients (9.0% asthma, 15.6% CPD, 3.2% asthma & CPD). Asthma patients were significantly more likely to receive critical care, CPD patients were significantly less likely to. In patients 16-49 years, only those with severe asthma had a significant increase in mortality (adjusted HR (95%CI): no therapy=1.21 (0.78-1.88), SABA-only=1.03 (0.66-1.62), ICS-only=1.01 (0.68-1.51), ICS+LABA=1.06 (0.70-1.61), severe=2.07 (1.35-3.18)). In patients ≥50 years, there was increased mortality associated with CPD and severe asthma. ICS use was associated with lower mortality (adjusted HR (95% CI): asthma+no\_ICS=0.97 (0.90-1.04), asthma+ICS=0.87 (0.81-0.93), CPD+no\_ICS=1.16 (1.11-1.21), CPD+ICS=1.10 (1.04-1.17), asthma+CPD+no\_ICS=1.13 (1.00-1.27), asthma+CPD+ICS=0.98 (0.89-1.07)).

### Interpretation

Underlying respiratory conditions are common in hospitalised COVID-19 patients. Regardless of admission severity and comorbidities, asthma patients were more likely to receive critical care than patients without underlying respiratory disease; CPD patients were less likely to. Severe asthma in ≥16-year olds was associated with increased mortality relative to other asthma patients. In patients ≥50 years, ICS use in asthma was associated with lower mortality relative to patients without an underlying respiratory condition; CPD patients had significantly increased mortality but ICS use did not have a significant effect on mortality.

### Funding

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### **Evidence before this study**

Early case series, at the beginning of the COVID-19 pandemic, suggested the prevalence of hospitalised COVID-19 patients with chronic respiratory disease was lower than the prevalence in the local population. Subsequently, several studies have specifically addressed the risk of adverse COVID-19 outcomes, including hospitalisation and death, in asthma and chronic obstructive pulmonary disease (COPD). Few observational studies have examined the effect of inhaled corticosteroids (ICS) on mortality. One large study, using the OpenSafely consortium which included primary care records linked to COVID-19 death data, found high-dose ICS use in asthma patients and any ICS use in COPD patients was associated with an increased mortality. They suggested the association could be explained, fully or in part, by unmeasured confounding due to disease severity.

### **Added value of this study**

Our study uses the largest cohort of hospitalised COVID-19 patients worldwide, the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) study. We inform on two major questions for people with underlying respiratory conditions. First, we describe the patients including the level of care they received and their mortality risk, comparing across ages and between common respiratory conditions. We found asthma patients were significantly more likely to receive critical care and ventilatory support even after adjusting for severity on admission, age and comorbidities; in contrast, CPD patients were significantly less likely to receive critical care. CPD patients and those with severe asthma had increased mortality. Second, we measured the association of mortality with ICS use. In contrast to OpenSafely, we demonstrated that use of ICS within two weeks of admission was associated with lower mortality in asthma but had no effect on mortality in CPD.

### **Implications of all the available evidence**

In the UK, there appears to be a disparity between patients with different respiratory conditions and the level of in-hospital care received, not accounted for by clinical severity, age or comorbidities. Both our secondary care study and the primary care OpenSafely study found patients with more severe asthma were at risk of increased mortality. Our study suggests that use of ICS within two weeks of admission may be beneficial, perhaps via a putative anti-inflammatory effect. The evidence from these two large observational cohorts report contrasting effects from ICS, although the timing of ICS use may have differed. Both studies are at risk of misclassification and confounding; the results of ongoing prospective randomised clinical trials evaluating the efficacy of ICS will be informative.

## Introduction

Coronavirus disease 2019 (COVID-19), caused by the virus SARS-CoV-2, was declared a pandemic on March 11<sup>th</sup> 2020, by the World Health Organisation (WHO). By the end of September 2020, there were over 1 million deaths, significant concern for a second wave of infections and a belief that the pandemic will not end for another two years.

