Inhaled Corticosteroids

Section last reviewed and updated 3/14/2022

Last literature search conducted 2/28/2022

Recommendation 1: Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel suggests against inhaled corticosteroids outside of the context of a clinical trial. (Conditional recommendation, Moderate certainty of evidence)

Why are inhaled corticosteroids considered for treatment?

Systemic corticosteroids have become a mainstay of therapy for the management of systemic inflammation seen in patients with severe COVID-19 infection as a result of the mortality reduction demonstrated in the RECOVERY trial [1]. In addition to their anti-inflammatory properties, some corticosteroids have been shown to inhibit viral replication of coronaviruses including MERS-CoV. Specifically, ciclesonide has demonstrated the ability to block SARS-CoV-2 viral replication *in vitro*, where fluticasone and dexamethasone did not [2]. Therefore, ciclesonide, and potentially other corticosteroids, may offer both anti-inflammatory and antiviral activity for the management of SARS-CoV-2. The antiviral mechanism may be related to the action of corticosteroids on both angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2), which mediate SARS-CoV-2 viral attachment and entry into host cells. Preliminary data from a clinical cohort of patients taking inhaled corticosteroids suggest a lower expression of ACE2 and TMPRSS2 compared to those not taking inhaled corticosteroids, and may suggest decreased susceptibility to SARS-CoV-2 in those taking inhaled corticosteroids [3].

Summary of the evidence

Five RCTs reported on the use of inhaled corticosteroids budesonide or ciclesonide compared to placebo or no treatment with inhaled corticosteroids for ambulatory or hospitalized patients with mild-to-moderate COVID-19 [4-8]. These trials reported on the outcomes of mortality, COVID-19-related hospitalization, and serious adverse events.

Benefits

Among patients with mild-to-moderate COVID-19, inhaled corticosteroids failed to show or exclude a beneficial effect on mortality or COVID-19-related hospitalization (risk ratio [RR]: 0.61; 95% confidence interval [CI]: 0.22, 1.67; absolute risk reduction: 3 fewer per 1,000 [from 7

fewer to 6 more and RR: 0.67; 95% CI: 0.36, 1.26; Moderate certainty of evidence, respectively]; moderate certainty of evidence [CoE]).

Harms

Serious adverse events may be less frequent among patients with mild-to-moderate disease receiving treatment with inhaled corticosteroids rather than no inhaled corticosteroids; however, this may not be meaningfully different from those not receiving not receiving inhaled corticosteroids (RR: 0.78; 95% CI: 0.29, 2.09; moderate CoE).

Other considerations

The panel determined the certainty of evidence of treatment of inhaled corticosteroids for patients with mild-to-moderate COVID-19 to be moderate due to concerns with imprecision, as effects failed to show or exclude a beneficial effect for mortality or COVID-19-related hospitalization. The guideline panel made a conditional recommendation against inhaled corticosteroids outside of the context of a clinical trial.

Conclusions and research needs for this recommendation

The guideline panel suggests against inhaled corticosteroids for the treatment of patients with mild-to-moderate COVID-19, unless in the context of a clinical trial. More information is needed about the interaction of inhaled corticosteroids with a 5-day course of ritonavir as part of nirmatrelvir/ritonavir treatment. When potent CYP 3A4 pharmacokinetic boosters like ritonavir or cobicistat are utilized for durations greater than 5 days in patients with HIV or hepatitis C, most inhaled corticosteroids are not recommended for coadministration due to the risk of Cushing's syndrome and adrenal suppression [9]. This may be a consideration when prescribing inhaled steroids if concomitantly used with nirmatrelvir/ritonavir.

Table 1. GRADE evidence profile, Recommendation 1

Question: Inhaled corticosteroids compared to no inhaled corticosteroids for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

New evidence profile developed 3/14/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	inhaled corticosteroids	no inhaled corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 14 days to 30 days)												
4 [1-4]	randomized trials	not serious [a]	not serious	not serious [b]	serious [c]	none	6/1127 (0.5%)	10/1135 (0.9%)	**RR 0.61** (0.22 to 1.67)	**3 fewer per 1,000** (from 7 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL
COVID-19-related hospitalizations (follow-up: range 14 days to 30 days)												
4 [1-3,5]	randomized trials	serious [a]	not serious	not serious [d]	serious [c]	none	78/1162 (6.7%)	109/1178 (9.3%)	**RR 0.67** (0.36 to 1.26)	**31 fewer per 1,000** (from 59 fewer to 24 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: range 14 days to 30 days)												
3 [1,3,4]	randomized trials	not serious [a]	not serious	not serious	serious [c]	none	7/928 (0.8%)	9/928 (1.0%)	**RR 0.78** (0.29 to 2.09)	**2 fewer per 1,000** (from 7 fewer to 11 more)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: confidence interval; **RR:** risk ratio

