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Original Article

Inhaled corticosteroid for patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials

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SARS-CoV-2

Abstract *Background:* The efficacy of inhaled corticosteroid (ICS) in the treatment of patients with COVID-19 has been evaluated in randomized controlled trials (RCTs), however, their findings are not consistent.
Methods: PubMed, Embase, Cochrane Library, ClinicalTrials.gov, Scopus, Web of Science and Google Scholar were searched to June 10, 2023. Only RCTs that investigated the clinical efficacy and safety of ICS for patients with COVID-19 were included.
Results: Eleven RCTs were included. ICS users had significantly higher rate of symptom alleviation at day 14 than the control group (risk ratio [RR], 1.13; 95% CI, 1.04–1.23; $I^2 = 42\%$). Additionally, no significant difference between the ICS users and the control group was observed in the composite outcome of urgent care, emergency department (ED) visit or hospitalization (RR, 0.43; 95% CI, 0.08–2.48; $I^2 = 85\%$) and hospitalization or death (RR, 0.85; 95% CI, 0.64–1.12; $I^2 = 0\%$). Finally, ICS user had a non-significantly lower risk of death at day 28 than the control group (0.63% vs 0.99%; RR, 0.82; 95% CI, 0.43–1.56; $I^2 = 0\%$).

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Conclusions: Additional ICS use, particularly inhaled budesonide may help symptom relief in patients with COVID-19. However, ICS use did not help reduce the risk of urgent care, ED visit, hospitalization, or death.

Introduction

Since the first outbreak of coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has rapidly become a great threat on public health.[1–3] However, only limited useful agents - nirmatrelvir plus ritonavir, remdesivir, and molnupiravir are recommended as therapeutic management of adults with COVID-19 during this period with prevalent omicron variant.[4–8] To expand the armament against SARS-CoV-2 infection, many researches have been conducted to assess the clinical efficacy of potential anti-COVID-19 treatments. In Steroids in COVID-19 (STOIC) trial,[9] Baker et al. showed that compared with patients without the deterioration of COVID-19, patients with COVID-19 progress had pronounced and persistent T-helper 2 inflammation. However, inhaled corticosteroid (ICS) can exhibit modulatory effect on T-helper 2 inflammation and may play a promising role in the treatment of patients with early COVID-19. In addition, ICS can downregulate SARS-CoV-2 related gene - angiotensin-converting enzyme-2 (ACE2), transmembrane protease serine 2 (TMPRSS2), and a disintegrin and metalloprotease 17 (ADAM17) in animal and clinical studies.[10–12] Finney and his colleague found that ICS administration would attenuate the expression of ACE2 in mice, and also in airway epithelial cell cultures from patients with chronic obstructive pulmonary disease (COPD).[10] Milne et al. reported that the additional use of ICS could downregulate bronchial epithelial expression of the SARS-CoV-2-related genes ACE2 and ADAM17 in patients with COPD.[11] Similarly, Peters et al. demonstrated that ICS was associated with lower expression of ACE2 and TMPRSS2 among patients with asthma.[12] All these findings suggested the potential role of ICS in the treatment of patients with COVID-19 and triggered the further randomized controlled trials (RCTs).[9–12] Furthermore, the results of several RCTs[13–17] were reported in 2021, but their findings were not consistent. Although several meta-analyses[18–20] were conducted to investigate this issue, their findings were based on only limited RCTs ($n \leq 5$) involving two types of ICSs — budesonide and ciclesonide. However, newly published results of RCTs have been reported in 2022[21–24] and one of them assessed another type of ICS — fluticasone.[23] Therefore, this systematic review and meta-analysis was conducted to provide updated information about the clinical efficacy and safety of ICS in the treatment of patients with COVID-19.

Methods

Inclusion and exclusion criteria

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)[25] and was registered in PROSPERO (registration number CRD42022357774). Only RCTs that assessed the clinical efficacy of ICS for patients with COVID-19 were included. No limitations were imposed regarding age; sex; race or ethnicity; types of ICS, or duration of treatment. Studies were included if they met the following criteria: (i) included patients with COVID, (ii) used ICS-containing treatment as an intervention, (iii) used placebo, standard care, or other alternative treatment as a comparator, (iv) study design was an RCT, and (v) reported clinical efficacy including symptom relief, the risk of hospitalization, urgent care, or emergency department (ED) visits, and mortality as a study outcome. The following were excluded: (i) non RCTs; (ii) studies that did not report the outcomes of interest; (iii) nonhuman studies, and (IV) studies which is still ongoing and do not have publication data. In addition, studies that assessed the effects of combination therapy involving ICS and other than corticosteroid medications were excluded. This approach enabled us to specifically focus on the effect of ICS alone.