People with chronic obstructive pulmonary disease (COPD) and asthma were initially judged to be at substantial risk of developing severe COVID-19(1, 2). These putative risk factors were based on knowledge that respiratory viruses are a major cause of disease exacerbations and because both diseases are associated with deficient innate immune responses to respiratory virus infections, likely vital in defence against a novel virus(1, 3). With increasing time and an accumulation of observational data, it appears that COPD is a definitive risk factor for severe COVID-19 outcomes(4, 5). For people with asthma, the predisposition to morbidity and mortality from COVID-19 is less straightforward. Early large case series of patients hospitalised with COVID-19 found the proportion with asthma to be lower than that of the local population(6-8), unlike during the 2009 influenza pandemic(9). These findings suggested asthma was associated with reduced susceptibility to severe COVID-19, with behavioural, pharmacological and immunopathological explanatory mechanisms proposed(10, 11). More recent epidemiological studies have further complicated understanding, as some signify an association with severe COVID-19 disease(5, 12, 13), while others do not(4, 14-17).

One mechanism postulated to correlate with protection is inhaled corticosteroid use (ICS)(10, 18). Experimental human and animal studies have shown that ICS use attenuates the expression of key SARS-CoV-2 related genes, in both asthma and COPD(19-21). Whilst two U.S. asthma cohorts found no association between ICS use and COVID-19 related hospitalisation, a large U.K. cohort found an increase in COVID-19 related mortality associated with high dose ICS use in asthma, and any ICS use in COPD(15, 22, 23). Understanding the impact of ICS is critical for respiratory patients. It was notable that at the beginning of the pandemic, in the UK, the demand for ICS prescriptions escalated to such an extent it caused distressing shortages.

Using data from the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) study, we aimed to characterise people admitted with underlying respiratory disease, the level of care received, measure in-hospital mortality, and the effect of ICS use.

## Methods

### Data source

The ISARIC WHO CCP-UK protocol was developed in 2009, with regular review and updates in response to potential threats posed by emerging infections. The study was activated in response to the SARS-CoV-2 pandemic on 17th January 2020. This is an actively recruiting, prospective cohort study of hospitalised patients with strongly suspected or confirmed COVID-19 recruiting across England, Scotland and Wales. The protocol, revision history, case report forms, study information and consent forms are available online (<https://isaric4c.net>). Data and analysis scripts are available on request.

### Study population

From 17th January until 3rd August 2020, patients admitted to hospital with a confirmed or highly suspected SARS-CoV-2 infection leading to COVID-19 disease were eligible for inclusion in this study.

Confirmation of SARS-CoV-2 was performed using reverse-transcriptase polymerase chain reaction (RT-PCR), the only testing modality available in the UK during the study period. Highly suspected but unproven cases were eligible for inclusion, given that SARS-CoV-2 was an emergent pathogen at time of protocol activation and confirmatory RT-PCR was contingent on local availability of tests. Patients who were admitted past the 3rd August 2020 were excluded to avoid bias from those who had not had adequate time to accrue an outcome. Follow-up of patients ended on 17th August.

### **Ethical approval**

Ethical approval was given by the South Central-Oxford C Research Ethics Committee in England (reference 13/SC/0149), and by the Scotland A Research Ethics Committee (reference 20/SS/0028). The study was registered at <https://www.isrctn.com/ISRCTN66726260>.

### **Variables**

Data were collected by clinical research staff using a standardised case report form and entered into a secure Research Electronic Data Capture secure online database. Data were captured across multiple timepoints, including at admission, during hospital stay (day 1, 3, 6 and 9) and discharge. Characteristics including age, sex, comorbidities; asthma, chronic pulmonary disease (CPD), chronic cardiac disease, chronic haematologic disease (excluding malignancy), chronic kidney disease, chronic neurological disease, HIV/AIDs, malignancy, liver disease, obesity, rheumatologic disorder and smoking history were captured. Physiological parameters at admission were recorded, including the components of the National Early Warning Score 2 (NEWS2); these last were categorised as low (<5), moderate (5-6) and severe ( $\geq 7$ ) clinical risk. We captured medications entered as free-text and subsequently mapped this to drug preparations using data provided by the NHS Technology Reference data Update Distribution Service. Index of Multiple Deprivation (IMD, an area-based measure of relative deprivation) was determined using the area of the patient's home (where the most deprived are represented by the 5<sup>th</sup> quintile). Where that was missing, a hospital-weighted average deprivation score was used.

