Efficacy and Safety of Different Doses of Systemic Corticosteroids in COPD Exacerbation

Xiaofeng Pu, Liang Liu, Bimin Feng, Maolin Wang, Limei Dong, Zhengji Zhang, Qingze Fan, Ying Li, and Guojun Wang

BACKGROUND: Although systemic corticosteroids (SCS) have long been used to treat patients with COPD exacerbation, the recommended dose remains controversial. We aimed to perform a meta-analysis and an indirect treatment comparison to investigate the efficacy and safety of different doses of SCS in subjects with COPD exacerbation. METHODS: Studies were identified by searching different databases for randomized controlled trials that investigated the efficacy and safety of SCS with placebo in subjects with exacerbation of COPD. The different doses of SCS were assigned to low-dose (ie, initial dose $\leq$ 40 mg prednisone equivalent/d [PE/d]), medium-dose (initial dose = 40–100 mg PE/d, and high-dose (initial dose > 100 mg PE/d) groups. The indirect treatment comparison was performed between low-, medium-, and high-dose SCS groups. RESULTS: Twelve trials with 1,375 participates were included. Compared to placebo, the risk of treatment failure was lower in the low-dose SCS groups (risk ratio 0.61 [95% CI 0.43–0.88], P = .007) and high-dose SCS groups (risk ratio 0.64 [95% CI 0.48–0.85], P = .002); the FEV_1 was significantly improved in low-dose (mean difference 0.09 [95% CI 0.06–0.12], P < .001), medium-dose (mean difference 0.23 [95% CI 0.02–0.44], P = .036), and high-dose SCS groups (mean difference 0.09, [95% CI 0.03–0.15], P < .001, respectively). Regarding safety, the incidence of hyperglycemia was higher in high-dose SCS groups versus placebo (risk ratio 2.52 [95% CI 1.13–5.62], P = .02). The indirect comparison between low-, medium-, and high-dose SCS found that the risk of treatment failure and changes in FEV_1 were similar between these doses of SCS. CONCLUSIONS: This meta-analysis indicates that low-dose SCS (initial dose $\leq$ 40 mg PE/d) was sufficient and safer for treating subjects with COPD exacerbation, and it was noninferior to higher doses of SCS (initial dose > 40 mg PE/d) in improving FEV_1 and reducing the risk of treatment failure. However, our findings need to be verified in head-to-head randomized controlled trials. *Key words: COPD exacerbation; systemic corticosteroids; different doses; meta-analysis; indirect treatment comparison.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

COPD is a common, preventable, controllable, and treatable disease. Patients with COPD are often exposed to large amounts of harmful particles or gases, resulting in abnormal airways and alveoli, persistent respiratory symptoms, and air flow limitations.[1] The psychological, mental, and economic burden of COPD often exceeds that of other diseases; meanwhile, quality of life and work productivity of individuals with COPD is frequently reduced.[2,3] To date, the morbidity of COPD has been estimated to be about 11.7% worldwide,

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with approximately 3 million people dying annually due to COPD. COPD has become one of the global leading causes of death.[4]

For individuals with COPD, symptoms develop over time and activities of daily living gradually decrease, with exacerbations of the disease occurring in many patients.[3] COPD exacerbations accelerate respiratory failure and increase mortality and relapse rates.[5,6] It is noteworthy that a remarkable number of COPD exacerbation patients who require hospitalization are readmitted within 6 months of the primary treatment.[7,8]

Several drugs are recommended for patients with COPD exacerbation, including bronchodilators (eg, β_2-agonists, long-acting muscarinic antagonists, theophylline), antibiotics, and inhaled or systemic corticosteroids.[9-13] Systemic corticosteroids (SCS) are commonly prescribed to treat patients with respiratory conditions such as asthma and to reduce the risk of flare-ups of inflammatory conditions, including rheumatologic and autoimmune diseases, allergic reactions, and inflammatory bowel disease. Although SCS have long been used to treat patients with COPD exacerbation, there have been no head-to-head randomized controlled trials (RCTs) to directly compare the effect of different dosage regimens of SCS. In addition, there is currently no consensus on the standard dose and duration of SCS in the treatment of COPD exacerbation. The Japanese Respiratory Society recommend oral prednisolone 30–40 mg/d for 7–10 d in patients with COPD exacerbation.[14] However, the Thoracic Society of Australia and New Zealand recommend a 5-d course of 30–50 mg oral prednisolone, which is adequate for the treatment of exacerbations of COPD.[15] Similarly, the steroid regimen recommended by the Global Obstructive Lung Disease (GOLD) guideline is 40 mg/d oral prednisolone for 5 d.[1] One systematic review compared different durations of SCS therapy for subjects with COPD exacerbation,[16] but the corresponding daily doses were not assessed. Another systematic review that concentrated on high-dose versus low-dose systemic steroids for treatment of exacerbation of COPD failed to identify any randomized trials comparing different doses of SCS.[17] In addition, Cheng et al[18] performed a meta-analysis to compare the efficacy and safety of different doses of SCS with placebo via subgroup analysis of high-dose and low-dose SCS, but this approach might not clearly explain which dose is better. Therefore, indirect treatment comparison could be used to obtain more rigorous results. We aimed to compare the efficacy and safety of different doses of SCS in subjects with COPD exacerbation using meta-analysis followed by an indirect treatment–comparison technique.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and
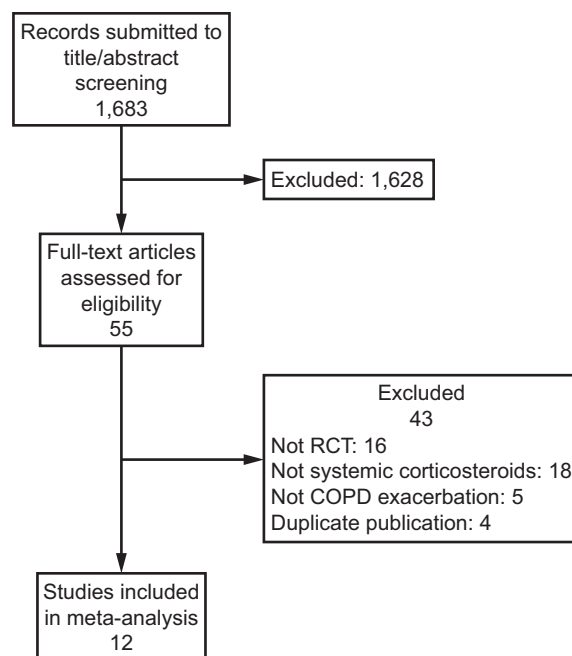

Fig. 1. Flow chart. RCT = randomized controlled trial.

