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Efficacy of corticosteroids as adjunct therapy in the treatment of community-acquired pneumonia: a systematic review and meta-analysis

Abstract

The objective of this study was to systematically evaluate the clinical efficacy of complementary use of corticosteroids in the treatment of community-acquired pneumonia (CAP). We searched all relevant documents in 5 scientific databases from inception to June 2022 to collect Clinical Trials: Randomized Controlled Trials (RCTs) and Controlled Trials (CT's) reporting on the adjunct use of corticosteroids when treating CAP. The primary outcome was mortality, and secondary outcomes included the time to clinical stability, therapeutic efficacy, duration of antibiotic treatment and length of hospital/ICU stay. Therapeutic efficacy was defined as the rate of achieving clinical recovery with no fever, improvement, or disappearance of cough, and clinical stability was the improvement in laboratory values. Two researchers independently screened literature according to the inclusion and exclusion criteria, extracted data and evaluated the quality of literature. Statistical analysis and Meta-analysis of intervention measures and indicators were performed using IBM SPSS and RevMan 5.4 software. Nine RCTs comprising of 2673 participants with CAP were identified and included in this study -1335 patients in the corticosteroid group and 1338 patients in the control group. The mean cumulative corticosteroid dose and treatment duration were 298.00±287.140mg and 5.22±1.787 days respectively. Corticosteroid treatment was not associated with a significant reduction in mortality (RR; 95% CI,0.96[0.67-1.38], P=0.83). Due to a low number of included patients in our study, more studies with larger sample sizes and high-quality randomized, double-blind controlled trials are needed to confirm this result.

Keywords: community-acquired pneumonia, corticosteroids, mortality

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1. Introduction

Pneumonia is an infectious condition where the air sacs in one or both lungs are inflamed. The air sacs may fill with fluid or pus, causing cough with phlegm or pus, leading to difficulties in breathing,fever and chills. In children under 5 years of age, who have cough and/or difficult breathing, with or without fever, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall in-drawing where their chest moves in or retracts during inhalation[1].Community-acquired pneumonia (CAP) is predominantly a weakened immune system disease. It manifests mostly in infants and young children, people older than 65 years,and people with underlying health problems [2]. A variety of organisms such as bacteria, viruses, fungi, can cause pneumonia and simultaneously increase the risk of hospitalization[3, 4].Pneumonia exists as a heterogenous disease, and two subclasses(viral and bacterial) pneumonia have been determined. The presenting features of viral and bacterial pneumonia are similar; however, the symptoms of viral pneumonia such as wheezing may be more numerous when compared to bacterial pneumonia [5].The seriousness of this disease can range from mild to life threating[6]. Severely ill patients require hospitalization; severely ill infants may be unable to feed or drink and may also experience unconsciousness, hypothermia and convulsions[7] Several risk factors such as infancy, premature birth, incomplete immunization, maternal smoking or household tobacco smoke exposure, indoor air pollution, low birthweight, malnutrion, lack of exclusive breastfeeding and overcrowding have been indicated to increase the chances of CAP onset[8, 9]. Pneumonia can spread in multiple ways. The viruses and bacteria that are found in the nose or throat, can infect the lungs if they are inhaled. They may also spread via air-borne droplets from a cough or sneeze[10],In addition, pneumonia may spread through blood during and shortly after birth[11]. Pneumonia is treated with antibiotics, amoxicillin being the first line of treatment[12]. The most effective preventive measure in this disease is immunization against Hemophilus Influenza type b (Hib), pneumococcus, measles, and whooping cough(pertussis)[13]. Adequate nutrition improves the child's natural defenses, starting with exclusive breastfeeding for the first six months of life[14]. Encouraging good hygiene and providing affordable clean indoor stoves (in crowded homes) helps to reduce pneumonia infection [15]. Children infected with HIV are given cotrimoxazole daily to decrease the risk of contracting pneumonia[16].