Explanations

a. Ramakrishnan 2021 & Yu 2021 were open-label trials, which may introduce bias into outcomes subjectively measured, such as COVID-19-related hospitalizations and SAEs.
b. 8/35 patients in Song 2021 received HCQ in addition to ciclesonide. All patients in Song 2021 had mild-to-moderate COVID-19 and were hospitalized.
c. Sparse data, few events, unable to excluded harms as well as benefits

d. In Yu 2021 the following patients were admitted to hospital without need for supplemental oxygen: budesonide 17/787 (2%) placebo 21/799 (3%).

References

1. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet **2021**; 398(10303): 843-55.
2. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA Intern Med **2022**; 182(1): 42-9.
3. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. BMJ **2021**; 375: e068060.
4. Song JY, Yoon JG, Seo YB, et al. Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial. J Clin Med **2021**; 10(16): 3545.
5. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med **2021**; 9(7): 763-72.

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med **2021**; 384: 693-704.
2. Matsuyama S, Kawase M, Nao N, et al. The Inhaled Steroid Ciclesonide Blocks SARS-CoV-2 RNA Replication by Targeting the Viral Replication-Transcription Complex in Cultured Cells. J Virol **2020**; 95(1).
3. Peters MC, Sajuthi S, Deford P, et al. COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. Am J Respir Crit Care Med **2020**; 202(1): 83-90.
4. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet **2021**; 398(10303): 843-55.
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9. Boyd SD, Hadigan C, McManus M, et al. Influence of low-dose ritonavir with and without darunavir on the pharmacokinetics and pharmacodynamics of inhaled beclomethasone. J Acquir Immune Defic Syndr **2013**; 63(3): 355-61.

Supplementary Materials

Study characteristics

- **Table s1.** Should ambulatory patients with mild-to-moderate COVID-19 receive treatment with **i**nhaled corticosteroids compared to no inhaled corticosteroids?

Forest plots

- **Figure s1a.** Outcome of mortality for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19
- **Figure s1b.** Outcome of COVID-19-related hospitalization for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19
- **Figure s1c.** Outcome of serious adverse events for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19

Risk of bias

- **Table s2.** Randomized controlled studies (inhaled corticosteroids vs. no inhaled corticosteroids)

Table s1. Should ambulatory patients with mild-to-moderate COVID-19 receive treatment with **i**nhaled corticosteroids compared to no inhaled corticosteroids?

Study / year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Clemency/ 2021 [1]	U.S./ 10 centers	RCT	400 (197/203)	55.3	Mean age: 43.3 (16.9)	Positive SARS-CoV-2 antigen test within 72 hours, non-hospitalized, not hypoxic, with at least 1 symptom of COVID-19 (fever, cough, dyspnea)	Ciclesonide MDI 160 mcg/actuation, 2 puffs twice daily plus standard supportive care for 30 days	(1) SoC	Supportive care at discretion of treating provider (4 patients received antivirals, 1 patient monoclonal antibodies)	Time to alleviation of all COVID-19 symptoms ED visits Hospitalizations All-cause mortality Proportion of patients with alleviation of COVID-19 symptoms Adverse events	Covis Pharma GmbH National Center for Advancing Translational Sciences National Heart, Lung, and Blood Institute
Ezer/ 2021 [2]	Canada/ Centers across 3 provinces (Quebec, Ontario, British Columbia)	RCT	203 (105/98)	53.7	Median age: 35 (27-47)	Positive SARS-CoV-2 PCR test within 5-6 days, unvaccinated, non-hospitalized, with at least 1 symptom of fever, cough, or shortness of breath	Inhaled ciclesonide 600 mcg twice daily plus intranasal ciclesonide 200 mcg/day for 14 days	Placebo	Not specified	Proportion with resolution of fever and respiratory symptoms at day 7 Hospitalizations COVID-19 mortality Resolution of fever and respiratory symptoms at day 14 Improvement in overall feeling at day 7 and 14	McGill University Health Centre Foundation McGill Interdisciplinary Initiative in Infection and Immunity