Search strategy and study selection

PubMed, Embase, Cochrane Library, ClinicalTrials.gov, Scopus, Web of Science and Google Scholar were searched from their inception to June 10, 2023. We also manually searched for additional eligible articles from the reference lists of relevant articles. The following medical subject headings terms were used: "COVID-19," "SARS-CoV-2," "coronavirus disease 2019", "severe acute respiratory syndrome coronavirus 2", "administration, Inhalation", "inhalational drug administration", "glucocorticoids," "budesonide," "ciclesonide," "pregnenediones," "fluticasone," and ''beclomethasone." No language restrictions were imposed. The detailed search strategies are listed in eTable 1.

Two investigators (CWH and MCL) independently screened the titles and abstracts of the records collected using the aforementioned search strategies to identify and assess potentially eligible studies. Disagreements were resolved by a third investigator (CCL). Full-text copies of

potentially relevant articles were obtained and reviewed for eligibility.

Data extraction

The following information was extracted: study design, study site, study duration, included patients, severity of COVID-19, the regimen of ICS, the clinical outcomes, and risk of adverse events (AEs). The primary outcome was the rate of symptom resolution, which was defined as the alleviation of all symptoms related to COVID-19, and secondary outcome included risk of hospitalization, urgent care, or ED visits, mortality, and the incidence of AEs, defined as any event that emerges during treatment. Two investigators (CCL and CMC) independently collected the data of each included study. Cohen's kappa was calculated to measure agreement between the two investigators. Any conflicts were resolved by consensus. The potency of different ICSs was defined according to their total daily doses as Global Initiative for Asthma guideline (budesonide: 200—400 mcg [low], >400—800 mcg [medium], >800 mcg [high]; ciclesonide: 80—160 mcg [low], >160—320 mcg [medium], >320 mcg [high]; fluticasone furoate: 100 mcg [low-medium]; 200 mcg [high])

Assessment of study quality and risk of bias

Two investigators (CWH and MCL) independently assessed the risk of bias for each of the included studies by using the Cochrane risk-of-bias tool 2.0.[26] Disagreements were resolved through discussion and consensus with a third investigator (CCL).

Statistical analysis

The statistical analysis was performed using Review Manager (version 5.4; Nordic Cochrane Center, Copenhagen, Denmark) and R software (version 4.3.1). We calculated the risk ratio (RR) with a 95% confidence interval (CI) for the clinical outcome and the risk of AEs. Potential publication bias was assessed with Egger's test.[27] Further leave-one-out sensitivity analyses were applied to evaluate whether individual studies had a large influence on the magnitude of the association between the study and the control group and subgroup analysis was conducted according to the type of ICS, comparators, the risk of COVID-19 progress and study quality. Random-effects meta-analyses using Mantel-Haenszel method were performed to pool the data. Heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic. Heterogeneity was categorized as low ($I^2 \leq 25\%$), moderate ($25\% < I^2 < 75\%$) or high ($I^2 \geq 75\%$).

Results

Search results

Initially, 4932 studies were identified from Pubmed (n = 711), Embase (n = 1061), Cochrane central (n = 131), Scopus (n = 365), Web of Science (n = 162), Google Scholar (n = 2500), and records identified through registry or other sources (n = 2). After excluding 271 duplicate articles, 4661 articles were screened. Then 4585 were excluded based on the title and abstract. The 76 remaining articles underwent a full-text review to assess their eligibility. Finally, a total of 11 studies[13—17,21—24,28,29] meeting the selection criteria were identified (Fig. 1).

Characteristics of included studies

Table 1 summarizes the characteristics of the eleven included studies.[13—17,21—24,28,29] Except one RCT,[23] all the other studies were conducted before omicron wave. Six RCTs focused on outpatients[13—15,17,22,23] and four only included hospitalized patients with COVID-19.[21,24,28,29] Two RCTs only included COVID-19 patients with the risk of clinical