Patients with respiratory disease, recorded in the case report form as asthma or CPD (no asthma), were stratified into three age groups: <16 years, 16- 49 years, and  $\geq 50$  years. Asthma spans all ages but the potential for misclassification due to other similar conditions increases from around 50 years of age. Stratifying by age reduces the risk of this bias and helps control for age, one of the main confounders for assessing COVID-19 outcomes. Due to the small number of children, descriptive analysis only was carried out. Asthma patients under 50 years old were identified using the case report form, or by patients without CPD who were taking inhaled asthma medication (ICS, short-acting  $\beta 2$ -agonists (SABA), long-acting  $\beta 2$ -agonists (LABA), theophylline or leukotriene receptor antagonists (LTRA)) within two weeks of admission. Patients prescribed ICS + LABA + another asthma medication (LAMA, LTRA or theophylline) were considered to have 'severe' asthma (equivalent to the highest steps in the asthma management stepwise approach). CPD patients were those that had entered CPD (no asthma) on the case report form. In patients over 50 years, those that had not entered asthma or CPD (no asthma) were classified as having no respiratory condition (Supplementary Table 1).

Further breakdown of the respiratory diagnoses within the CPD category were not recorded but were mostly likely to be predominantly COPD.

### **Outcomes**

The primary outcome was in-hospital survival from onset of symptoms, measured as time in days to death. Secondary outcomes, during the index hospital admission, included any admission to critical



care (Level 3- Intensive Care Unit or Level 2 – High Dependency Unit), and whether the patient received invasive mechanical ventilation (IMV), non-invasive ventilation (NIV) or oxygen (O<sub>2</sub>).

### **Statistical Analysis**

Categorical data were summarised as frequencies and percentages and tested using the Chi-square statistic, except for when cell counts were five or fewer, where Fisher's exact was used (all p-values are based on non-missing values). For continuous data, normally distributed variables were summarised as mean (SD, standard deviation) and non-normally distributed variables as median (IQR, interquartile range). Continuous variables where appropriate were analysed using a two-sample Welch's T-test for normally distributed data, or a Mann-Whitney U or Kruskal-Wallis for data that was not normally distributed.

Time to in-hospital death (survival) was modelled using Cox proportional hazards regression and logistic regression was used for modelling of binary outcomes. For survival models, the reported date of symptom onset was taken as day zero and discharge from hospital was considered an absorbing state (once discharged, patients were considered no longer at risk of death). Discharge did not compete with death as discharged patients were not censored and included in the risk set until the end of follow-up. After building the survival models we confirmed the assumptions of proportional hazards were met by plotting the Schoenfeld residuals and inspecting for symmetry over time. An iterative modelling approach was adopted where clinically plausible variables which could explain differences in mortality were entered into preliminary multivariable models. We selected the final models through minimisation of the Akaike Information Criterion (AIC). Variables that did not reduce AIC were dropped to minimise over-fitting. Where data on predictor (explanatory) variables were missing, we used multiple imputation by chained equations to generate 5 imputed datasets with 5 iterations of imputation per dataset. Models were then fitted on each imputed dataset and the final models pooled using Rubin's rules.

First order interactions were checked, and any significant interactions retained. Covariates included were age, sex, ethnicity, deprivation, obesity, smoking, chronic cardiac disease, chronic kidney disease and malignancy.

Both survival models and logistic regression models took variation across healthcare facilities into account by using mixed effects models. Patient level risk factors were modelled as fixed effects and the healthcare facility as a random effect. We performed three post-hoc sensitivity analyses, first, excluding patients with obesity, second, excluding patients without a positive RT-PCR test result. Third, in the  $\geq 50$  years, including all medication strata (not only ICS) but excluding patients with missing variable for asthma or CPD. Effect estimates are presented as hazard ratios (HR) for time to death and odds ratios (OR) for binary outcome data, alongside their corresponding 95% confidence intervals. Statistical significance was taken at the level of  $P < 0.05$ .

Data were analysed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, AUT) using the tidyverse, finalfit and mice packages.

### **Role of the funding source**

The sponsor had no role in the study design, collection, analysis, data interpretation or report writing. TMD, CIB, ABD and EMH had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

## Results

Up to 17th August 2020, 78,674 patients were enrolled into the ISARIC CCP-UK cohort across 258 healthcare facilities; 75,463 patients had comorbidity data available (**Figure 1**). Chronic respiratory disease (including asthma and/or CPD) was the most prevalent comorbidity (20,196/75,463; 26.8%). 97.4% of patients (73,500) had PCR positive SARS-CoV-2 infection.