										Adverse events	
Ramakrishnan/ 2021[3]	Oxfordshire, United Kingdom	RCT	139 (70/69)	57.6	Mean age: Intervention: 44 (No SD reported) Control: 46 (No SD reported)	Onset of COVID-19 symptoms within 7 days of trial enrollment and non-hospitalized	Budesonide dry powder inhaler 400 mcg/actuation, 2 puffs twice daily plus supportive care per NHS guidelines until patient felt better or the primary outcome was achieved	Supportive care	Not specified	COVID-19 related urgent care visit, ER visit, or hospitalization Time to symptom resolution Viral symptoms measure by Common Cold Questionnaire Influenza Patient-reported Outcome questionnaire Oxygen saturation Body temperature Viral load Adverse events	National Institute for Health Research Biomedical Research Centre AstraZeneca
Song/ 2021[4]	South Korea/ 6 hospitals	RCT	61 (35/26)	53	Median age: 53 (35-61)	Hospitalized patients with positive SARS-CoV-2 PCR within 3 days of diagnosis or 7 days from symptom onset, with mild-moderate disease (National Early Warning Score of 0-4 and O_2 sat ≥95% on RA)	Ciclesonide 320 mcg inhaler twice daily for 14 days plus standard of care	(1) SoC	Hydroxychloroquine 400mg daily for 14 days (8 patients in ciclesonide group)	SARS-CoV-2 eradication rate based on qRT-PCR on day 14 SARS-CoV-2 eradication rate at day 7 and 10 Rate of clinical improvement at day 7, 10, 14 Rate of clinical failure within 28 days Adverse events	National Research Foundation of Korea Korea University Guro Hospital

Yu/ 2021 [5]	United Kingdom	RCT	1959 (833/1126)	51.8	Mean age: 64.2 (7.6)	Patients in the community age ≥ 65 or ≥ 50 with comorbidities with suspected or confirmed COVID-19 within 14 days with ongoing symptoms (fever, cough, or loss of taste or smell)	Budesonide 800 mcg inhaler twice daily for 14 days plus standard of care	(1) SoC	None	COVID-19 related hospital admission or death within 28 days Time to first reported recovery Time to sustained recovery Time to alleviation of symptoms Oxygen use ICU admission Mechanical ventilation WHO-5 Wellbeing Index New household infections Adverse events	National Institute of Health Research United Kingdom Research Innovation

Figure s1a. Forest plot for the outcome of mortality for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19

