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Outcomes of COVID-19 amongst patients with ongoing use of inhaled corticosteroids - a systematic review & meta-analysis

Syed Nazeer Mahmood	MD, Department of Medicine, Section of Pulmonary/Critical Care, MedStar Washington Hospital Center, Washington, DC, USA
Viraj Shah	MBBS, Department of Internal Medicine, Hackensack Meridian Health Ocean University Medical Center, NJ, USA
Urvish Patel	MD, MPH, Department of Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA
Muhammad Umair Nawaz	MD, Department of Internal Medicine, Griffin Hospital, Derby, CT, USA
Narayana Varalakshmi Akula	MBBS, Department of Internal Medicine, Carle Foundation Hospital, Champaign, IL, USA
Irina Balan	MD, Department of Family Medicine, Montefiore Medical Center, Wakefield, Bronx, NY, USA
Divya Manivannan	MBBS, Sri Ramachandra Institute of Higher Education and Research, India
Yelena Pleshkova	MD, MBA, Department of Internal Medicine, Adventhealth, Sebring, FL, USA
Shayaan Negit	MD, American University of the Caribbean, School of Medicine, Sint Marteen
Prarthana Desai	MBBS, Department of Internal Medicine, Danbury Hospital, Danbury, CT, USA
Richa Jaiswal	MBBS, MSCR, Department of Internal Medicine, Medical University of South Carolina, SC, USA
Neel Patel*	MBBS, MPH, Department of Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA*Corresponding Author
Raghvendra Tirupathi	MD, FACP, FRCP, FIDSA, Department of Internal Medicine, Keystone Health, Chambersburg, PA, USA
Thoyaja Koritala	MD, FACP, FHM, Department of Internal Medicine, Mayo Clinic Health System, Mankato, MN, USA

ABSTRACT

Background The numbers quoted by WHO for the Coronavirus disease 2019 (COVID-19) pandemic as of August 2021 were 200 million cases with over 4 million deaths globally. COVID-19 is associated with several respiratory pathologies. Inhaled corticosteroids (ICS) are used to improve lung function by reducing inflammation, edema, mucus secretion, and inhibiting various cytokine activities. However, there is limited data on the effect of ICS usage in patients with COVID-19. In this study, we aim to evaluate the association between the effectiveness of ICS and the outcomes in COVID-19 patients compared to standard COVID-19 treatment. **Methods** We followed PRISMA guidelines and MOOSE protocol for conducting the systematic review and meta-analysis comparing ICS and standard COVID-19 therapy. A search on PubMed is conducted yielding 270 articles of which 6 manuscripts are finalized for inclusion in the study. Patients with COVID-19 are identified from the studies based on confirmed positive RT-PCR tests. Hospitalization, ICU admission, and mortality are selected as the outcomes of our study. Using RevMan 5.3, we performed random-effects models to estimate the pooled effect size (pooled odds ratio), 95% confidence interval (95% CI), and heterogeneity (I2). Forest plots are obtained and $p < 0.05$ is considered statistically significant. **Results** Of the six studies, five reported mortality. We noted a higher prevalence of mortality in patients with asthma (60.88%, 107/160) and chronic obstructive pulmonary disease (COPD) (68.46%, 382/558). The overall mortality is 7.49% (107/1428). We found that ICS use was associated with higher odds of mortality (OR=1.45 95%CI: 1.10-1.91; p=0.009, I2= 68%) amongst COVID-19 patients. In subgroup analysis, higher odds of mortality among COPD patients using ICS was noted [pooled OR: 1.52 (1.24-1.86); p<0.0001; I2=0%]. However, no significant association between ICS and mortality was observed among asthma patients. **Conclusion** ICS is associated with increased mortality and risk for hospitalization in patients with COVID-19 as compared to standard non-steroid-based COVID-19 therapy. Future studies are needed to support the evidence of ICS discontinuation in COVID-19 patients.