Meta-analyses (PRISMA) statement,[19] and it was registered in the International Database of Prospectively Registered Systematic Reviews (PROSPERO; CRD42019122267). The selection process of the present meta-analysis is illustrated in Figure 1.

Two reviewers performed a comprehensive literature search for RCTs investigating the effects of different doses of SCS in subjects with COPD exacerbation. The relevant terms were searched in PubMed, Embase, Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov to retrieve studies available up to December 4, 2019. The following key words were used in the literature search: corticosteroids (glucocorticoid, hydrocortisone, prednisone, prednisolone, methylprednisone, methylprednisolone, dexamethasone, triamcinolone, beclomethasone, betamethasone, fluticasone), and exacerbations of COPD (acute or chronic). Only articles published in English or Chinese were included. The detailed search strategy is shown in the supplementary materials (available at: http://www.rcjournal.com).

The criteria were selected via the framework of patient problem, intervention, comparison, outcomes, and study. Briefly, studies that met the following criteria were included in the analysis: the included patient problem was diagnosed as exacerbation of COPD according to the GOLD criteria[1]; intervention was SCS with usual treatment (eg, antibiotics and inhaled bronchodilators); comparison was usual treatment (eg, antibiotics and inhaled bronchodilators) versus placebo; outcomes were changes in FEV_1, treatment failure (eg, death from any cause or the need for

intubation and mechanical ventilation, readmission because of COPD, the need for additional treatment), relapse after treatment (eg, treatment for new exacerbation, readmission or hospitalization for COPD), hospital length of stay (LOS), mortality, and adverse effects. The study included RCTs comparing the efficacy and safety of SCS versus placebo in subjects with COPD exacerbation. We excluded studies using the following criteria: subjects with complications including allergic rhinitis, pulmonary infarction, pulmonary encephalopathy, asthma, atopy, pneumoconiosis, and active tuberculosis; studies of inhaled corticosteroids; non-RCTs; and review articles or other types of article.

We assessed the quality of each included study according to the Cochrane Handbook for Systematic Reviews of Interventions.[20] We assessed risk of bias according to the following items: random-sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting. Two reviewers independently assessed the risk of bias and resolved disagreements by discussion.

The following study characteristics were extracted by 2 reviewers from included studies: publication details (eg, title, authors, and year of publication); subjects (eg, sample size, mean age, gender, smoking history, and inclusion criteria); interventions (eg, type of SCS, administration route, dose, and duration); outcomes (eg, changes in FEV_1, treatment failure, relapse after treatment, hospital LOS, mortality, and adverse effects).

The primary outcomes of the current meta-analysis were treatment failure and relapse after treatment. The secondary outcomes were changes in FEV_1, hospital LOS, mortality, and adverse effects. Dosing categories were assigned as follows: low-dose (initial dose $\leq$ 40 mg prednisone equivalent/d [PE/d]), medium-dose (initial dose = 40–100 mg PE/d), and high-dose (initial dose > 100 mg PE/d) groups recommended in established criteria of the literature and guideline.[1,21] The SCS equivalent doses were used according to each drug's relative anti-inflammatory potency.[22]

Data Analysis

Review Manager 5.3 software was used to perform statistical analysis. Statistical heterogeneity was assessed using the chi-square test and I^2 statistical values. Random-effects models were used for significant heterogeneity, represented by I^2 values > 50%; otherwise, a fixed-effects model was utilized. For continuous outcomes (ie, changes in FEV_1 and hospital LOS), mean differences (MDs) with corresponding 95% CIs were used as effective measures. The risk ratio (RR) with corresponding 95% CIs was calculated as an effective measure for dichotomous outcomes (ie, treatment failure, relapse after treatment, mortality, and adverse effects). For outcome indicators with large heterogeneity, sensitivity analysis was used to find the source of

heterogeneity. The subgroup analysis was performed if the duration of SCS was $\leq$ 5 d to verify the efficacy of the short-duration regimen in subjects with COPD exacerbation according to GOLD.[1]

Indirect treatment comparison was performed according to Bucher et al.[23] If the pooled effect estimate for each group was statistically different compared with the placebo, the RR or MD for each indirect comparison was calculated using ITC (Indirect Treatment Comparison, Version 1.0, Ottawa: Canadian Agency for Drugs and Technologies in Health) software. This indirect comparison was made through a common comparator (placebo group). The efficacy or safety between 2 SCS doses was considered significantly different if the 95% CI did not contain a RR = 1 or MD = 0.

Results

Characteristics and Risk of Bias of Included Studies

Of the 1,683 studies we retrieved from the aforementioned databases, we screened 12 RCTs[24-35] with 1,375 subjects that met the inclusion criteria. Two studies[24,35] included outpatients (assigned to low- and medium-dose SCS groups, respectively), and the other studies involved inpatients. Detailed features included in RCTs are presented in Table 1. In addition, risk of bias is shown in Figure 2. Eight studies described random-sequence generation, whereas in 4 studies the indicators were insufficient or unclear. Allocation concealment was adequate in 6 studies; however, the other 6 studies did not describe this aspect sufficiently or allocation concealment was not mentioned. Ten studies reported adequate blinding of subjects and investigators, whereas 2 studies did not state blinding of subjects and investigators. In addition, only 4 of the 12 included studies described blinding of outcome assessment. Ten studies were considered to have a low risk of attrition bias because no outcome data were missing or the data existed but did not have an impact on observed clinical effects; risk of bias was unclear for 1 study because it did not address the question of completeness, and 1 study was considered to have a high risk of bias due to incomplete outcome data, which had an impact on observed clinical effects. Selective outcome reporting did not appear in 10 studies, whereas it remained elusive in the other 2 studies. Finally, we did not identify other sources of bias in 6 studies, and they were unclear in the other 6 studies.

Meta-Analysis Outcomes

Table 2 shows details of the meta-analysis results of all outcomes. Overall, 12 studies mentioned the outcome of treatment failure. The risk of treatment failure was significantly lower in low-dose and high-dose SCS groups compared to placebo (RR 0.61 [95% CI 0.43–0.88], P = .007;