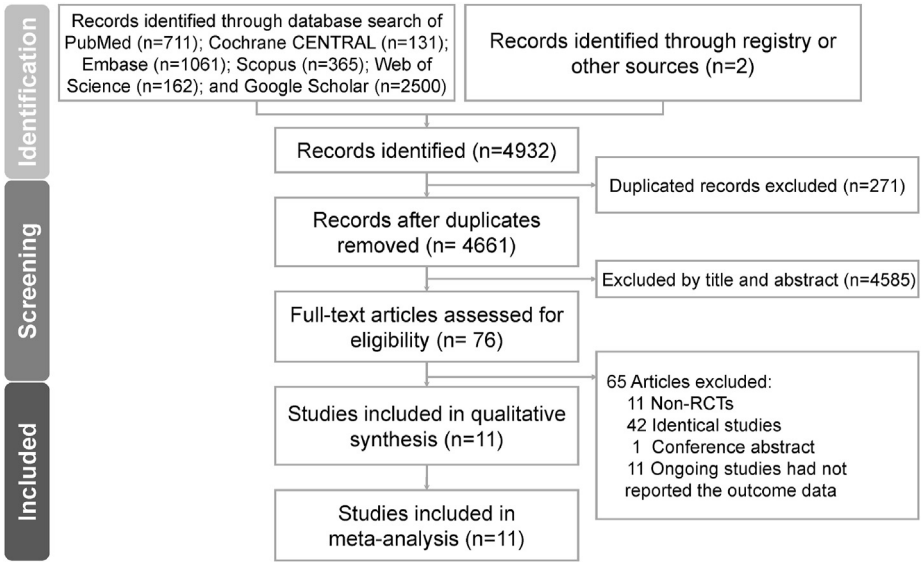

Figure 1. The algorithm of study selection.

Table 1 The characteristics of included studies.

Study	Design	Site	Study period	Patients	Regimen of Inhaled corticosteroid	Comparator
Ciclesonide						
Clemency et al., 2021[13]	Phase 3, double-blind, randomized controlled trial	US	From June 11, 2020 to November 3, 2020	Outpatients with symptomatic COVID-19 confirmed by PCR or antigen test	320 μg twice daily for 30 days	Placebo
Duvignaud et al., 2022[22]	Phase 3, open-label, controlled trial	France	From December 29 2020 to July 23, 2021	Outpatients with PCR- or antigen confirmed COVID-19 and had risks for deterioration	320 μg twice daily for 10 days	Vitamins and trace elements
Ezer et al., 2021[14]	Phase 2 randomized, double blind, placebo-controlled trial	Canada	From September 15, 2020 to June 8, 2021	Outpatient adult with PCR-confirmed COVID-19 and predominantly respiratory symptom	600 μg twice daily for 14 days	Placebo
Song et al., 2021[16]	Phase 2 randomized, open-label, clinical trial	South Korea	From May 8, 2020 to March 31, 2021	Patients with mild-to-moderate PCR-confirmed COVID-19	320 μg twice daily for 14 days	Standard care
Terada-Hirashima et al., 2022[29]	Phase 3, open-label, controlled trial	Japan	Between April 3, 2020 and September 18, 2020	Hospitalized patients with asymptomatic or mild COVID-19	400 μg thrice daily for 7 days	Standard care
Brodin et al., 2023[28]	Phase 3, open-label, controlled trial	Sweden	Between June 1, 2020 and May 17, 2021	Hospitalized patients with COVID-19 receiving oxygen therapy	320 μg twice daily for 14 days	Standard care
Budesonide						
Agusti et al., 2022[21]	randomized, controlled, open-label trial	Spain, Argentina	From April 21, 2020 until March 16 2021	Hospitalized PCR-confirmed COVID-19 patients with radiological evidence of pneumonia	400 μg twice daily	Usual care
Alsultan et al., 2021[24]	randomized, controlled, trial	Syria	Between August 1 and 30, 2021	Hospitalized patients with severe COVID-19 confirmed by PCR or compatible symptoms and radiographic findings	200 μg twice daily for 5 days	Usual care
Ramakrishnan et al., 2021[15]	Phase 2 randomized, open-label, parallel-group, clinical trial	UK	From July 16 to Dec 9, 2020	Outpatients with mild COVID-19 confirmed by PCR	800 μg twice daily until symptom resolution	Usual care
Yu et al., 2021[17]	randomized, controlled, open-label, adaptive platform trial	UK	From Nov 27, 2020 to March 31, 2021	Outpatient patients aged ≥65 years or ≥50 years with comorbidities and PCR-confirmed or clinically suspected COVID	800 μg twice daily for 14 days	Usual care

Fluticasone furoate						
Naggie et al., 2022[23]	Phase 3 double-blind, randomized, placebo-controlled platform trial	US	From August 10, 2021 to February 12, 2022	Outpatients with mild-to-moderate COVID-19 confirmed by PCR or antigen test	200 μg once daily for 14 days	Placebo

PCR, positive polymerase chain reaction.