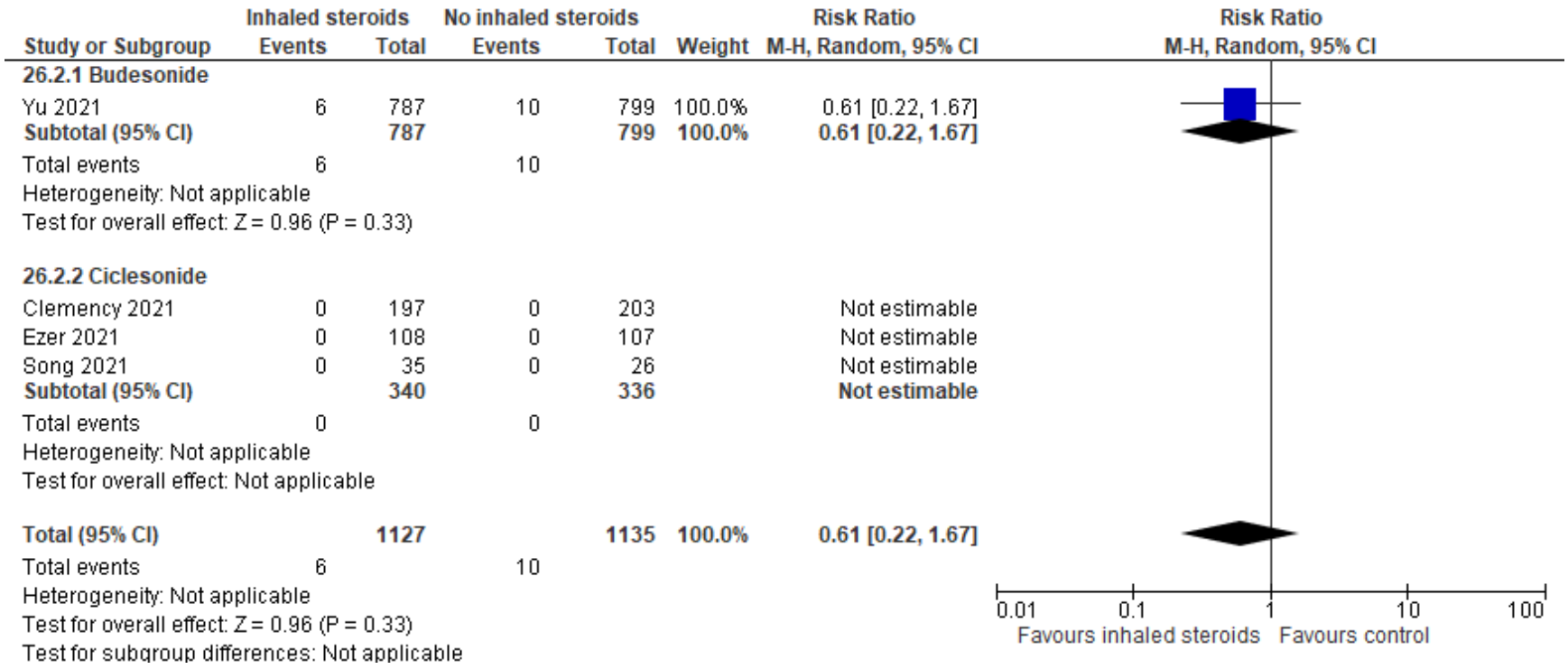

Figure s1b. Forest plot for the outcome of COVID-19-related hospitalization for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19