Medical practitioners may perform multiple diagnosis tests if pneumonia is suspected. Clinically, CAP presents with tachypnoea, hypoxia, cough, fatigue, dyspnea, pleuritic chest pain and increased rate of breathing[17].Depending on the pathogen, a patient's cough may be persistent and dry, or it may produce sputum[18].The etiological diagnosis of CAP is mostly attributed to viral infections, mostly by respiratory syncytial virus which is more common in young children[19]. In older children, the most identified pathogen is streptococcus pneumoniae, followed by mycoplasma and chlamydia[20]. Modalities available for etiological diagnosis include molecular diagnostics, microscopy, culture, and antigen detection[21]. Both bacterial and viral pneumonia exhibit a wide distribution of acute phase reactants (blood count, C reactive protein, erythrocyte sedimentation rate)[19].Upper respiratory tract secretions are useful in virological diagnosis. Pulmonary TB should be considered in a child presenting with severe pneumonia or pneumonia with a known TB contact[22].The radiological signs of pneumonia overlap with those of collapse. Chest radiography does not distinguish between viral and

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bacterial infection and is unable to detect early changes in pneumonia[9].However, chest radiography improves the diagnosis of pediatric CAP to a certain degree and may prevent overtreatment with antibiotics[23] .

There has been an increase in reported cases of pneumonia over the years probably due to the rapidly increased cases among children, particularly in sub-Saharan Africa and in East Asian countries, such as Korea, Japan, and China[21].PStatistics have shown pneumonia as one of the leading causes of death worldwide- CAPbeing the most common type of pneumonia(pulmonary parenchymal infection) , as it is acquiredoutside of hospitals and other healthcare facilities[2, 24, 25]..There are available antibiotic therapies for treatment and management of CAP, however these can lead to antibiotic resistance and also carry a risk of long-term morbidity and mortality[26, 27]. The use complementary therapeutic interventions, such as systematic corticosteroid administration, could improve the outcome of patients with CAP[28-30]. In patients with CAP, there is an increase in pulmonary and circulating inflammatory cytokine concentrations, which serve as effective mechanism for the elimination of invading pathogens[31]. This excessive local inflammatory response fills the pulmonary compartment, resulting in a spill of cytokines into the systemic circulation, generating the systemic inflammatory response that is associated with severe CAP[32]. The excess release of inflammatory cytokines can be harmful and cause pulmonary dysfunction[31, 33]. On the other hand, a reduced inflammatory reaction in immunosuppressed patients or the elderly can be dangerous and lead to worse outcomes. Corticosteroids have anti-inflammatory, vasoconstrictive and immune-suppressive properties[34]. They work primarily by modulating transcriptional, post-transcriptional and post-translational mechanisms within cellular nuclei to decrease the production of inflammatory mediators[35]. These properties may be favorable in patients with CAP. Positive effects of corticosteroids in CAP were reported in patients with pneumococcal pneumonia from the 1950's[36],since then, the adjunct use of corticosteroids in the treatment of CAP has been discussed. Several randomized controlled trials (RCTs) have investigated the efficacy and safety of corticosteroids for CAP. Furthermore, some systematic reviews of such clinical questions have been conducted previously[37-40]. However, since most of their study search occurred over 5 years ago, the results of recent studies such asWittermans et al[41] were not included in these reviews. Here we performed a novel systematic review and meta-analysis of RCTs to assess the efficacy of corticosteroids for CAP.

2. Methods

The present systematic review and meta-analysis was performed in accordance with the Cochrane handbook for Systematic reviews and interventions. This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis(PRISMA) statement for

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healthcare interventions[42].The methodology was based on recommendations from the Cochrane Collaboration; the results were evaluated according to Grading of Recommendations Assessment, Development and Evaluation(GRADE) guidelines[43].

2.1 Search strategy

Our search strategy was developed based on systematic review best practices. To identify relevant studies, we performed an extensive search across 5 electronic full-text databases: Medline/PubMed, Embase, the Cochrane Library, Scopus, and Web of Science, with no language restrictions. **Table 1** gives information about the databases. Databases were searched using keywords for "CAP" AND "corticosteroid"as shown in **Table 2.**Database specific Boolean search strategies were developed and follow the general format: "corticosteroid" terms AND/ OR "CAP" terms. We searched articles published from January 1967 to June 2022 using a protocol designed for this study.