Table 1.   Characteristics of Enrolled Studies

Study	Inclusion Criteria	Age, y	Subjects, N	Male Subjects, n	Smokers, n	Systemic Corticosteroid Regime	Follow-Up, d
Aaron et al[24]	Age ≥ 35 y; smoking history ≥ 15 pack-years; FEV$_1$/FVC < 0.7	69.4 ± 10.8	147	84	65	Prednisolone 40 mg/d (10 d)	30
Abroug et al[25]	Age ≥ 40 y; smoking history ≥ 20 pack-years; FEV$_1$/FVC < 0.7	69 ± 7.2	217	191	ND	Oral prednisolone 1 mg/kg/d (10 d)	ND
Albert et al[26]	Acute respiratory insufficiency; acute and chronic bronchitis, and chronic airflow obstruction	61.5 ± 9.5	44	44	ND	IV Methylprednisolone 0.5 mg/kg every 6 h (3 d)	3
Alía et al[27]	Age ≥ 18 y, with known COPD exacerbation	68.4 ± 10.2	83	68	ND	Methylprednisolone 0.5 mg/kg every 6 h (3 d), then every 12 h (3 d), then daily (4 d)	ND
Bullard et al[28]	Ages ≥ 40 y; FEV$_1$ < 0.6; FEV$_1$/FVC < 0.6	66.0 ± 10.9	113	97	ND	IV Hydrocortisone 100 mg every 4 h (4 d), oral prednisolone 40 mg every 6 h (4 d)	14
Chen et al[29]	FEV$_1$/FVC < 0.7; history of cough and sputum ≥ 2 y	71.7 ± 7.3	130	98	ND	(1) Oral prednisolone 30 mg/d (7 d); (2) prednisolone 30 mg/d (10 d), 15 mg/d (4 d)	30
Davies et al[30]	Age 40–80 y; FEV$_1$ < 0.7; FEV$_1$/FVC < 0.75	67.3 ± 8.4	56	39	29	Prednisolone 30 mg/d (14 d)	42
Emerman et al[31]	Age > 50 y; FEV$_1$ < 0.7 or FEV$_1$/FVC < 0.6	64.0 ± 7.8	96	50	ND	Methylprednisolone 100 mg once	2
Maltais et al[32]	Age ≥ 50 y; smoking history ≥ 20 pack-years; postbronchodilator FEV$_1$ < 0.7 normal predicted value; FEV$_1$/FVC < 0.7	70.4 ± 8.3	128	105	45	Prednisolone 30 mg every 12 h (3 d), then prednisolone 40 mg/d (7 d)	10
Niewoehner et al[33]	Age ≥ 50 y; smoking history ≥ 30 pack-years; FEV$_1$ < 1.5 L	67.7 ± 9.3	271	268	138	(1) Methylprednisolone 125 mg every 6 h (3 d); prednisolone 60 mg/d (4 d), 40 mg/d (4 d), 20 mg/d (32 d), 10 mg/d (7 d), 5 mg/d (7 d); (2) methylprednisolone 125 mg every 6 h (3 d) and prednisolone 60 mg/d (4 d), 40 mg/d (4 d), 20 mg/d (4 d)	180
Sun et al[34]	Age ≥ 35 y; COPD exacerbation; the diagnostic criteria of CIRCI	72.3 ± 16.6	63	50	ND	IV hydrocortisone 50 mg every 8 h (7 d)	28
Thomson et al[35]	FEV$_1$ ≤ 0.6, FEV$_1$/FVC < 0.65	67.8 ± 8.6	27	26	8	Oral prednisone 60 mg/d (3 d), 40 mg/d (3 d), 20 mg/d (3 d)	14

ND = no data, not reported
IV = intravenous
CIRCI = critical illness-related corticosteroid insufficiency

RR 0.64 [95% CI 0.48–0.85], P = .002) (Fig. 3). However, the medium-dose SCS group and the high-dose SCS group with duration ≤ 5 d did not show significant difference of treatment failure versus placebo (RR 0.56 [95% CI 0.18–1.71], P = .31; RR 1.47 [95% CI 0.56–3.85], P = .43) (Fig. 3). When the outpatient studies were removed, the pooled effect estimates decreased slightly in the low-dose SCS groups, and the risk of treatment failure was then not significantly lower than placebo (RR 0.59 [95% CI 0.34–1.02] P = .057; see the supplementary materials at http://www.rcjournal.com). The pooled effect estimates slightly increased in the medium-dose SCS group but was still not
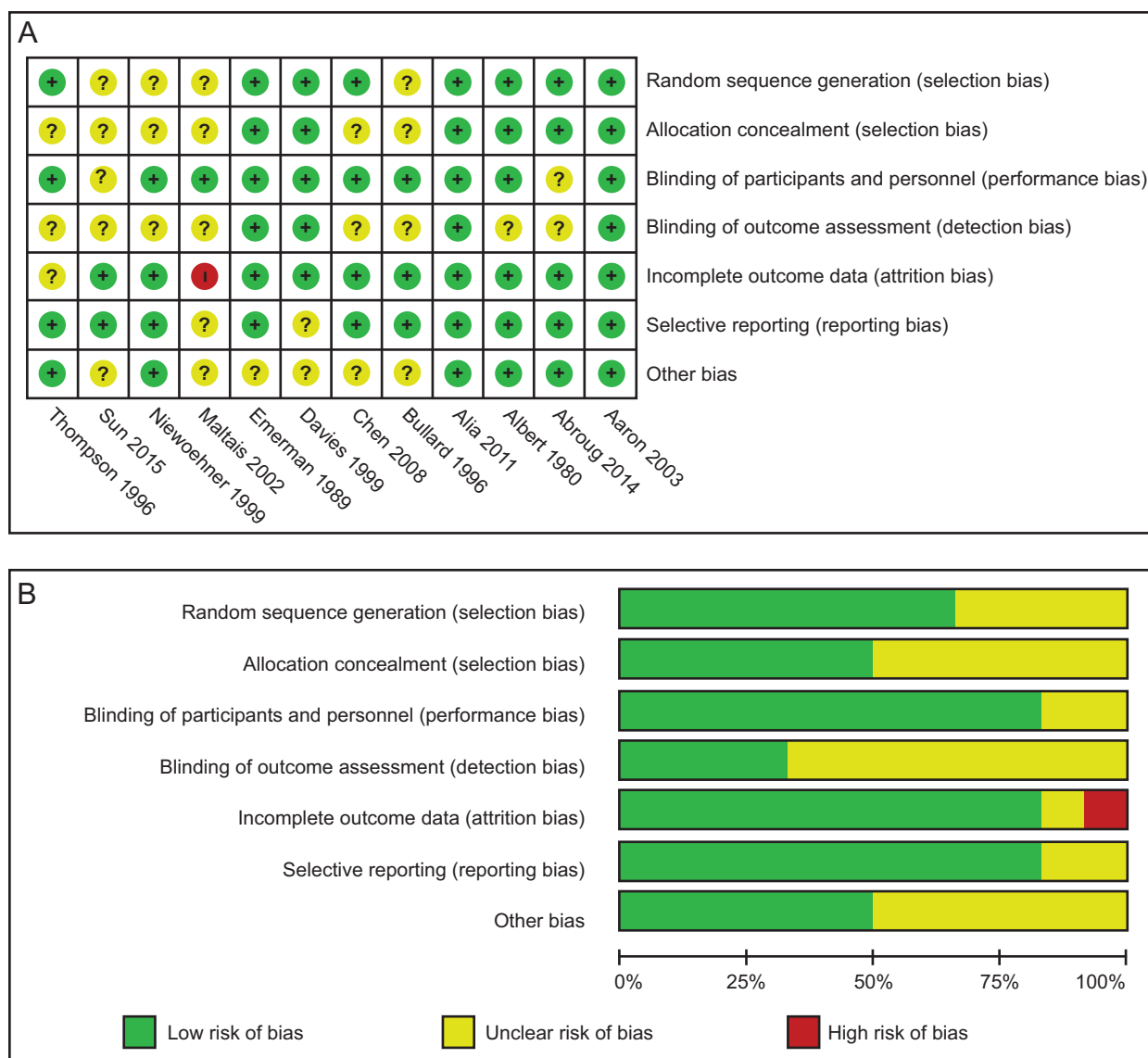
Fig. 2. A: Risk of bias summary for included studies, showing each risk of bias item for every included study. B: Risk of bias graph presenting each risk of bias item as percentages across all included studies.