KEY WORDS :

***Corresponding Author Neel Patel**

MD, MPH, Department of Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) and has been declared a global pandemic by the World Health Organization (WHO) . COVID-19 is the third outbreak of beta coronaviruses in the twenty-first century with over 200 million confirmed cases and over 4 million deaths globally . Approximately 40-60% of chronic obstructive pulmonary disease (COPD) and up to 80% of asthma exacerbations are due to viral infections and include those caused by coronaviruses. Patients with underlying lung diseases like COPD, asthma who develop COVID-19 have worse outcomes with a case fatality rate of 6.3% .

In humans, the SARS-CoV2 virus targets an essential angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in the epithelial cells of the upper respiratory tract. As a result, it replicates within cells causing cellular injury or death with the release of pro-inflammatory cytokines. In addition, viral particles can stimulate an innate immune response, activating alveolar macrophages and the complement system. This, in turn, causes alveolar and vascular damage, vascular thrombosis, and ventilation-perfusion mismatch gradually involving other organs leading to multiorgan failure and death. Pulmonary inflammation in some cases leads to pulmonary fibrosis as well .

Corticosteroids improve lung physiology by reducing inflammation, edema, mucus secretions and extending inhibitory actions on the transcription and activity of various cytokines at any therapeutically relevant dose through classic genomic mechanisms. In addition, they inhibit SARS-CoV-2 replication in infected epithelial cells by decreasing the expression of ACE2 receptors. Five randomized controlled trials involving 7,692 patients showed that the overall mortality of patients treated with systemic corticosteroids was lower than those not receiving corticosteroids (26% vs. 28%, relative risk {RR} = 0.89 [95% confidence interval {CI} 0.82-0.96], p = 0.003) .

Given the benefits of systemic corticosteroids, the use of inhaled corticosteroids (ICS) has been proposed. Yamaya et al. described an in-vitro study where pre-treatment of human respiratory epithelial cells with budesonide combined with long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA), showed inhibition of human coronavirus HCV-229E replication and cytokine production . Another study reported a 50% reduction in ARDS in at-risk patients using ICS before hospital admission, even after controlling for age, sex, and chronic respiratory diseases . In COVID-19, The Cleveland clinic's COVID-19 registry analysis revealed that ICS therapy did not increase COVID-19 related healthcare utilization, ICU admission, need for intubation, or mortality outcome in patients with COPD. However, the PRINCIPLE trial in the UK noted that the use of Budesonide improves time to recovery and may reduce hospital admissions and death . At this time, there is limited and occasionally conflicting evidence in the literature when analyzing the safety and efficacy of ICS in patients with COVID-19. Therefore, we performed this meta-analysis to address the effectiveness of ICS along with the standard of care in COVID-19.

METHODS

Aim/Endpoint:

The primary aim of the study is to evaluate outcomes of COVID-19 amongst patients with pre-existing use of ICS or use of ICS as part of COVID-19 therapy compared to standard COVID-19 treatment. Standard COVID-19 treatment in our study did not involve systemic corticosteroids.

We identified patients with COVID-19 from the studies based on confirmed positive RT-PCR tests. We selected hospitalization, ICU admission, need for mechanical ventilation, mortality, and poor composite outcome as the outcomes of our study.

Search strategy

We followed PRISMA guidelines and MOOSE protocol in conducting the systematic review and meta-analysis comparing the outcomes of ICS and standard COVID-19 therapy. We searched articles on PubMed with keywords coronavirus disease 2019, COVID-19, SARS CoV 2, severe acute respiratory syndrome coronavirus 2, and coronavirus to identify our study population; an inhaled corticosteroid, ICS, inhaled dexamethasone, nebulized dexamethasone, and nebulized corticosteroid to identify the intervention/comparison group from December 2019 to December 2021.

Inclusion Criteria: Observation studies and clinical trials describing COVID-19 positive cases and pre-existing use of ICS or ICS as a part of treatment for COVID-19 or clinical trial intervention were included in our meta-analysis.

Exclusion Criteria: Non-human, non-English, and studied pediatrics populations were excluded.