2.2 Study selection, quality assessment, and data extraction

Studies were screened by two independent reviewers based on the title and abstract, followed by full-text screening. The literature selection process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement[44]. The quality of the selected studies was assessed using the Cochrane Risk of Bias Tools for RCTs. Data extracted included the following information: first author, year of publication, population in each group, antibiotic treatment (macrolides/comparator) and outcomes (mortality, durations of fever and hospitalization and therapeutic efficacy). Therapeutic(clinical) efficacy was defined as the rate of achieving clinical recovery with no fever, improvement, or disappearance of cough, and improved or normal laboratory values.. Any disagreements were resolved through discussion. When the results of the selected studies were unclear or missing, we contacted with the corresponding study investigators to obtain or confirm data.

2.3 Eligibility criteria

Articles that met the following inclusion criteria were included: (1) the study topic was CAP, defined as a disease showing no clinical or radiological improvement 48–72 h after macrolide administration; (2) the subjects are patients diagnosed with CAP; (3) the study was designed as a randomized controlled trial (RCT)or clinical trial (CT) ; (4) the intervention agent was a corticosteroid known to be active against CAP such as methylprednisolone; (5) the control was a placebo; and (6) reported mortality rate, either in-hospital,30-day mortality or mortality without an explanation. Animal and preclinical studies, as well as articles other than original research articles (e.g., reviews, editorials, letters, conference abstracts, and comments) and observational studies were excluded. Studies with duplicate subjects (i.e., different studies using the same outcome indicators in the same number of patients) were also excluded. Our search strategy implemented no language restrictions, and non-English articles were translated to be included for evaluation.

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2.4 Data synthesis

A systematic narrative synthesis is provided with the information presented in text and tables to summarize and explain the characteristics and findings of the included studies.The following is a tentative outline of how we synthesized the findings; firstly, CAP in patients with CAP conceptualizations was summarized. This included definitions provided by CAP researchers. Secondly, the antecedents of CAP in these patients were summarized. This likely included the grouping of corticosteroid therapies in the treatment of CAP in patients from literature. Finally, the evidence on recent advances in efficacy of corticosteroids therapies in the treatment of CAP was incorporated into the theoretical framework.

2.5 Statistical analysis

Data were analyzed from July to August 2022.We pooled the findings from the included studies such as calculated mean, standard deviation and sample size. All statistical analysis and meta-analysis were performed using IBM SPSS 21 and Review Manager (RevMan), version 5.3 (The Cochrane Collaboration, London, UK). Dichotomous data were analyzed using risk ratios (RR) with 95% confidence intervals (CIs). Continuous data were analyzed as mean differences with 95% CIs when the measurements used the same scale. The pooled RR was calculated by the random-effect model using the Mantel-Haenszel method. For the assessment of statistical heterogeneity, we utilized the I^2 statistic. Significant heterogeneity was defined as I^2 statistics value of above 50%. Two-sided $P < 0.05$ was considered significant and was calculated using the z test of the null hypothesis indicating that there was no average effect in the random effect model of corticosteroids vs placebo.

We performed predefined subgroup analyses of mortality according to the effects model; type of mortality, duration of corticosteroid treatment, severity of CAP, use of loading dose, cumulative dose of corticosteroids, effective pharmacological effect reached, and inflammatory response. The stability of the results was confirmed by sensitivity analysis.

2.6 Risk of Bias Assessment

To assess the risk of publication bias, we used funnel plots for visual inspection. The strength of the body of evidence was assessed using GRADE approach [18]. As recommended by the Cochrane Collaboration[45], domains of bias of the studies included for efficacy of results were reviewed, including random sequence generation, allocation concealment, blinding of participants and stuff, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other biases. Other biases included the balance among patients with diabetes, asthma, and shock; whether the trial was terminated early and sponsor bias. Domains of bias of the studies that fulfilled more than six, four to six and fewer than four items were judged as being of high, fair and poor quality, respectively. The quality of evidence for the mortality and adverse events was evaluated according to the GRADE methodology. Risk of bias, inconsistency, indirectness, imprecision and publication bias were evaluated and classified as very low, low, moderate, or high[43].