deterioration.[17,22] Three types of ICSs were assessed in the included RCTs. Six RCTs used ciclesonide as the intervention,[13,14,16,22,28,29] four used budesonide[15,17,21,24] and one used fluticasone furoate.[23] The treatment duration of ICS varied, and the daily dosage of ICSs ranged from low (budesonide, n = 1), medium (budesonide, n = 1), and high (ciclesonide, n = 6; budesonide, n = 2; fluticasone furoate, n = 1). In addition to ICS, one study added intranasal ciclesonide (200 ug/day) as combination treatment[14] and Song et al.'s study used ICS with or without hydroxychloroquine as intervention due to data indicating that hydroxychloroquine is not effective.[16] A total of 4605 patients were included in this meta-analysis, in which 2170 patients were randomly assigned to receive ICSs as intervention (budesonide, n = 978; fluticasonefuroate, n = 656; ciclesonide, n = 536) (Table 2). The agreement of data extraction between the two investigators reached a Cohen's kappa value of 0.963. Fig. 2 summarizes the results of the trial quality assessment. Seven of eleven RCTs had low risk in domain of overall risk of bias.[13—15,17,23,28] Some concerns of overall risk of bias were rated in two studies, in which Duvignaud et al. did not implement allocation concealment in randomization process[22] and Agusti et al. did not provide the information regarding analysis of adhering to treatment and missing data.[21] The other two studies had high risk of overall bias.[16,24] Song et al.'s study had high risk in domain deviations from the intended interventions because of unblinding and lack of description of patients' adherence to treatment.[16] Alsultan et al. did not disclose the outcomes of interest, therefore, domain of deviations from the intended interventions was rated high risk.[24] The study by Ezer et al.[14] was terminated early for expected futility to meet total enrolment due to a rapid decline in cases of COVID-19 in Canada following increases in vaccination. There was no evidence for publication bias (Egger's test $P = 0.8898$).

Primary outcome

The study group had a insignificantly higher alleviation of symptoms at day 7 than the control group (RR, 1.06; 95% CI, 0.96—1.17; $I^2 = 0\%$), but ICS users had significantly higher rate of symptom alleviation at day 14 than the control group (RR, 1.13; 95% CI, 1.04—1.23; $I^2 = 42\%$) (Fig. 3). Except the sensitivity test excluding Yu et al.[17] for day 14 symptom alleviation yielded an RR of 1.11 (95% CI, 1.00—1.23), which indicated a borderline response, all the other findings remained unchanged using leave-one-out sensitivity test after excluding individual RCT accordingly. In the pooled analysis of six RCTs involving only outpatients with COVID-19,[13—15,17,22,23] we have the similar findings that high-dose ICS users were associated with a higher symptom relief rate than the control group at day 14 (RR, 1.12; 95% CI, 1.03—1.23; $I^2 = 46\%$) and no different in response rate at day 7 between groups (RR, 1.07; 95% CI, 0.96—1.18; $I^2 = 0\%$) (Fig. 3).

Further subgroup analysis according to the type of ICS, no significant difference in the symptom relief rate at day 7 and day 14 was observed between the patients receiving inhaled ciclesonide or fluticasone and the control group (Table 3). Inhaled budesonide was associated with a higher symptom relief rate than the control group at day 14 (RR,

Table 2 The characteristics of included patients.

Study	No of patients under randomization		Age, mean (SD) or medium (IQR)		Male, no (%)		Days between diagnosis or symptom onset and enrollment, medium (IQR)	
	ICS	Control	ICS	Control	ICS	Control	ICS	Control
Ciclesonide								
Clemency et al., 2021[13]	197	203	43.7 (17.5)	42.9 (16.3)	85 (43.1)	94 (46.3)	Within 3 days	
Duvignaud et al., 2022[22]	110	107	62 (57–67)	63 (59–70)	58 (52.7)	58 (44.9)	Within 7 days	
Ezer et al., 2021[14]	105	98	35 (27–47)	35 (27–45)	51 (49)	43 (44)	3 (2–4)	3 (2–4)
Song et al., 2021[16]	35	26	44.9 (17.9)	49 (16.8)	11 (31.4)	9 (34.6)	4 (2–7)	3 (1.5–5.5)
Terada-Hirashima et al., 2022[29]	41	48	23.2 (3.9)		20 (48.8)	24 (50.0)	5	5.5
Brodin et al., 2023[28]	48	50	61 (49–67)	59 (49–67)	34 (71)	33 (66)	9 (7.5–11.5)	10 (8–11)
Budesonide								
Agusti et al., 2022[21]	58	62	50.6 (13.7)	51.6 (13.8)	24 (42.1)	32 (51.6)	NA	NA
Alsultan et al., 2021[24]	14	21	NA	NA	5 (35.7)	9 (42.9)	NA	NA
Ramakrishnan et al., 2021[15]	73	73	44 (19–71)[a]	46 (19–79)[a]	31 (44)	28 (41)	Within 7 days	
Yu et al., 2021[17]	833	1126	64.7 (7.3)	63.8 (7.8)	404 (48)	540 (48)	Within 14 days	
Fluticasone furoate								
Naggie et al., 2022[23]	656	621	43 (37–55)	46 (38–56)	225 (34.3)	245 (39.5)	6 (4–7) days	5 (4–7) days

[a] Mean (range).
ICS, inhaled corticosteroid; NA, non-applicable.