### Patient characteristics

#### *Under 16 years old*

There were 860 children, <16 years, 786 (91.4%) without asthma and 74 (8.6%) with asthma. Patients with asthma were older, more likely to be of white ethnicity, but had similar clinical characteristics to children without asthma (**Supplementary Table 2**). Around forty percent were using ICS (41.9%). Five patients were using monoclonal antibodies for severe asthma.

#### *16 to 49 years old*

There were 8,950 patients, 16-49 years, 7,083 (79.1%) without asthma and 1,867 (20.9%) with asthma. Age was similar for patients with and without asthma (mean, years (SD): asthma=38.79 (8.6), no asthma=38.9 years (8.6)) but there were more females, higher proportions of white ethnicity and obese, and similar proportion of smokers in those with asthma (**Table 1 and Supplementary Table 3**). The prevalence of other co-morbidities was low, with small differences between those with and without asthma. Just over half of asthma patients were using ICS (ICS only=22.7%, combination ICS+LABA=22.7%, severe=10.8%). Five patients were using monoclonal antibodies for severe asthma.

#### *50 years old and over*

There were 65,653 patients, ≥50 years, 47,398 (72.2%) patients without a respiratory condition, 5,918 (9.0%) with asthma alone, 10,266 (15.6%) with CPD (no asthma) and 2,071 (3.2%) with co-diagnosis of asthma and CPD. Patients with asthma were slightly younger, more likely to be female and obese but less likely to be of white ethnicity or a current smoker, than patients with CPD (no asthma) (**Table 2 and Supplementary Table 4**). Those with asthma were less likely to have chronic cardiac disease, but other comorbidities were of similar prevalence. There was a higher proportion of patients using ICS in those with asthma than those with CPD alone (asthma alone=61.7%, asthma & CPD=68.1%, CPD (no asthma)=41.3%).

### Symptoms and severity on admission (all age groups)

Patients with a respiratory condition were significantly more likely to have dyspnoea, wheeze and cough, but in those aged ≥16 years, only around 1 in 7 presented with wheeze (**Table 3 & Supplementary Table 5**). In children, <16 years, 40% presented with wheeze (**Supplementary Table 5**). In those aged ≥50 years, over two-thirds presented with dyspnoea, as compared to just over half of patients without a respiratory condition (**Table 3**).

Asthma patients, aged ≥16 years, had a similar level of severity on admission to patients with no respiratory condition, whereas patients with CPD (with or without asthma) presented with higher NEWS2 scores (**Table 3**).

### Level of care during hospital admission (all age groups)

No children (aged <16 years) with asthma died but ten were transferred to critical care (**Supplementary Table 5**). Asthma patients, aged 16-50 years and ≥50 years, were significantly more likely to receive critical care, NIV and oxygen than patients without a respiratory condition after

adjusting for age, gender, ethnicity, obesity, smoking and comorbidities (**Table 4**). Whereas, CPD patients, aged  $\geq 50$  years, were significantly less likely to receive critical care or IMV, but there was an increased association with NIV and oxygen supplementation, as compared to patients without a respiratory condition (**Table 4**). On additionally adjusting for NEWS2 score there was minimal change to effect estimates, except a reduction in adjusted OR for NIV use in CPD (no asthma) (adjusted OR=1.04, 95% CI 0.97-1.12) and CPD & asthma patients (adjusted OR=1.09, 95% CI 0.95-1.25).

## **Survival**

### ***In asthma (16-49 years) by asthma therapy***

6.5% of patients with asthma and 5.4% of patients without asthma died (**Supplementary Figure 1**). After adjusting for multiple risk factors, only asthma patients with severe asthma had higher rates of in-hospital mortality (adjusted HR (95%CI): no therapy=1.17 (0.73-1.86), SABA-only=0.99 (0.61-1.58), ICS-only=0.94 (0.62-1.43), ICS+LABA=1.02 (0.67-1.54), severe=1.96 (1.25-3.08)) (**Figure 2 and Supplementary Table 6**).