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3. Results

3.1 Characteristics of included studies

Nine RCTs on corticosteroids vs. placebo involving 2673 patients were included in this meta-analysis[41, 46-53].There were 1335 individuals in the intervention group and 1338 individuals in the control group,The RCT's were either carried out in multi-centers[41, 46, 48-50, 52] or a single-center[47, 50, 51]. Six studies were double blind RCTs. Sample sizes ranged from 31 to 785 hospitalized CAP patients with ages ≥18 years. The type of corticosteroid treatment received by patients varied-dexamethasone[41, 49],prednisone[46, 52],methylprednisolone[48, 53],prednisolone[47, 51] or hydrocortisone[50]. Similarly, the length of corticosteroid use also varied, ranging from 3 -7 days (mean 5.22±1.787days). A placebo was used in the control group in all studies. Studies often excluded patients at high risks for adverse effects from corticosteroids. The characteristics of the included studied are illustrated in **Table 3**, and their efficacy outcomes are shown in **Table 4**. The severity of CAP differed in most studies-two studies involved patients with severe CAP, with a mean Acute Physiology and Chronic Health Evaluation Simplified Acute Physiology Score II score of about 15 or the Pneumonia Severity Index score VI-V rate> 50%; six studies involved patients with mixed CAP (mild to severe) and one study involved patients with less severe CAP. No study in abstract form was found.

3.2 Primary outcome

All nine trials with 2673 randomized patients were included in the analysis of mortality.The corticosteroid group had a total of 1335 patients, of which 56 patients died of CAP, whilst in the placebo group 59 mortality events were recorded in 1338 patients.**Figure 1** illustrates the pooled results in a forest plot of mortality in patients with CAP from the random-effects model combining the relative risks (RRs). The use of corticosteroid in CAP patients was not associated with a significant reduction in mortality (RR 0.96 (95% CI 0.67-1.38, P=0.83). The grade quality was judged to be moderate, mainly because several studies had inadequate sample size and medium risk of bias. **Figure 2** displays the funnel plot of the included studies and illustrates the number of deaths in each study group And the bar chart illustrates how many people died in each study (both corticosteroid and placebo groups) in Figure 3.

3.3 Subgroup Analyses and risk of bias

All subgroups showed no significant differences in mortality of patients with CAP (**Table 5**). Two RCT's reported the effects of corticosteroids on mortality of patients with severe CAP. Use of corticosteroids did not significantly reduce mortality rates in these patients (168 patients with 17 events; RR,0.55; 95% CI,0.22-1.37) with no significant heterogeneity (I^2=0%). Similarly, six RCT's whose patients presented with mixed CAP, corticosteroids did not significantly reduce mortality in these patients (2460 patients with 97 events; RR,1.07;95% CI,0.73-1.58). This finding indicates no significance in mortality with corticosteroids despite the severity of CAP. In the same line, treatment

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with corticosteroids for a short period of time (⩽ 4 days) did not significantly reduce mortality in patients with CAP (901 patients with 44 events; RR,0.76; 95% CI,0.43-1.33). Regarding subgroup analysis of mortality in severe and less severe CAP patients,30-day mortality and mortality in CAP patients who received a loading dose, we couldn't provide analysis figures for these subgroups due to a low number of studies. However, the findings from the analyzed subgroups accentuates the insignificance of corticosteroids in reducing mortality in CAP patients. These subgroup results should be interpreted with caution because of limited sample size and potential bias inherent to subgroup analysis. The risk of bias relative to reports of mortality is shown in Table 7. The selection and attrition biases were well controlled in most studies. However, imbalances were reported in patients with severe CAP[48, 50], and high level of inflammation[53].One study was judged to be of high quality, six studies were judged to be of fair quality, mainly because of the adverse events were not prespecified and because the outcome assessment was not specified, and two studies were judged to be of low quality as their studies were neither blinded nor the allocation of drugs concealed.

3.4 Sensitivity Analysis

A sensitivity analysis was carried out by the sequential dropping of each study in Table 5. Significant differences were observed for two studies[47, 49], resulting in no significant mortality reduction. Although the study by Blum et al[46] ,had a heavy weight of 24.8%,when excluded from the data, the pooled results showed no effect of corticosteroids in patients with CAP. Publication bias was not assessed because of limited(<10) number of studies included in this analysis.