significantly different than placebo (RR 0.76 [95% CI 0.29–1.98], $P = .58$; see the supplementary materials at http://www.rcjournal.com).

There were 7 studies that reported the outcome of relapse after treatment, and the forest plot indicates that low-, medium-, high-dose SCS groups were all not significantly different versus placebo (RR 0.68 [95% CI 0.45–1.04], $P = .08$; RR 0.4 [95% CI 0.11–1.44], $P = .36$; and RR 0.65 [95% CI 0.38–1.12], $P = .12$, respectively) (Fig. 4). Nevertheless, subgroup analysis indicated that the incidence of relapse after treatment was lower in high-dose SCS group for > 5 d compared to placebo (RR 0.48 [95% CI 0.26–0.91], $P = .02$) (Fig. 4). When the outpatient study was removed, the direction of the pooled effect estimates

did not change in the low-dose SCS group versus placebo (RR 0.86 [95% CI 0.33–2.28], $P = .77$; see the supplementary materials at http://www.rcjournal.com).

The effects of low-, medium-, high-dose SCS groups versus placebo on the changes in FEV_1 are shown in Figure 5 and Table 2. The pooled effect estimates showed that the changes in FEV_1 were not noted between high-dose SCS for ≤ 5 d and placebo (MD 0.1 [95% CI –0.02 to 0.21], $P = .09$); but there was significant difference between high-dose SCS for > 5 d (MD 0.09 [95% CI 0.03–0.15], $P = .004$), medium-dose SCS (MD 0.23 [95% CI 0.02–0.44, $P = .036$), and low-dose SCS (MD 0.09 [95% CI 0.06–0.12, $P < .001$) and placebo (Fig. 5). The pooled MD of low-dose SCS group remained unchanged when the

Table 2. Pooled Effect Estimates of Studied Outcomes

Outcomes	SCS Groups vs Placebo			SCS Subgroups vs Placebo	
	Low Dose	Medium Dose	High Dose	High Dose With Short-Term SCS	High Dose With Long-Term SCS
Treatment failure*	0.61 (0.43–0.88)	0.56 (0.18–1.71)	0.64 (0.48–0.85)	1.47 (0.56–3.85)	0.57 (0.42–0.78)
	$I^2 = 0\%$ $P = .007$	$I^2 = 69\%$ $P = .31$	$I^2 = 31\%$ $P = .02$	$I^2 = 0\%$ $P = .43$	$I^2 = 15\%$ $P < .001$
Relapse after treatment*	0.68 (0.45–1.04)	0.40 (0.11–1.44)	0.65 (0.38–1.12)	1.69 (0.55–5.24)	0.48 (0.26–0.91)
	$I^2 = 0\%$ $P = .08$	$I^2 = $ NA	$I^2 = 42\%$ $P = .12$	$I^2 = $ NA	$I^2 = 0\%$ $P = .02$
Changes in FEV_1#	0.09 (0.06–0.12)	0.23 (0.02–0.44)	0.09 (0.04–0.15)	0.10 (–0.02 to 0.21)	0.09 (0.03–0.15)
	$I^2 = 0\%$ $P < .001$	$I^2 = 74\%$ $P = .036$	$I^2 = 14\%$ $P < .001$	$I^2 = 43\%$ $P = .09$	$I^2 = 41\%$ $P = .004$
Length of hospital stay#	–1.21 (–2.24 to –0.19)	1.00 (–0.58 to 2.58)	–2.00 (–5.68 to 1.68)	NA	NA
	$I^2 = 0\%$ $P = .02$	$I^2 = $ NA	$I^2 = $ NA		
Mortality*	1.97 (0.18–21.29)	1.15 (0.61–2.14)	0.96 (0.49–1.88)	3.00 (0.13–69.87)	0.89 (0.44–1.79)
	$I^2 = $ NA	$I^2 = 0\%$ $P = .67$	$I^2 = 0\%$ $P = .9$	$I^2 = $ NA	$I^2 = 0\%$ $P = .75$
Adverse effect of hyperglycemia*	3.26 (0.81–13.23)	3.29 (0.33–32.84)	2.52 (1.13–5.62)	NA	NA
	$I^2 = 57\%$ $P = .1$	$I^2 = 66\%$ $P = .31$	$I^2 = 47\%$ $P = .02$		
Risk of gastrointestinal bleeding*	1.26 (0.33–4.80)	NA	0.60 (0.22–1.67)	1.00 (0.07–15.00)	0.55 (0.18–1.68)
	$I^2 = 0\%$ $P = .74$		$I^2 = 0\%$ $P = .33$	$I^2 = $ NA	$I^2 = 0\%$ $P = .29$

Short-term means duration of SCS $\leq$ 5 d and long-term means duration of SCS > 5 d.
* Data presented as risk ratio (95% CI).
# Data presented as mean difference (95% CI), expressed in L for changes in FEV_1.
SCS = systemic corticosteroids
NA = not applicable

outpatient study was removed (MD 0.09 [95% CI 0.06–0.12], $P < .001$), and only 1 study was left in the medium-dose SCS group (MD 0.14 [95% CI 0.13–0.16], $P < .001$; see the supplementary materials at http://www.rcjournal.com).

The low-dose SCS group exhibited decreased hospital LOS versus placebo (MD –1.21 [95% CI –2.24 to –0.19], $P = .02$) using a fixed effects model ($I^2 = 47\%$). For the medium- and high-dose SCS groups, there was only 1 study in each group, and the SCS did not show significant differences compared to placebo (Table 2). Meanwhile, SCS groups did not show significant difference in mortality compared to placebo (Table 2; see the supplementary materials at http://www.rcjournal.com).