Study selection

Using keywords and study criteria, we derived appropriate studies. We reviewed abstracts followed by full-length articles to obtain data from the studies for quantitative analysis. VS, UN, and NA independently screened all of the identified studies and assessed full texts to determine eligibility. Any disagreement was resolved through consensus with UP and NG. Figure 1 describes the literature search and study selection process.

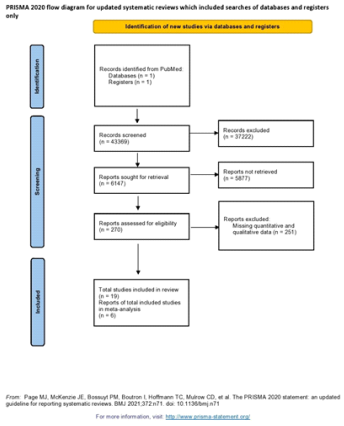


Figure 1: PRISMA Flow chart describing the literature search and study selection process

Data extraction:

Data on study name, design, period, country, sample size, mean/median age, sex, population characteristics, type of intervention, and various outcomes were collected by IB, NA, RJ, VS using a standard template form, and any disagreement was resolved through consensus with UP and NG. Study characteristics and outcomes were described in Table 1.

Statistical Analysis:

Excel sheet was used to collect the data and Review Manager version 5.3 software was used to analyze the data. We performed random-effects models to estimate the pooled effect size (pooled odds ratio) and 95% confidence interval (95% CI). Forest plots obtained $p<0.05$ were considered statistically significant. Heterogeneity (I2 values) was identified and I2>75% represented as high heterogeneity. In such circumstances, sensitivity analysis was performed and studies with higher variability were removed using a funnel plot. Risk of bias analysis was performed and described using the Newcastle-Ottawa Scale (NOS).

Table 1: Studies describing the use of ICS amongst COVID-19

Study name, year	Country	Study design	Study period	Sample size	Mean/ median age (years)	Sex (Male %)	Population	Intervention vs Standard care [ICS vs Standard Care]	Outcomes [Events in Intervention vs Events in Standard care]
Schultze et al., 2020	UK	Cohort (Observational) study	Mar 2020 - May 2020	COPD: 148,557 Asthma: 818,490	COPD: 72 (64–78) Asthma (High dose ICS): 55 (44–67)	COPD: 53·7 % Asthma: High dose ICS: 38·2 %	COVID-19 (EHR of primary care patients with COPD and Asthma)	COPD: ICS combination (n=105,249) vs LAMA-LABA combination (n=43,308) Asthma: ICS-High dose (n=101,077) vs SABA only (n=108,411)	Mortality [COPD: 338/105249 vs 91/43308] [Asthma: 105/101077 vs 49/108441]
Sen et al., 2021 ——'	USA	Cross-sectional study	Mar 8, 2020 - Sep 16, 2020	COPD: 27810 Covi +ve: 1288 568vs720 (using ICS Inhaler Vs Not using ICS Inhaler	63.7	38.8 %	COVID-19 with COPD	COPD ICS vs No ICS (568 vs 720)	Mortality [COPD: 37/568 vs 34/720] Hospital admissions: [201/568 vs 170 vs 720]
Choi et al., 2020 ——	Korea	Nested Case-Control	Til May 15, 2020	7341 (114 vs 7221) Total (ICS vs non-ICS)	57.4	40%	COVID-19 with COPD or Asthma	Overall ICS vs Non-ICS 7341 (114 vs 7221) COPD ICS vs Non-ICS 678 (52 vs 626) Asthma ICS vs Non-ICS 123 (61 vs 62)	Mortality [COPD: 7/45 vs 51/540 Asthma: 2/55 vs 4/52] ICU admissions [34/114 vs 900/7227]
Chiba et al., 2020	USA	Retrospective Cohort Study	Mar 1 - Apr 15, 2020	1526 (1306 vs 220) Total (No asthma vs asthma)	55.3 (40-59)	47%	COVID-19 with Asthma	ICS vs ICS+LABA vs Non ICS (26 vs 80 vs 114)	Hospitalization [61/106 vs 54/114 ICU admission [13/106 vs 6/114]
Wang et al., 2020	USA	Cross-sectional study	Mar 3, 2020 - Jun 8, 2020	1827 (1262 vs 565) Hospitalization (no vs yes)	54 (37-66)	32.6 %	COVID-19 with Asthma	Overall ICS vs ICS+LABA vs Non ICS (310 vs 289 vs 1228)	Mortality [28/98 vs 568/1729] Hospitalization [187/599 vs 224/842] ICU admission [13/19 vs 48/96]
Husby et al., 2021	Denmark	Observational Cohort	Til Jul 16, 2020	6267	62 (47–77)	51.8 %	COVID-19	ICS vs non ICS (649 vs 5618)	Mortality [70/649 vs 544/5618] ICU admission [69/644 vs 545/1824]