3.5 Secondary outcomes

Because the data were reported inconsistently (data were shown as median [interquartile mean] or were not reported), we did not get a synthesized analysis of other efficacy outcomes. Although a pooled outcome was lacking, nearly all included studies show that corticosteroid treatment tended to reduce the lengths of hospital and ICU stays, the duration of antibiotic treatment, and the time to clinical stability (**Table 4**).Six trials reported data on the total adverse events that occurred during the study period.These adverse events included hyperglycemia[41, 47-49], superinfection[47] and empyema/pleural effusion[49]. Other adverse events recorded included falls with structure, cardiac decompensation (more in placebo), cardiac events, stroke and thromboembolic events[46], and gastric perforation [49]. Unspecified major complications were mentioned in one study [50]. The GRADE quality was judged to range from very low to low. This index was not prespecified in the included studies, and the result was dominated by an unclear bias study, so it should be interpreted with caution. And Table 6 shows paired samples statistics for secondary outcomes.

4. Discussion

We conducted a review of multiple RCTs investigating the efficacy of corticosteroids for CAP. This is a novel review in that the search strategy did not segregate on the severity of illness, the target population was not limited to age and the results of the latest RCTs were included. In the current

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review, when comparing the incidence of primary outcomes between corticosteroids and placebo, there was no significant difference. On the other hand, as a remarkable point in the secondary outcomes there is a possibility that corticosteroids may reduce length of hospital stay, time to reach clinical stability and duration of antibiotic treatment.

The detection that complementary corticosteroid use was not associated with a reduced mortality rate may be due to late administration of corticosteroids and inadequate therapeutic dose. This might have resulted in the reduced effective serum concentration lowering the treatment response due to the decreased half-life of corticosteroids. Meijvis et al. [49] highlighted that early administration of dexamethasone changes the immune response due to the accelerated return to normal concentrations of CRP and interleukin 6 that were noted in the dexamethasone group. This might be because of the long half-life of dexamethasone, where a more gradual reduction in biological effects might be expected, allowing for a gradual increase in intracellular glucocorticoid receptor number and recovery of the hypothalamic-adrenal axis.

In their study Huang et al.[54], one old study completed in 1993 was included in their meta-analysis [55], but excluded in our study. The exclusion was due to the type and principles of antibiotic use and other medical procedures which were used during those times that greatly differs from the current medical protocols. Also,the definition of CAP was not clear in this study. Secondary outcomes, such as the length of hospital stay and ICU stay, duration of antibiotic treatment, and the time to clinical stability, in 5 included studies were shown as median and interquartile ranges [46-48, 52, 53].All of these studies stated that their data were substantially skewed distributions. Pooled and converted data were not recommended by the Cochrane collaboration and the result may be misleading. Three studies were also excluded from our study though they reported the mortality rates associated with the complementary use of corticosteroids in CAP[56-58]. This is because these studies did not explicitly specify nor categorize the mortality rates within the different intervention groups, they all stated the overall mortality rates. To avoid the possible bias resulting from data conversion, we only retrieved qualitative descriptions with estimations, thus our results may be more believable.

Corticosteroids may regulate inflammatory biomarkers such that patients with CAP are offered earlier effective treatment. Studies have analyzed the effect of inflammatory biomarkers in order to improve parameters in CAP. The study by Raess N et al. explored how inflammatory biomarkers differ between the prednisone and controlled groups[59]. In this study,corticosteroids decreased CRP levels, increased leukocyte and neutrophil counts and had no effect on procalcitonin levels. A rebound effect of CRP levels was indicated after stopping prednisone. In another study,acute administration of methylprednisolone was associated with less treatment failure and a lower inflammatory response[48]. Controversially, a study comparing the inflammatory cytokines in patients with CAP argued that the imbalance of high inflammatory state and low cortisol levels did not predict treatment response to corticosteroids with in patients with CAP. Popovic M et al. showed that corticosteroids did not reduce copeptin levels to a higher extent than placebo over time. Also, the effect of corticosteroids on neurons seemed to be only present in patients pre-treated with corticosteroids before inflammation reached its maximum[60].On the other hand, several studies highlighted a faster reduction in blood interleukin-6