The incidence of hyperglycemia in low-dose and medium-dose SCS groups did not show significant difference versus placebo (Table 2). However, the high-dose SCS group had a significantly increased incidence of hyperglycemia versus placebo (RR 2.52 [95% CI 1.13–5.62], $P = .02$) using a fixed-effects model ($I^2 = 47\%$). For increasing the risk of gastrointestinal bleeding, each SCS group was not statistically different compared to placebo (Table 2; see the supplementary materials at http://www.rcjournal.com).

Table 3 shows details of the results of indirect treatment comparison. For each outcome, the indirect treatment comparison was performed when there were at least 2 SCS groups or subgroups in which the pooled effect estimates were statistically different compared to the placebo. Thus we indirectly compared treatment failure and changes in

FEV_1 between SCS groups (or subgroups) using placebo as the common comparator. For treatment failure, there was no significant difference between the low-dose group and the high-dose group (RR 0.95 [95% CI 0.62–1.47], $P = .92$), nor was there a significant difference between the low-dose group and the high-dose for > 5 d subgroup (RR 1.07 [95% CI 0.67–1.72], $P = .89$). For changes in FEV_1, the low-, medium-, high-dose groups and high-dose for > 5 d subgroup were indirectly compared, and there was no significant difference in any comparison with the P values ranging from .47 to .99 (Table 3).

Discussion

Our meta-analysis investigated the safety and efficacy of different doses of SCS in subjects with COPD exacerbation. The results of this meta-analysis indicate that low-dose SCS (ie, initial dose $\leq$ 40 mg PE/d) was a sufficient and safer treatment for subjects with COPD exacerbation, and it was noninferior to higher-dose SCS (ie, initial dose > 40 mg PE/d) for improving FEV_1, reducing the risk of treatment failure, and shortening hospital LOS.

Over the past several decades, SCS drugs have been approved for the clinical treatment of COPD exacerbation. However, the most appropriate dose for patients with exacerbation of COPD remains elusive. Because there are no direct RCT comparisons between various doses of SCS, we used indirect comparison techniques to explore the efficacy and safety of different doses of SCS to treat subjects with a
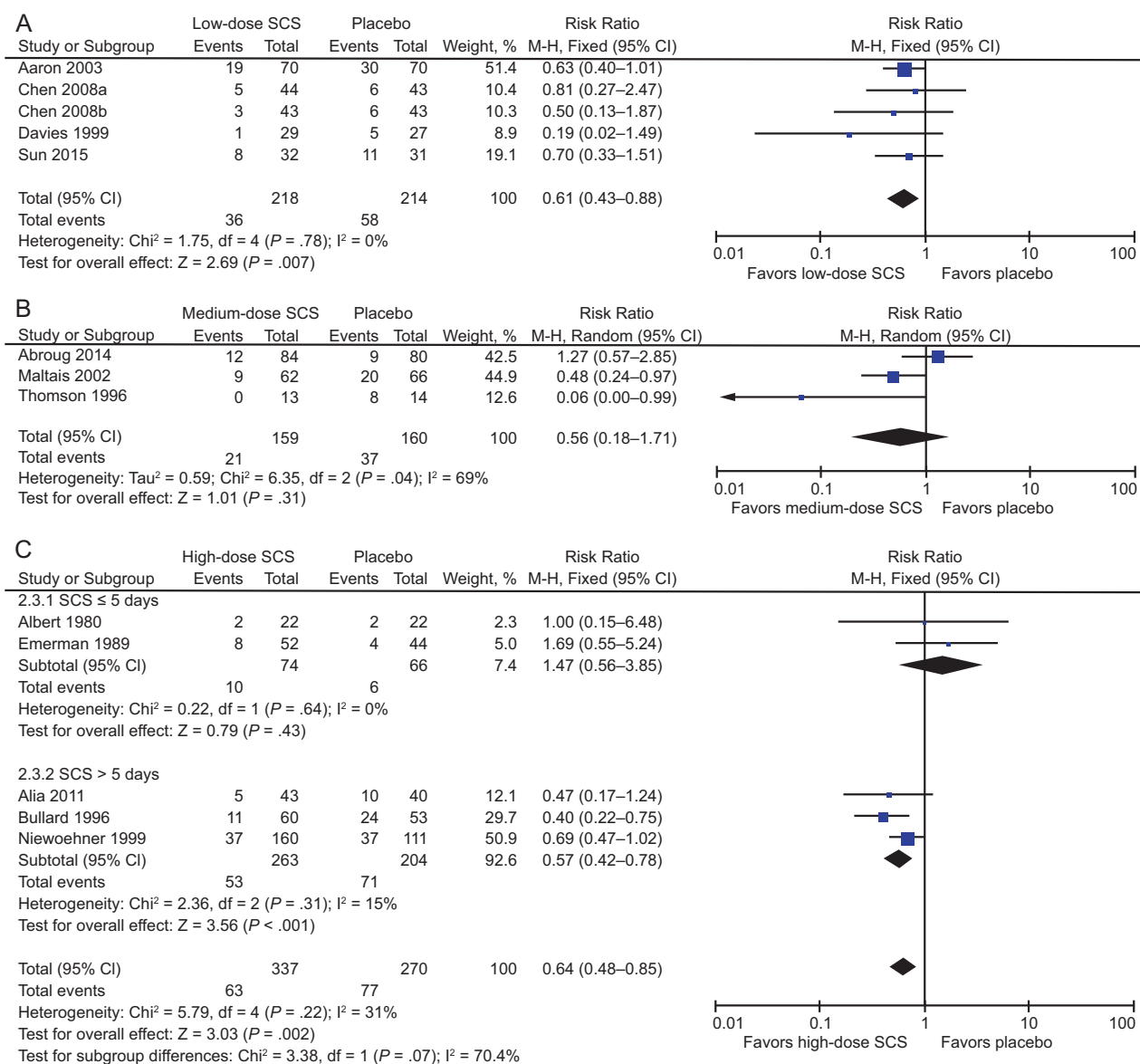
Fig. 3. Forest plots for the effect of different doses of SCS on treatment failure. A: Low-dose SCS versus placebo; (B) medium-dose SCS versus placebo; (C) high-dose SCS versus placebo. SCS = systemic corticosteroids.