Respiratory outcome: A composite variable that included conventional oxygen therapy, high flow nasal cannula, mechanical ventilation, and extracorporeal membrane oxygenation.

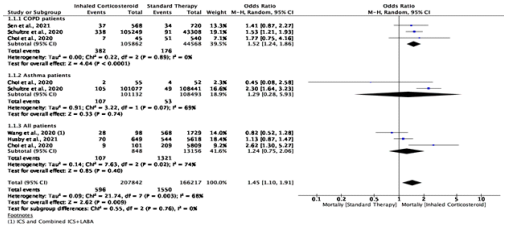
RESULTS

Based on eligibility criteria, we included 6 observation studies or clinical trials in our meta-analysis.

COVID-19 specific mortality in ICS users vs non-ICS users

Amongst 5 studies reporting data on mortality, mortality prevalence was high in patients with asthma (60.88% 107/160) and COPD (68.46% 382/558). All other patients had a mortality rate of 7.49% (107/1428). We found that use of ICS was associated with 1.45 higher odds of mortality (95%CI: 1.10-1.91; p=0.009) with 68% of heterogeneity (p=0.003). In the subgroup analysis, COPD patients had higher odds of death [pooled OR: 1.52 (1.24-1.86); p<0.0001; I2 =0%; p for I2 = 0.89] while there was no significant increase in mortality in patients with asthma [pooled OR: 1.29 (0.28-5.93); p=0.74; I2 =69%; p for I2 = 0.07]. We did not conduct sensitivity analysis as I2 was <75%. [Figure 2].

Figure 2: COVID-19 specific mortality in ICS users vs non-ICS users



COVID-19 specific ICU admission

In the 5 studies reporting the need for ICU admission, ICU admission among ICS users was higher 18.7% (203/1084) in comparison to those not receiving ICS 16.4% (1552/9425). This was however not statistically significant with pooled OR 1.37 (95%CI: .43-4.36; p=.59) with 96% of heterogeneity (p<.00001) Figure 3.1. We conducted sensitivity analysis as I2 was >75%. In the sensitivity analysis, the odds ratio was noted to be significant at OR 2.06;(95% CI: 1.23-3.45; p=.05) Figure 3.2. after removing the outlying study of Husby et al. Figure 3: COVID-19 specific ICU admission (Fig 3.1) with sensitivity analysis (Fig 3.2)

Figure 3.1

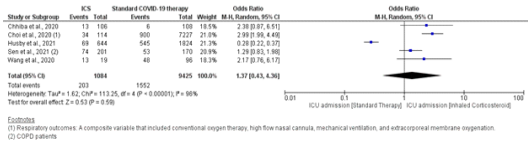
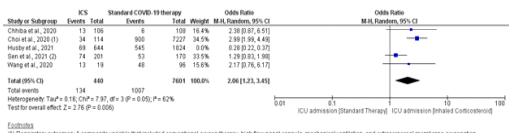


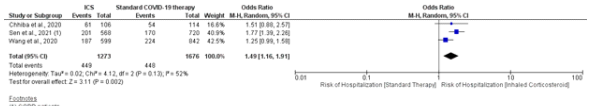
Figure 3.2



COVID-19 specific Risk of Hospitalization

Amongst the 5 studies, the prevalence of risk of hospitalization among ICS users was higher 35.27% (449/1273) in comparison to non-ICS users 26.73% (448/1676). This was also statistically significant with Pooled OR 1.49 (95%CI: 1.16-1.91; p=.002) with 52% of heterogeneity (p.13) (Figure 4). We did not conduct sensitivity analysis as I2 was <75%.