### ***In respiratory conditions ( $\geq 50$ years) by ICS use only***

A high proportion of patients with CPD died (41.6%) during their hospital admission, compared to those with asthma (28.2%) or no underlying respiratory condition (34.0%) (**Table 3 and Supplementary Figure 2**). Asthma patients had a 13% significant reduction in mortality risk if they were using ICS compared to those with no underlying respiratory condition, but no reduction if they were not using ICS (asthma-no ICS: adjusted HR=0.97, 95% CI 0.89-1.05; asthma+ICS: adjusted HR=0.86, 95% CI 0.80-0.92) (**Figure 3 and Supplementary Table 7**). When stratifying on patients with asthma alone, patients with severe asthma had an increased mortality compared to those on no therapy (**Supplementary Figure 3 and Supplementary Table 8**). CPD patients (no asthma) had a statistically significant increase in mortality risk, regardless of ICS use, as compared to patients without an underlying respiratory condition (CPD-no-asthma-no-ICS: adjusted HR=1.16, 95% CI 1.12-1.22; CPD-no-asthma + ICS: adjusted HR=1.10, 95% CI 1.04-1.16) (**Figure 3 and Supplementary Table 7**). Patients with CPD and asthma, had a non-significant increased mortality risk if they were not using ICS, as compared to patients without an underlying respiratory condition (CPD-with-asthma-no-ICS: adjusted HR=1.13, 95% CI 1.01-1.28; CPD-with-asthma + ICS: adjusted HR=0.97, 95% CI 0.89-1.06).

On stratifying by NEWS2 score, in all strata and respiratory condition, there was a lower mortality rate in patients using ICS as compared to patients not using ICS (**Supplementary Table 9**).

### ***Sensitivity analyses***

After removing patients with obesity, associations with mortality did not differ from those found in the main analyses (**Supplementary Figures 4 and 5**). Only including patients with positive RT-PCR, did not affect associations found in the main analyses (**Supplementary Figures 6 and 7**). Bronchodilators, or number of long-acting inhalers used, did not affect the effect estimates in the CPD patients (**Supplementary Figure 8**). Modelling age as a continuous transformed variable, did not affect associations as compared to including age as a categorical variable (Supplementary Tables 10 & 11, Supplementary Figures 9 and 10).

### ***Effect of different ICS on survival (grouping together all adults with an underlying respiratory condition)***

After adjusting for mortality risk factors, beclometasone had a 9% significantly reduced risk of in-hospital mortality compared to no ICS (adjusted HR=0.93, 95% CI 0.89-0.98); fluticasone and

ciclesonide did not have a significant association with mortality (**Supplementary Figure 11 and Supplementary Table 12**).

### Discussion

The ISARIC CCP-UK is to our knowledge, the largest cohort of hospital admissions for COVID-19 worldwide. In contrast to some other cohorts, we found that the proportion of people with asthma admitted to hospital with COVID-19 (8.6% <16 years, 20.9% in 16-49 years and 12.2% in ≥50 years) was considerably higher than the national prevalence of asthma which is around 7% for each age group(24). Patients with underlying respiratory conditions were more likely to present with respiratory symptoms, dyspnoea and cough, but wheeze was uncommon except in children with asthma (<16 years old).

CPD patients had a high mortality rate of around 40% but were significantly less likely to receive critical care or invasive ventilatory support than patients with no underlying respiratory condition, even after considering age and comorbidities. In contrast, adult asthma patients were significantly more likely to receive critical care and ventilatory support. This did not seem to be associated with clinical severity on admission, as measured by NEWS2 score, suggesting other factors were contributing towards the decision to provide critical care. For example, it is likely these markers did not fully account for frailty, when treatment escalation discussions were held, and a low threshold for admitting patients with asthma to critical care for observation, given their potential to deteriorate quickly. All respiratory patients were more likely to receive NIV and oxygen supplementation than patients without an underlying respiratory condition, even after accounting for age, comorbidities and admission severity.

Patients with the severe asthma (denoted by their maintenance medication use prior to admission), had worse survival than patients without an underlying respiratory condition. In all other asthma patients, there was no significant difference in mortality except in those using ICS, aged 50 years or more, who had decreased mortality. It is possible these differential effects with age and mortality are related to immune senescence, which can occur from 55 years of age(25). One aspect includes an increase in inflammation that may inhibit immunity to viruses or worsen hyperinflammation at the time of infection; ICS has been postulated to reverse this affect(26, 27). Another possibility is that ICS exhibits its apparent age preferential effect through inhibition of ACE2 as expression of ACE2 is relatively higher with older age(28).