COPD exacerbation. In this meta-analysis, we investigated the safety and efficacy of different doses of SCS in subjects with exacerbation of COPD. The enrolled studies were assigned to low-dose, medium-dose, and high-dose SCS groups. The grouping of SCS dose regimens that we used were different from those used in the study by Cheng et al.[18] They defined low-dose SCS as an initial dose < 80 mg PE/d, but this may not be precise due to the wide range of dosages. For example, combining outcomes from the study performed by Maltais et al,[32] in which 60 mg prednisolone/d was used, with outcomes from other RCTs in which a dose regimen < 40 mg prednisolone/d was used might impact the pooled effect estimates. Therefore, we assigned the studies

in which doses were < 40 mg prednisolone/d to the low-dose SCS group according to GOLD guidelines, which recommend 40 mg prednisolone/d for COPD exacerbation.[1] We defined the high-dose SCS as an initial dose > 100 mg PE/d based on a previous review.[21] Compared to placebo, high-dose SCS with a duration > 5 d was associated with lower risk of treatment failure or relapse and improved FEV_1; however, this treatment significantly increased the incidence of hyperglycemia, which was demonstrated in a previous cohort study.[36] Medium-dose SCS improved FEV_1 versus placebo, but it did not show superiority in other outcomes. Interestingly, only low-dose SCS significantly shortened the hospital LOS versus placebo, which was consistent
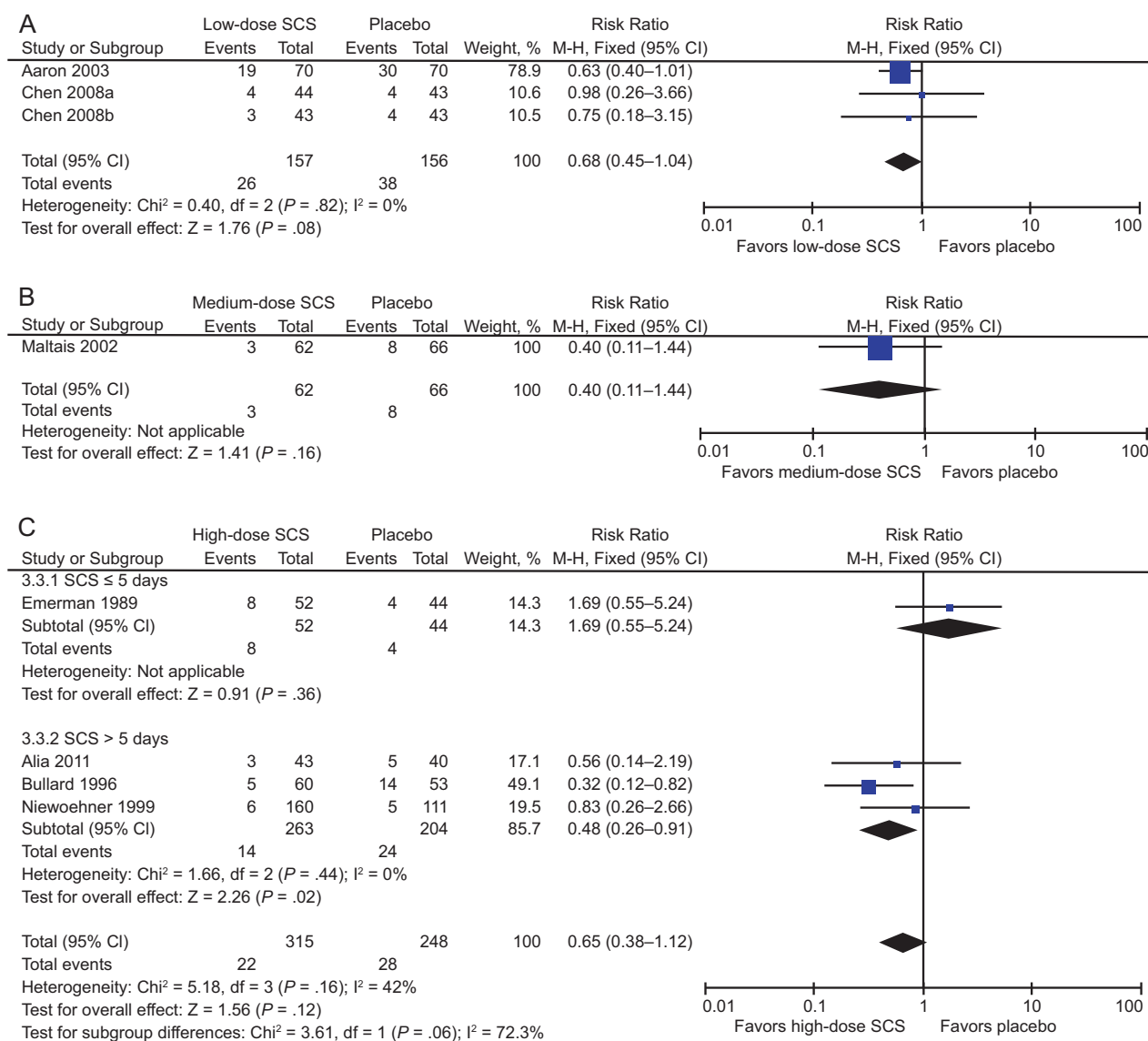
Fig. 4. Forest plots for the effect of different doses of SCS on relapse after treatment. A: Low-dose SCS versus placebo; (B) medium-dose SCS versus placebo; (C) high-dose SCS versus placebo. SCS = systemic corticosteroids.

with previous observational studies.[37,38] Generally, COPD severity in outpatients differed from that of inpatients. When outpatient studies were removed, the pooled effect estimates of changes in FEV_1 and relapse remained largely unchanged; the risk of treatment failure of the low-dose SCS group was no longer significantly different from placebo, but showed a trend ($P = .057$) that should be interpreted with caution.

The results of our indirect comparisons indicate that there was no significant difference between various SCS doses and treatment failure or changes in FEV_1. Meanwhile, the SCS subgroup with SCS > 5 d did not show superiority compared to other SCS groups in reducing the risk of treatment failure and improving FEV_1. Leuppi et al[39] performed an RCT and reported that, in the long-term SCS group, mean

cumulative prednisone dose was statistically higher, but no significant difference was noted in time to death or in the combined end point of exacerbation and recovery of lung function compared to short-term SCS. The results of this RCT are consistent with ours. The current meta-analysis results were also accordant with previous observational studies.[36-38] High-dose and long-term SCS should be used with caution due to the risk of hyperglycemia, and these regimens did not show superiority in improving lung function or prognosis compared with lower dose SCS.