1.22; 95% CI, 1.13–1.33; I^2 = 0%), but no significant difference was observed between inhaled budesonide and comparator in the symptom response rate at day 7 (RR, 1.12; 95% CI, 0.98–1.27; I^2 = 0%) (Table 3).

Finally, we did subgroup analysis according to the comparators. Compared to standard care or usual care, ICS was associated with a higher response rate at day 14 (RR, 1.23; 95% CI, 1.13–1.33) in the pooled analysis of three RCTs.[15–17] However, no significant difference was observed between ICS and placebo for symptom response in the pooled analysis of three RCTs.[13,14,23] In addition, subgroup analyses according to the study quality had the similar findings (eFig. 1), except no significant difference between ICS and control in the symptom relief rate at day 14 among the analysis of studies with some concerns or high risk of bias (RR, 1.10; 95% CI, 0.77–1.58) (eFig. 2).

Secondary outcomes

First, no significant difference between the ICS users and the control group was observed in the composite outcome of urgent care, ED visit or hospitalization, which was define if patient had any one of urgent care, ED visit or hospitalization during the follow-up period (0.43; 95% CI, 0.08–2.48; I^2 = 85%) in the pooled analysis of outpatients in three RCTs(Fig. 4).[13,15,23] Similarly, there was no significant difference between the ICS users and the control group in the composite outcome of hospitalization or death (RR, 0.85; 95% CI, 0.64–1.12; I^2 = 0%) in the pooled analysis of outpatients in five RCTs (Fig. 4).[13,14,17,22,23] Although ICS user had a lower risk of death at day 28 than the control group, these differences did not reach statistical significance (0.63% vs 0.99%; RR, 0.83; 95% CI, 0.44–1.57;

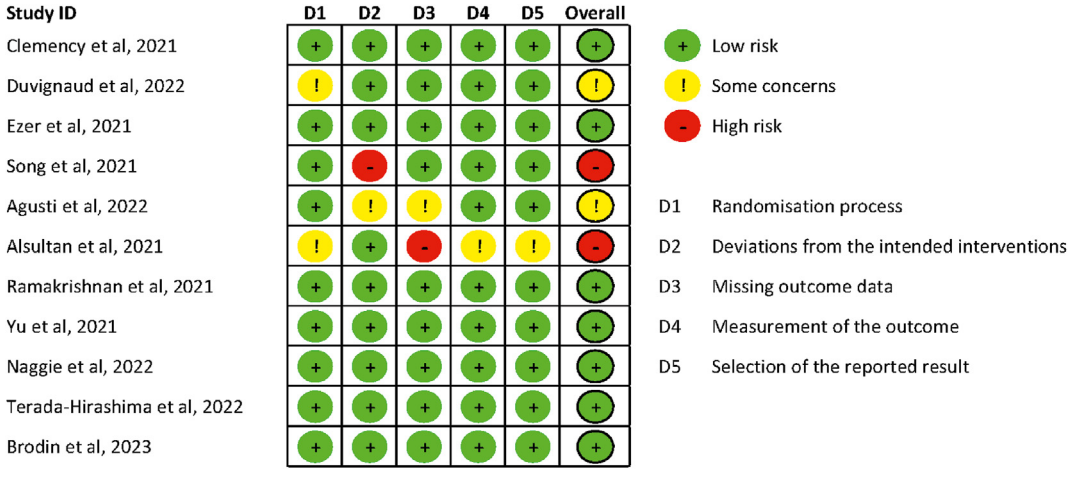

Figure 2. Summary of the risks of bias in each domain.