Our findings in asthma patients correspond with work from the OpenSafely primary care consortium. Using over 17 million UK medical records linked to COVID-19 deaths, they found only patients with severe asthma (defined by the prescription of oral corticosteroids in the past year) were predisposed to increased mortality(23). Another large study, using UK Biobank data from over 65,000 people with asthma (enrolled at ages 40-59 years), found non-allergic asthma, or asthma with a co-diagnosis of COPD, to be associated with increased risk of hospitalisation for COVID-19; while allergic asthma showed a non-significant association with reduced hospitalisation(13). These studies engaged large numbers but being observational were all susceptible to inherent misclassification of asthma, due to self-reporting or diagnosis by a non-specialist, as well as limited information on underlying asthma severity and phenotypes. Small case series, using well defined asthma patients (diagnosed by specialists with detailed medical records) found asthma to be associated with an increased risk of severe COVID-19(29, 30). We found asthma to be associated with an increased level of care, even after adjusting for clinical severity on admission, but not with an increased risk of death (except for those

with severe asthma); similar to findings with the 2009 influenza pandemic(9). In our study, we attempted to further refine asthma classification by using an age cut-off and, in the older cohort, separating those documented as having asthma alone from patients with asthma and another CPD.

The first published cohorts of hospitalised COVID-19 patients from China, US and Europe, found a variable prevalence of COPD, sometimes below the expected population prevalence, leading to an initial debate about possible protection(10). Subsequently, the OpenSafely collaborative found COPD to be a highly significant risk factor, seemingly in agreement with the findings from ISARIC-CCP-UK which addressed patients with CPD, rather than COPD(4, 5). A possible mechanism for the increased susceptibility may be related to the elevated expression of ACE2 in the airway epithelial cells in COPD patients and smokers(31, 32) .

The question of whether ICS use is protective is raised by studies demonstrating decreased ACE2 in sputum with ICS use in asthma and ICS-induced downregulation of ACE2 at gene and protein levels in COPD(19-21). The OpenSafely collaborative conducted an analysis, using an asthma cohort and a separate COPD cohort, and reported that ICS was not protective for COVID-19 related survival(23). Indeed, they reported worse outcomes associated with high dose ICS use in asthma, and all ICS use in COPD. However, further analyses revealed considerable residual confounding, thought to be unaccounted for respiratory disease severity(23). Their asthma findings are potentially in keeping with this study as although we could not address ICS dose, we found patients with more severe disease (more likely to be using high-dose ICS) had reduced survival. It is postulated that the timing of ICS use may be critical in terms of the effect of ICS on infection versus the effect on the host response to infection(18). In this regard our study patients reported using their medication within two weeks of admission, i.e. at the time of severe COVID-19. Pointedly, in the OpenSafely study patients could be prescribed ICS any time within four months before entering the study cohort. Our study also includes a different population, ISARIC CCP-UK only includes hospitalised patients with COVID-19, OpenSafely included the general population, those infected and not infected by SARS-CoV-2. Two US studies using electronic medical records from asthma patients only (n=1,526 and n=1,827) addressed the risk of COVID-19 hospitalisation(14, 22) - Wang *et al* also addressed critical care admission and death(33). Both studies found ICS use was not associated with hospitalisation, but Wang *et al* found there was a non-significant effect for reduced critical care admission and improved survival. A Korean study including 218 hospitalised asthma patients, found no significant association between mortality and any asthma medications in COVID-19 hospitalised patients(34).

To date, there is no prior observational data addressing the impact of different ICS drugs. In-vitro data indicates that ciclesonide can suppress SARS-CoV-2 replication(35). Due to the small number of patients prescribed ciclesonide inhalers in the UK this analysis did not have sufficient power to assess its association with mortality.