A previous Cochrane review[16] reported that shorter courses of SCS (ie, ~ 5 d) did not lead to worse outcomes compared with longer courses (ie, 10–14 d). The RECUT trial, which is currently recruiting subjects, is designed to
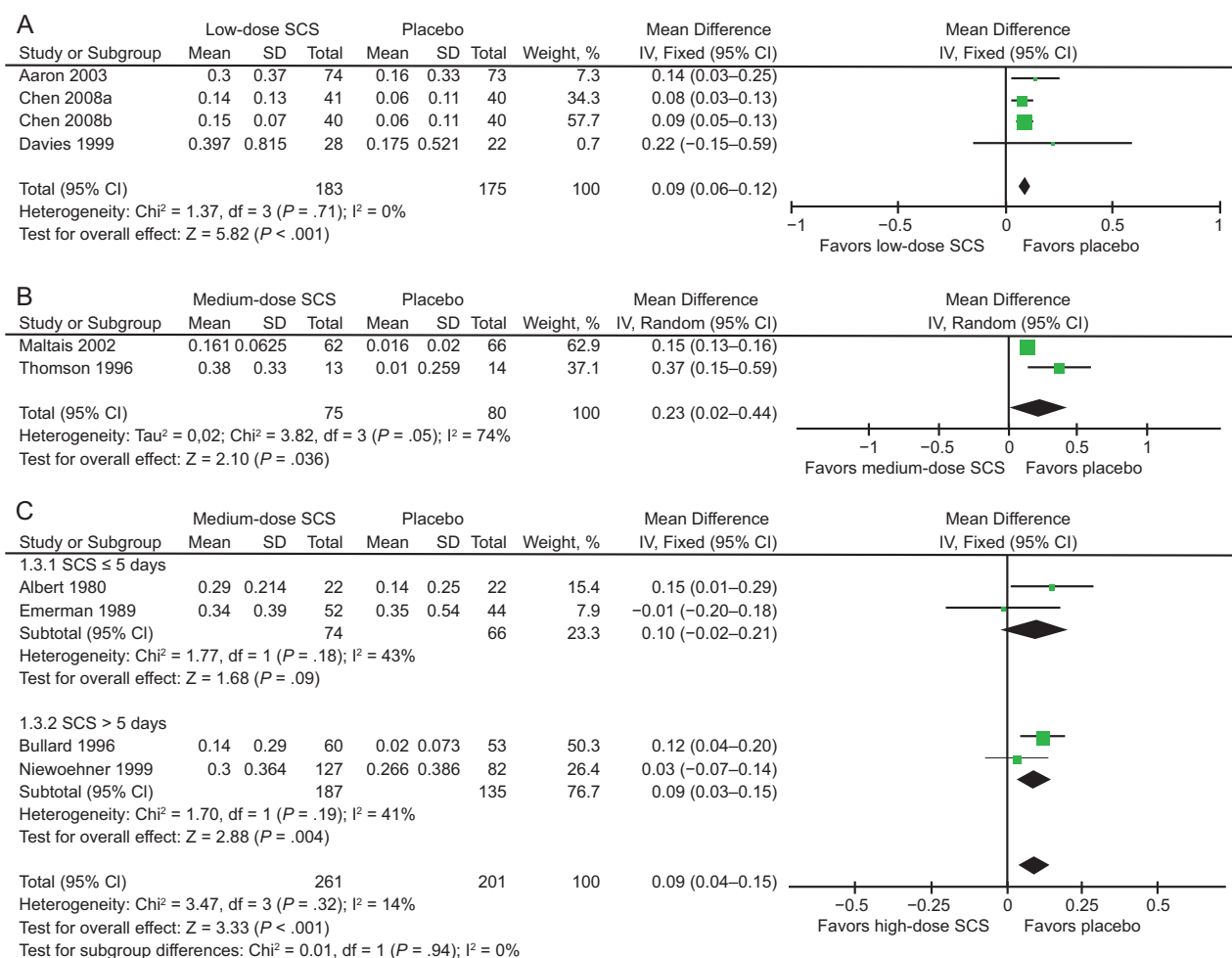
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Fig. 5. Forest plots for the effect of different doses of SCS on changes in FEV_1. A: Low-dose SCS versus placebo; (B) medium-dose SCS versus placebo; (C) high-dose SCS versus placebo. SCS = systemic corticosteroids.

Table 3. Indirect Comparisons Between Low, Medium, and High Doses of SCS in COPD

Outcomes	Comparisons	Effect Size (95% CI)	P
Treatment failure	Low dose/high dose with long-term SCS	1.07 (0.67–1.72)	.89
	Low dose/high dose	0.95 (0.62–1.47)	.92
Changes in FEV_1	Low dose/medium dose	−0.14 (−0.35 to 0.07)	.49
	Low dose/high dose	−0.001 (−0.06 to 0.06)	.99
	Low dose/high dose with long-term SCS	0.002 (−0.06 to 0.07)	.98
	Medium dose/high dose	0.14 (−0.08 to 0.36)	.47
	Medium dose/high dose with long-term SCS	0.14 (−0.07 to 0.36)	.99

Effect sizes are as follows: risk ratio for treatment failure; mean difference for changes in FEV_1 (expressed in L).
SCS = systemic corticosteroids
Long-term = SCS duration > 5 d

explore whether a 3-d treatment with orally administered SCS is noninferior to 5-d treatment in subjects with COPD exacerbation, and whether total corticosteroid exposure can be reduced by shorter therapy duration.[40] In the current investigation, there is a trend to reduce the duration of SCS courses in subjects with COPD exacerbation. In the

meantime, to reduce exposure of patients with COPD exacerbation to SCS, the daily dose should also be considered. A current RCT (NCT01742338) has been designed to perform a direct, head-to-head comparison of different doses of corticosteroids to determine whether a high-dose corticosteroid regimen in subjects with COPD exacerbations is associated with better clinical outcomes and at acceptable risk of adverse effects compared to a low-dose corticosteroid regimen, but that study is still recruiting. In this meta-analysis, we noted that an initial SCS dose $\leq$ 40 mg PE/d was noninferior for reducing the risk of treatment failure and for improving FEV_1 compared to a higher dose of SCS, and it appears sufficient to treat patients with COPD exacerbation. However, an indirect treatment comparison is not as precise as direct research. Therefore, RCTs evaluating various SCS doses in COPD exacerbation are needed to define the most appropriate dose for patients with COPD exacerbation and to promote the rational clinical use of SCS.

This meta-analysis has several limitations. First, the common comparator (in this case, placebo) should be similar across the included RCTs; however, the characteristics (eg, the follow-up protocols) of the included studies may not be totally consistent. Second, only outcomes (ie, changes in FEV_1 and treatment failure) were indirectly compared. Due to the lack of pooled statistically significant data in each group, we could not detect differences in other outcomes (eg, relapse after treatment, hospital LOS, mortality, and adverse effects) between various doses of SCS to treat COPD exacerbation. Third, there was significant heterogeneity in some outcomes, while the effect estimates remained stable after removing 1 study at a time. Fourth, some studies in this review had relatively small sample sizes, although no significant risk of bias was noted. The study with small sample size likely lacks sufficient statistical power to detect true positive associations; however, pooling these high-quality studies could achieve reliable results.