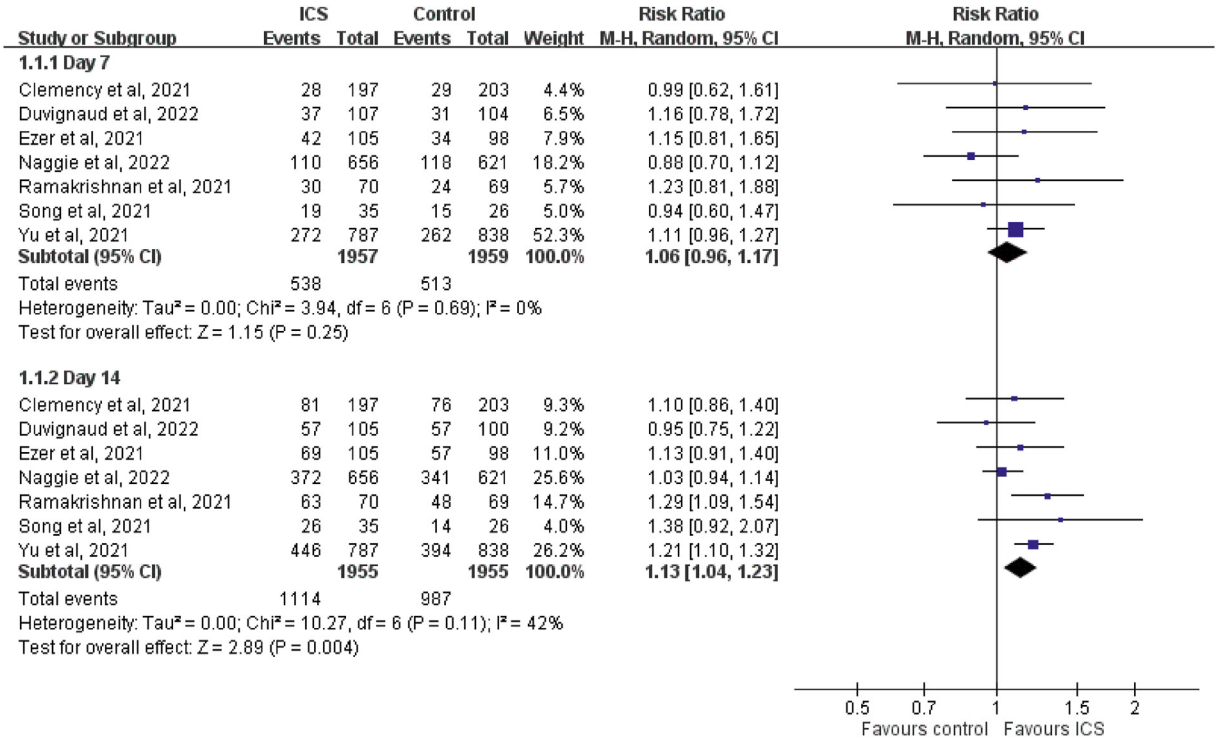

Figure 3. Forest plot of the rate of symptom alleviation between inhaled corticosteroid (ICS) users and controls.

I^2 = 0%; Fig. 5) in the pooled analysis of ten RCTs.[13,14,16,17,21–24,28,29] Finally, ICS was associated with the similar risk of AE to the control group (RR, 1.04; 95% CI, 0.84–1.28; I^2 = 0%) (see Fig. 6).

Discussion

The present study is the meta-analysis of the efficacy and safety of ICS for the treatment of patients with COVID-19. Most importantly, we found that additional ICSmay help resolution of COVID-19 related symptoms, which was supported by the following evidence. First, ICS use was associated with a significantly higher symptom resolution rate at day 14 than the control group and this finding remained unchanged in the further leave-one-out sensitivity test. Second, although the subgroup analysis of studies with some concerns or high risk of bias did not find significant difference between ICS and control in symptom resolution rate at day 14, which may be related to lower rate of comorbidity in control group than in ciclesonide group in Duvignaud et al.,[22] the pooled analysis of study with low risk of bias showed ICS was associated a higher recover rate at day 14 than the control. Third, the higher alleviation rates of symptom at day 7 was also observed in the study group receiving ICS than the control group, despite these differences did not reach statistical significance. These findings are consistent with previous two meta-analyses.[18,19] However, in contrast to the study[18] by Chen et al. only included five RCTs with 1243 patients who received ICS and 1526 patients with placebo or usual care, and the Cochrane review[19] by Griesel et al. only three RCTs involving 3607 participants with mild COVID-19, which focused on outpatients and the use of budesonide and ciclesonide, the present analysis of nine RCTs involving more than four thousand patients can provide updated information with stronger evidence. Moreover, our study also evaluated the usefulness of fluticasone furoate and

Table 3 The results of subgroup analysis.

	No of study	No of patients	Risk ratio	95% confidence interval	p value	*df*	I^2
Symptom relief at day 7							
Ciclesonide	4	875	1.08	0.88–1.32	0.48	3	0%
Budesonide	2	1764	1.12	0.98–1.27	0.10	1	0%
Fluticasone	1	1277	0.88	0.70–1.12	0.30	–	–
Symptom relief at day 14							
Ciclesonide	4	869	1.09	0.96–1.24	0.18	3	0%
Budesonide	2	1995	1.22	1.13–1.33	<0.00001	1	0%
Fluticasone	1	1277	1.03	0.94–1.14	0.52	–	–