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and CRP levels in CAP patients administered corticosteroids [50, 53, 59]. In the same line,children with severe CAP on methylprednisolone regiment showed positive clinical utility in decreasing the duration of fever and the levels of CRP by 50%[61]. Reduction in CRP levels supports the notion that containment of systemic inflammation is an imperative priority in the management of patients with CAP. Cortisol is another biomarker which might be useful in prognosis of CAP as it is the predominant secretion by the adrenal cortex and is an important endogenous regulator of inflammation. A high serum cortisol concentration on hospital admission was associated with an adverse outcome resulting in CAP patients having an uneventful recovery[62]. On the other hand, Blum C et al. argued that treatment decision for/against adjunct corticosteroid use in CAP should not be made depending on cortisol values or cosyntropin testing results. This was due to neither the baseline/ stimulated cortisol after low dose cosyntropin testing in predicting glucocorticoid responsiveness in mild to moderate CAP[63]. Henceforth, using biomarker values in CAP is conflicting,thus, biomarker values should not be used in isolation. Rather, they should be considered in conjunction with the patients' clinical presentation and history, imaging and other lab results, as well as in light of the medical practitioner's clinical experience and judgement.

More recently, a significant reduction of median length of stay and ICU admission rate in adult patients hospitalized with CAP was noted in a RCT (n=401) testing a 4-day continuous dose of oral dexamethasone (6mg/day) versus placebo[41]. Another study (n=726) including 19% of patients with diabetes mellitus, time to reach clinical stability was seen to be reduced in both the diabetic and non-diabetic patients[52, 64].These observations exhibit the validity and benefit of complementary prednisone administration for patients with diabetes or hyperglycemia on hospital admission.. On the other hand, Ceccato et al. concluded that the glucocorticosteroid and macrolide combination had no statistically significant association with clinical outcomes compared with other combinations in patients with severe CAP and a high inflammatory response after taking account potential confounders[56].Four meta-analyses showed ths complementary systematic use of corticosteroids in CAP safe and beneficial for patients hospitalized with CAP[37, 38, 54, 65].

Ttherapeutic doses of corticosteroids vary greatly, as do adverse effects. Patients require education on what to expect with corticosteroid use, whether it be short course or long-term use. Other pharmacological therapies may be necessary to counteract corticosteroid-related adverse effects, such as gastric acid suppression, calcium and vitamin D supplementation, and opportunistic infection prophylaxis[66-69]. Providers must weigh the risks versus benefits of corticosteroid use and utilize the lowest effective dose for the least duration possible to avoid or minimize serious corticosteroid-induced toxicities.

Another factor to consider in patients with CAP is the recognized risk of Coronavirus 2019 (Covid-19)[70].The clinical manifestations of Covid-19 resembles CAP[71].Henceforth, several observational, retrospective and comparative studies have been carried out to distinguish clinical characteristics between CAP and Covid-19[71-77].In one study,Covid-19 patients expressed an increase in copeptin levels and a decrease in leucocyte count when compared to CAP patients[71].This finding highlights that biomarkers might serve as predictors in differentiating between Covid-19 and

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CAP. Other clinical manifestations such as diarrhea, lymphocyte and eosinophil counts could distinguish CAP from Covid-19[75]. In addition, the use of artificial intelligence using chest computed tomography (CT) scans has been proposed to accurately differentiate and detect CAP from Covid-19, with Covid-19 patients exhibiting more extensive radiographic involvement[78-81].CT images are accurate and can rapidly accelerate diagnosis. Lung ultrasound has also been used distinguish the sonographic features between Covid-19 and CAP[82],Off note ,a guideline for the treatment of adults with CAP amid the Covid-19 pandemic has been established[83]. Interpretations of this guideline's application to the evaluation and treatment ,which includes diagnostic testing, determination of site of care, selection of initial empiric antibiotic therapy, and subsequent management decisions have been explained[84].Constructively,COVID-19 preventive measures and personal hygiene were effective measures in preventing the spreading of CAP.A multicenter study in Japan revealed a reduction of CAP hospitals amid the Covid-19 pandemic[85]. In summary,an in-depth understanding of lung tissue-based immunity may lead to improved diagnostic and prognostic procedures in CAP. Novel treatment strategies aimed at reducing the disease burden and avoiding the systemic manifestations of infection reducing mortality and morbidity are imperative.