### **Limitations**

The dataset is not currently linked to primary or secondary care records, and where data were obtained from self-reporting (medication and diagnoses of conditions, including asthma), these could not be confirmed. This could have resulted in misclassification of the prescriptions and diagnoses. We also did not have information on the severity of the underlying respiratory condition, except by their admission medications. Information on the dose of inhaled corticosteroids was often missing, such that this variable was not used. We have assumed patients were using their prescribed medications on admission, this may not have been the case for some. For this reason, we were unable to classify the severity of asthma, except to assume those on three maintenance asthma medications in the two weeks before admission had more severe asthma than the other patients. We did not know the reason

for any oral corticosteroids that may have been prescribed pre-admission. Conditions not included on the study case report forms could not be evaluated separately, including atopy, and COPD and bronchiectasis which were likely included in the CPD (no asthma) category. Physiological measurements for clinical severity were limited to ones included in the NEWS2 score and were only available on admission. Finally, we were interested in the outcome of in-hospital mortality (incorporating palliative discharge), which could have led to some patients who were discharged and died in the community being missed. Our analysis used discharge as an absorbing state, considering all these patients as being alive, discharge is associated with outcome (i.e. is informative) and therefore should not be used as a censoring event in this analysis. This is a reasonable assumption given our methods of data collection, but it is a limitation.

## **Conclusion**

Chronic respiratory disease was the most prevalent comorbidity in the ISARIC CCP-UK cohort. However, there was a disparity between different respiratory conditions and the level of in-hospital care received. CPD patients had a high level of mortality with a prevalence of 40% for in-hospital death. Only asthma patients with severe asthma had increased mortality compared to those without an underlying respiratory condition. Patients with asthma (aged 50 years or more) had a lower mortality risk if they had used ICS within two weeks of admission. These results confirm that many patients with existing respiratory conditions are high risk and should continue to take precautions against exposure to SARS-CoV-2. The role of ICS in COVID-19 remains unclear, but ICS protect against exacerbations of respiratory disease and may protect against severe COVID-19.

## Figure legends

Figure 1. Flow diagram of patient by inclusion and exclusion criteria

Figure 2. Association between asthma and COVID-19 related mortality in 16-50 years old. SABA=short-acting beta-agonist, LABA=long-acting beta-agonist, ICS=inhaled corticosteroid, IMD=index of multiple deprivation

Figure 3. Association between ICS use, respiratory condition and in-hospital mortality in  $\geq 50$  years old. CPD= chronic pulmonary disease, ICS=inhaled corticosteroid, IMD=index of multiple deprivation

Supplementary Figure 1. Time to in-hospital death by asthma and asthma treatment.

Supplementary Figure 2. Time to in-hospital death by respiratory condition and ICS.

Supplementary Figure 3. Association between asthma and COVID-19 related mortality, by their asthma treatment, in patients aged 50 years and over. SABA=short-acting beta-agonist, LABA=long-acting beta-agonist, ICS=inhaled corticosteroid, IMD=index of multiple deprivation

Supplementary Figure 4. Association between asthma and COVID-19 related mortality in 16-50 years old; removing obese patients.

Supplementary Figure 5. Association between ICS use, respiratory condition and in-hospital mortality in  $\geq 50$  years; removing obese patients.

Supplementary Figure 6. Association between asthma and COVID-19 related mortality in 16-50 years old; including only RT-PCR positive patients.

Supplementary Figure 7. Association between ICS use, respiratory condition and in-hospital mortality in  $\geq 50$  years; including only RT-PCR positive patients.

Supplementary Figure 8. Association between ICS use, respiratory condition and in-hospital mortality in  $\geq 50$  years including all medication strata.

Supplementary Figure 9. Association between ICS use, respiratory condition and in-hospital mortality in 16-50 years old, including age as a continuous transformed variable

Supplementary Figure 10. Association between ICS use, respiratory condition and in-hospital mortality in  $\geq 50$  years old, including age as a continuous transformed variable

Supplementary Figure 11 - Effect of different ICS on in-hospital mortality.

## Author's Contributions

Conceptualisation: PJMO, PC, CIB, BJL, SLJ, JKB, JD, GC, JSN-V-T, MGS

Data curation: TMD, CIB

Formal analysis and methodology: TMD, CIB, PC, EMH, ABD, BJL, SLJ

Supervision: PC, PJMO, ABD, CIB, EMH, MGS

Writing original draft: CIB, TMD

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Funding acquisition: JKB, GC, PWH, PJMO, MGS

TMD and CIB confirm that they have verified the data used in the study.



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**Conflict of interest**

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