Conclusions

This meta-analysis indicates that low-dose SCS (ie, initial dose $\leq$ 40 mg PE/d) is sufficient and safer for treatment of subjects with COPD exacerbation, and that it was noninferior to higher-dose SCS (ie, initial dose > 40 mg PE/d) in improving FEV_1, reducing the risk of treatment failure, and shortening hospital LOS. However, further RCTs that directly compare the efficacy and safety of different SCS doses in COPD exacerbation are required.

REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med 2017;195(5):557-582.

2. Pleasants RA, Heidari K, Wheaton AG, Ohar JA, Strange C, Croft JB, et al. Targeting persons with or at high risk for chronic obstructive pulmonary disease by state-based surveillance. COPD 2015;12(6):680-689.

3. Ding B, Small M, Bergstrom G, Holmgren U. COPD symptom burden: impact on health care resource utilization, and work and activity impairment. Int J Chron Obstruct Pulmon Dis 2017;12:677-689.

4. Ntritsos G, Franek J, Belbasis L, Christou MA, Markozannes G, Altman P, et al. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2018;13:1507-1514.

5. Chaguza C, Cornick JE, Everett DB. Mechanisms and impact of genetic recombination in the evolution of Streptococcus pneumoniae. Comput Struct Biotechnol J 2015;13:241-247.

6. Shin B, Kim SH, Yong SJ, Lee WY, Park S, Lee SJ, et al. Early readmission and mortality in acute exacerbation of chronic obstructive pulmonary disease with community-acquired pneumonia. Chron Respir Dis 2019;16:147997231880948.

7. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57(10):847-852.

8. Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;8:CD011682.

9. Cowan J, Gaudet L, Mulpuru S, Corrales-Medina V, Hawken S, Cameron C, et al. A retrospective longitudinal within-subject risk interval analysis of immunoglobulin treatment for recurrent acute exacerbation of chronic obstructive pulmonary disease. PLoS One 2015;10(11):e0142205.

10. Zhang HL, Tan M, Qiu AM, Tao Z, Wang CH. Antibiotics for treatment of acute exacerbation of chronic obstructive pulmonary disease: a network meta-analysis. BMC Pulm Med 2017;17(1):196.

11. Woods JA, Wheeler JS, Finch CK, Pinner NA. Corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2014;9:421-430.

12. Mehić B. The role of inhalatory corticosteroids and long acting beta(2) agonists in the treatment of patients admitted to hospital due to acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Bosn J Basic Med Sci 2007;7(4):352-357.

13. Tichter AM, Ostrovskiy G. Emergency department antibiotic use for exacerbations of COPD. Open Access Emerg Med 2018;10:193-200.

14. Japanese Respiratory Society. Guidelines for the Diagnosis and Treatment of COPD, 3rd edition. 2010. Available at: https://www.jrs.or.jp/uploads/uploads/files/photos/765.pdf. Accessed 25 May 2020.

15. Thoracic Society of Australia and New Zealand. The COPD-X-plan. Available at: https://copdx.org.au/wp-content/uploads/2020/04/copdx-v2-61-feb-2020-final.pdf. Accessed 25 May 2020.

16. Walters JA, Tan DJ, White CJ, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2018;3:CD006897.

17. Bonilla Arcos D, Krishnan JA, Vandivier RW, Sevransky JE, Checkley W, Kiser TH, et al. High-dose versus low-dose systemic steroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease: systematic review. Chronic Obstr Pulm Dis 2016;3(2):580-588.

18. Cheng T, Gong Y, Guo Y, Cheng Q, Zhou M, Shi G, et al. Systemic corticosteroid for COPD exacerbations, whether the higher dose is better? A meta-analysis of randomized controlled trials. Clin Respir J 2013;7(4):305-318.

19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

20. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

21. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. Cochrane Database Syst Rev 2000;2:CD001740.

22. Brunton LL, Hilal-Dandan RH, Knollman BC. Goodman & Gilman's: The Pharmaceutical Basis of Therapeutics, 13th edition. New York: McGraw-Hill; 2018:2501.

23. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50(6):683-691.

24. Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med 2003;348(26):2618-2625.

25. Abroug F, Ouanes-Besbes L, Fkih-Hassen M, Ouanes I, Ayed S, Dachraoui F, et al. Prednisone in COPD exacerbation requiring ventilatory support: an open-label randomised evaluation. Eur Respir J 2014;43(3):717-724.

26. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methyl-prednisolone in patients with chronic bronchitis and acute respiratory insufficiency. Ann Intern Med 1980;92(6):753-758.

27. Alía I, de la Cal MA, Esteban A, Abella A, Ferrer R, Molina FJ, et al. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. Arch Intern Med 2011;171(21):1939-1946.

28. Bullard MJ, Liaw SJ, Tsai YH, Min HP. Early corticosteroid use in acute exacerbations of chronic airflow obstruction. Am J Emerg Med 1996;14(2):139-143.

29. Chen G, Xie CM, Luo YF. The effects and therapeutic duration of oral corticosteroids in patients with acute exacerbation of chronic obstructive pulmonary diseases. Zhonghua Jie He He Hu Xi Za Zhi 2008;31(8):577-580.

30. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999;354(9177):456-460.

31. Emerman CL, Connors AF, Lukens TW, May ME, Effron D. A randomized controlled trial of methylprednisolone in the emergency treatment of acute exacerbations of COPD. Chest 1989;95(3):563-567.

32. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med 2002;165(5):698-703.

33. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med 1999;340(25):1941-1947.

34. Sun WP, Yuan GX, Hu YJ, Liao LZ, Fu L. Effect of low-dose glucocorticoid on corticosteroid insufficient patients with acute exacerbation of chronic obstructive pulmonary disease. World J Emerg Med 2015;6(1):34-39.

35. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 1996;154(2 Pt 1):407-412.

36. Hemenway AN, Terry AM. Evaluation of corticosteroid dose in acute exacerbation of chronic obstructive pulmonary disease. Hosp Pharm 2017;52(8):546-550.

37. Kiser TH, Allen RR, Valuck RJ, Moss M, Vandivier RW. Outcomes associated with corticosteroid dosage in critically ill patients with acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;189(9):1052-1064.

38. Petite SE, Murphy JA. Systemic corticosteroid and antibiotic use in hospitalized patients with chronic obstructive pulmonary disease exacerbation. Ann Pharmacother 2019;53(2):144-150.

39. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA 2013;309(21):2223-2231.

40. Urwyler P, Boesing M, Abig K, Cattaneo M, Dieterle T, Zeller A, et al. Reduction of corticosteroid use in outpatient treatment of exacerbated COPD: study protocol for a randomized, double-blind, non-inferiority study, (The RECUT-trial). Trials 2019;20(1):727.