This systematic review has limitations. Firstly, the severity of illness was not consistent across the studies, Secondly, the number of patients with CAP was low suggesting that the results may not be stabilized, and lastly, most studies did not report related data emphasizing the need of additional studies.

5. Conclusion

We performed the latest review to assess the efficacy of corticosteroids for CAP which included up-to-date clinical trials in the search scope. Our study suggests that complementary corticosteroid treatment is not significantly associated with reduced mortality rates in patients with CAP. In the secondary outcomes, it was suggested that the adjunctive use of corticosteroids may be effective in reducing the length of time taken to reach clinical stability, length of hospital/ ICU stays, and duration of antibiotic treatment. Due to a low number of patients in our study, more studies are needed to confirm this result.

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7. Tables and figures

Table 1.Databases searched in the systematic review

Databases	URL
Web of science	www.webofknowledge.com
Medline/PubMed	pubmed.ncbi.nlm.nih.gov/
Embase	www.embase.com
Scopus	www.elsevier.com
The Cochrane Library	www.cochranelibrary.com/
World Health Organization	www.who.int/health-topics/pneumonia

Table 2. Search keywords

Corticosteroid terms	Pneumonia terms
“Corticosteroids”	“Community-acquired pneumonia”
“Prednisolone”	“CAP”
“Glucocorticoids”	
“Hydrocortisone”	
“Prednisone”	
“Dexamethasone”	

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Table 3.The table gives information about the characteristics of included studies.MC=multi-center; SC=single center; DB=double blind RCT=randomized control trial; IV=intravenous

Study	Country	Study Design	Total Number of patients	Corticosteroid	Dose	Duration (days)	Cumulative corticosteroid dose	CAP severity
Wittermans E et al,2021[41]	Netherlands	MC,DB,RCT	401	Dexamethasone (n=203)	6mg/day, orally	4	24mg	Mixed
Blum C A et al,2015[46]	Switzerland	MC,DB,RCT	785	Prednisone (n=392)	50mg/ Day, oral	7	350mg	Mixed
Snijders D et al,2010[47]	Netherlands	SC,DB,RCT	213	Prednisolone (n=104)	40mg/Day	7	280mg	Mixed
Torres A et al,2015[48]	Spain	MC,DB,RCT	120	Méthylprednisolone (n=61)	0.5mg/kg per 12hrs	5	N/A	Severe
Meijvis SC et al,2011[49]	Netherlands	MC,DB,RCT	304	Dexamethasone (n=151)	5mg/Day, IV	4	20mg	Mixed
Confalonieri M et al,2005[50]	Italy	MC,DB,RCT	48	Hydrocortisone (n=24)	200mg intravenous loading bolus followed by an infusion (hydrocortisone 240 mg in 500 cc 0.9% saline) at a rate of 10 mg/hour	7	920mg	Severe

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Mikami K et al,2007[51]	Japan	SC,RCT	31	Prednisolone (n=15)	40mg/Day, IV	3	120mg	Mixed
Fernandez-Serrano S et al, 2011[53]	Spain	SC,RCT	55	Methylprednisolone (n=23)	200mg loading bolus followed by 20mg/12hrs	3	320mg	Less severe
Wirz S A et al, 2016[52]	Switzerland	MC,RCT	726	Prednisone (n=362)	50mg/day, oral	7	350mg	Mixed

Table 4; The table gives information on efficacy of outcomes of the included studies. All data are median