Figure 4: COVID-19 specific Risk of Hospitalization



Our study has also assessed risk of bias analysis using the Newcastle-Ottawa Scale and it shows moderate quality of evidence. [Table 2]

Table 2: Newcastle-Ottawa Scale for Risk of Bias Assessment

Newcastle–Ottawa Scale (NOS)				
Study name, Year	Selection	Comparability	Outcome	Overall Risk of Bias
Schultze et al., 2020 [10]	***	**	*	Low
Sen et al., 2021 [11]	***		*	High
Choi et al., 2020 [12]	***	**	*	Low
Chiba et al., 2020 [13]	***	*	*	High
Wang et al., 2020 [14]	***	*	*	High
Husby et al., 2021 [15]	***	*	**	Moderate

DISCUSSION

ICS has been shown to lower ACE2 and TMPRSS2 gene expression in sputum cells 16 and as SARS CoV-2 targets the ACE2 receptors, the protective effect of ICS has been theorized. In vitro studies by Jeon et al and Yamaya et al. also noted an antiviral effect of ICS8,17. These findings have prompted research into the effectiveness of ICS in COVID-19. Multiple studies have been published over the last year comparing the use of ICS in the management of COVID-19 to standard, non-corticosteroid-based management of the disease. However, the data has been conflicting and to our knowledge, no other meta-analysis has been performed to evaluate the effectiveness of ICS.

We found 6 studies that reported our primary endpoint of mortality and other endpoints of risk for hospitalization and need for ICU admission. In our study, the overall mortality was higher in ICU users with 1.45 higher odds of mortality (95%CI: 1.10-1.91; p=0.009). In the mortality subgroup analysis, we also found that the use of ICS in patients with COPD patients had a higher odd of death but the use of ICS in patients with asthma was not significantly associated with mortality [pooled OR: 1.29 (0.28-5.93); p=0.74]. The use of ICS is known to increase the risk of pneumonia in patients with COPD while the risk of pneumonia is not increased in patients with asthma18,19. This may explain the higher mortality in the COPD subgroup.

Our study also found that the need for ICU admission was higher in patients using ICS as compared to those not using ICS (18.7% vs 16.4%) however this was not statistically significant. Husby et al. reported a higher need for ICU admission in patients not using ICS while all the other studies either reported no difference or higher mortality in the ICS group. When this study was removed from our analysis, the odds ratio for the need for ICU admission was noted to be higher in the ICS group [pooled OR 2.06 (1.23-3.45); p=.05].

The need for hospitalization was also much higher in the ICS group (35.27% vs 26.73%) with an OR of 1.49 (95%CI: 1.16-1.91; p=.002).

The higher mortality, need for hospitalization, and ICU admission with ICS use seen in our study is likely due to the increased burden of pulmonary complications in this population. ICS is currently used in patients for conditions that cause increased bronchial hyperreactivity like asthma and asthma-COPD overlap conditions. Therefore, patients already on ICS who contract COVID-19 may be at a higher risk for worsening pulmonary disease and subsequent complications.

The strengths of this meta-analysis include lower overall heterogeneity due to the included clinical trials and observational studies being performed in different countries. The sub-group analysis of mortality amongst ICS users with COPD or asthma patients compared to non-ICS users augments the generalizability of our conclusions.

Our study is also not without limitations. Studies published in languages apart from English were not identified or included. We were unable to adjust risk with the inability to ascertain severity indexes. Data regarding pre-existing comorbidities was also lacking.

CONCLUSION

In conclusion, our study shows that inhaled corticosteroids are associated with increased mortality and risk for hospitalization in patients with COVID-19 as compared to non-steroid-based management of the disease. Future studies are needed to support the evidence of ICS discontinuation in COVID-19 patients. More significant, high-quality randomized clinical trials on this topic are warranted before implementing this treatment worldwide.

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