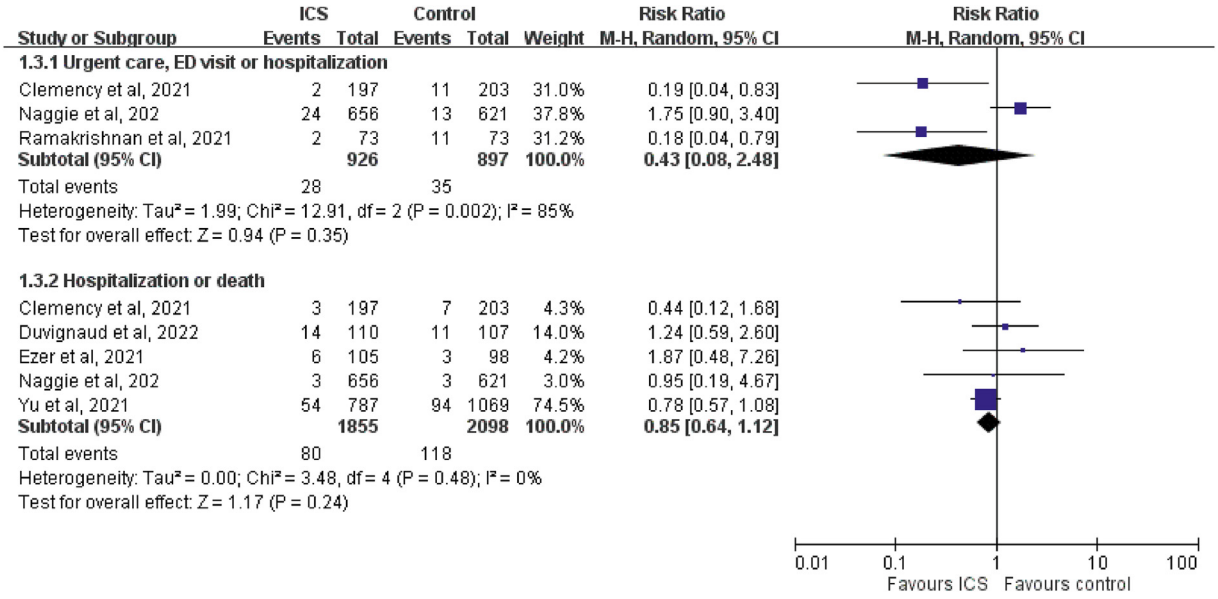

Figure 4. Forest plot of the risk of urgent care, emergency department (ED) visit, hospitalization or death between inhaled corticosteroid (ICS) users and controls among outpatients with COVID-19.

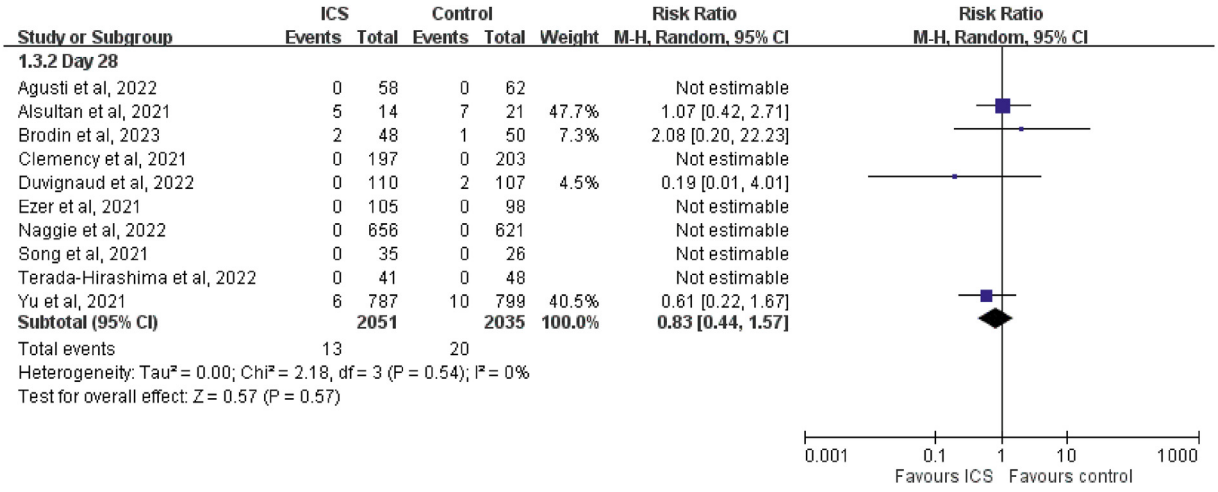

Figure 5. Forest plot of the risk of 28-day mortality between inhaled corticosteroid (ICS) users and controls among outpatients with COVID-19.