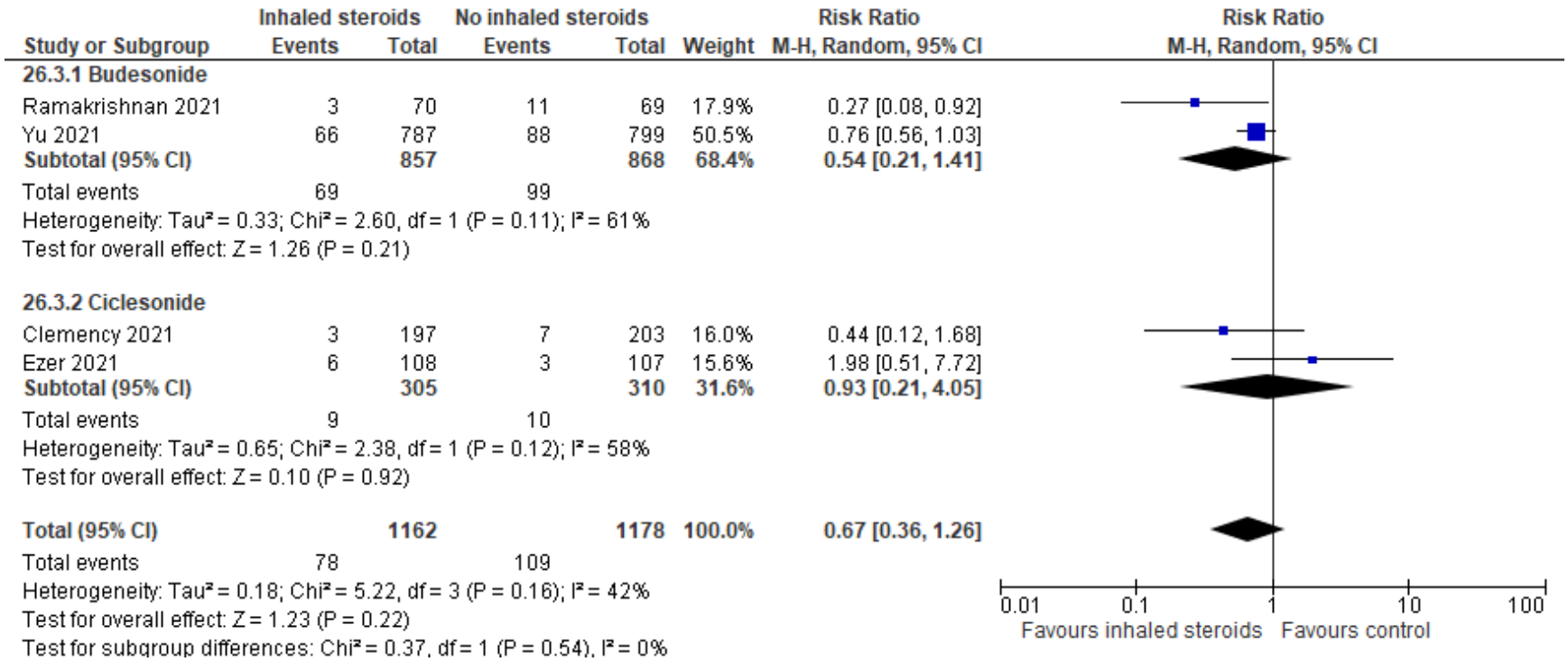

Figure s1c. Forest plot for the outcome of serious adverse events for **i**nhaled corticosteroids compared to no inhaled corticosteroids in patients with mild-to-moderate COVID-19

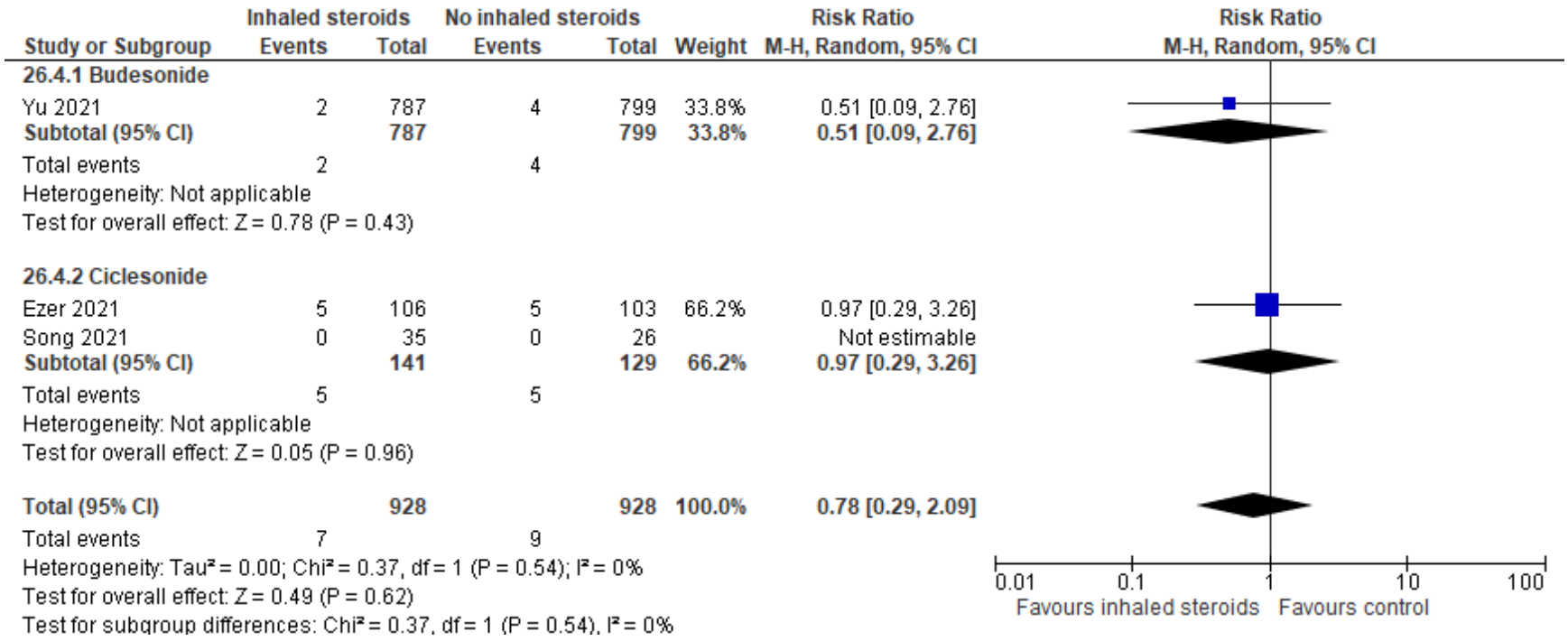

Table s2. Risk of bias for randomized controlled studies (inhaled corticosteroids vs. no inhaled corticosteroids)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Clemency 2021 [1]							
Ezer 2021 [2]							
Ramakrishnan 2021 [3]							
Song 2021 [4]							
Yu 2021 [5]							

Low	High	Unclear

References for Supplementary Materials

1. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA Intern Med **2022**; 182(1): 42-9.
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