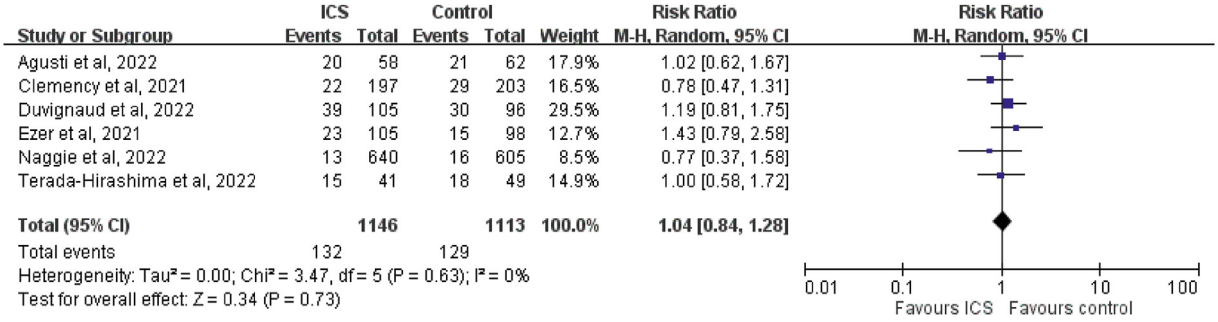

Figure 6. Forest plot of the risk of adverse event between inhaled corticosteroid (ICS) users and controls.

included hospitalized patient with COVID-19. Overall, all these findings suggest the potential role of ICS in the symptom resolution of patients with COVID-19.

In addition to overall response, we did further subgroup analysis according to the type of ICS and found that only budesonide was associated with a significantly better symptom relief. By contrast, the symptom resolution rate was similar between the control group and the study group using ciclesonide or fluticasone furoate. Except two RCTs[21,24] using low-to-medium dose of budesonide as intervention, the dose of ICS in the other studies were high dose. Therefore, the possible intra-class difference of ICSs may be explained by the characteristics of budesonide — shorter residence time of lung deposition, and lesser immunosuppressive potency than other ICSs.[30—32] Additionally, the different treatment duration and timing of administering ICS after onset of COVID-19 may contribute to the different effects of ICSs. In summary, our findings, and previous study[18] may suggest the promising use of inhaled budesonide and did not support the use of inhaled ciclesonide and fluticasone furoate[20,23]; however, further study is warranted to confirm this issue.

In contrast to the additional benefit on the symptom relief, ICS was not associated with the significant lower risks of urgent care, ED visit, hospitalization, or death than the comparators. Similar findings were observed in the subgroup analysis of patients at high risk. The analysis of mortality in the present work as well as previous meta-analyses showed the similar findings — ICS was not associated with additional survival benefit. Overall, these findings indicated that ICS could not help reduce the risk of death in this clinical entity.

This meta-analysis has several limitations. First, only one RCT was conducted within the period overlapping the omicron (BA.1.1) variants wave and in the post-vaccine era, in which 64.8% (n = 827) patient had received ≥ two doses of vaccines.[23] In other two RCTs with available vaccine status reported that only two (1%) of 207 and 14 (0.7%) of 1959 patients had received two doses of vaccine.[17,22] Although Nakajima et al. reported that ICS would not reduce the antibody titer against SARS-CoV-2 spike protein in BNT162b2 mRNA vaccinated patients,[23] further study is warranted to assess the association between ICS and SARS-CoV-2 variant and the status of vaccination. Second, Zein et al. demonstrated that among ICS users, eosinophilia was associated with lower risk for hospitalization, ICU admission, and mortality.[32] However, the effect of eosinophils was not evaluated in the present work. Third, among the included RCTs, one was a pre-print article[23] and the intervention group in another study used ICS ± hydroxychloroquine.[16] These two issues may distort our findings. However, the finding of the primary outcome analysis remained unchanged after excluding these two studies.[16,23] Lastly, this study reported the similar risk of AE between ICS group and control group, however, it could be underestimated due to this meta-analysis only included the study with efficacy outcomes. Even more, only several included RCTs reported the specific ICS-associated AE. Brodin et al.[28] and Clemency et al.[13] reported two (0.42%) and one (0.5%) using inhaled ciclesonide had development of oral candidiasis. Regarding budesonide, Ramakrishnan et al.[15] showed that the adverse event was reported in five participants (four had sore throat; one had dizziness) but all were self-limiting and fully resolved on cessation of ICS. However, further study is warranted to assess the tolerability of ICS for patients with COVID-19.

In conclusion, additional ICS use, particularly inhaled budesonide may help symptom relief in patients with COVID-19. However, ICS use did not help reduce the risk of urgent care, ED visit, hospitalization, or death. Although these findings suggest the potential role of ICS for alleviating the symptoms of patients with COVID-19, further large study is warranted.

Funding

None.

Data availability

All data extracted from included studies.

Conflict of interests

All authors declared there was no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.07.008.