(Interquartile mean) or mean ±SD

Study	Total number of patients	Mortality(death) Corticosteroid/ control	Length of hospital stay, corticosteroid/ control	ICU admission or stay(days), corticosteroid/ control	Duration of antibiotic treatment (days) corticosteroid/ control	Time to clinical stability (days) corticosteroid/ control
Wittermans E et al,2021[41]	401	4 / 7	4.5(95% CI,4-5) / 5 (95% CI, 4.6-5.4)	5(3%) / 11(7%)	NA	NA
Blum C A et al,2015[46]	785	16 (4%) / 22 (6%)	6.0(6.0-7.0) / 7.0(7.0-8.0)	16(4%) / 22 (6%)	9.0(7.0-11.0) / 9.0(7.0-12.0)	3.0(2.5- 3.4) / 4.4 (4.0-5.0)
Snijders D et al,2010[47]	213	6(5.8%) / 6 (5.9%)	10.0±12.0 / 10.6±12.8	NA	NA	4.9±6.8 / 4.9± 5.2
Torres A et al,2015[48]	120	6 (10%) / 9 (15%)	11(7.5-14) / 10.5 (8.0-15.0)	5(3-8) / 6(4-8)	NA	4 (3-6) / 5 (3-7)

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Mikami K et al,2007[51]	31	1 / 0	11.3±5.5 / 15.5 ±10.7	NA	8.5±3.2 /12.3 ±5.5	NA
Meijvis SC et al,2011[49]	304	8(5%) / 8 (5%)	6.5 (5.0-9.0) / 7.5(5.3-11.5)	7(5%) / 10(7%)	NA	NA
Confalonieri M et al,2005[50]	46	0 / 2	13 (10-53) / 21(3-72)	10(4-3) / 18(3-45)	NA	NA
Wirz S A et al,2016[52]	726	15/13	N/A	2(0.5%) / 10(2,7%)	N/A	3,4(1.5-8.5)
Fernandez-Serrano S et al, 2011[53]	55	0/1	10(9-13) / 12(9-18)	6.5(5.5-9) / 10.5(6.24-24.5)	N/A	5(2-6) / 7(3-10)

Table 5; Subgroup Analysis and Sensitivity Analysis

Classification	Number of patients (studies)	Number of events/Number in group		RR (95% CI)	P value
		Corticosteroid	Placebo		
Sample size					
⩽200	244(4)	7/123	12/121	0.62(0.27-1.39)	.25
＞200	2429(5)	49/1212	47/1217	1.05(0.75-1.55)	.81
Type of mortality					
In-hospital	873(4)	18/439	26/434	0.69 (0.39-1.22)	.20
30-day	213(1)	6/104	6/109	0.75 (0.39-1.22)	.93
Without explanation	1587(4)	32/792	27/795	1.18 (0.72-1.94)	.50
CAP severity					
Severe	168(2)	6/85	11/83	0.55(0.22-1.37)	.20
Less severe	45(1)	0/23	1/25	0.32(0.01-7.45)	.48
Mixed	2460(6)	50/1277	47/1233	1.07(0.73-1.58)	.72
Cumulative dose					
⩽300mg	949(4)	19/473	21/476	0.92 (0.51, 1.67)	.79

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＞300mg	1604(4)	31/801	29/803	1.07 (0.66, 1.74)	.79
Use of loading dose					
YES	93(2)	0/47	3/46	0.25(0.03-2.12)	.20
NO	2580(7)	56/1288	56/1292	1.00(0.70-1.44)	.99
Duration of corticosteroid treatment					
⩽4 days	781(4)	13/392	16/389	0.82 (0.41-1.64)	.58
>4 days	1892(5)	43/943	43/949	1.00 (0.67, 1.51)	.99
Sensitivity Analysis					
Multicenter	2384(6)	49/1193	52/1191	0.94 (0.64-1.37)	.75
Low-medium risk of bias	1871(6)	40/935	45/936	0.89 (0.59-1.34)	.58
Confalonieri et al[50] excluded	2625(8)	56/1311	57/1314	0.98(0.69-1.41)	.93
Mikami et al[51] excluded	2642(8)	55/1320	59/1322	0.95(0.66-1.36)	.81
Snijders et al[47] excluded	2550(8)	50/1321	53/1229	0.95(0.65-1.39)	.75
Fernandez et al[53] excluded	2628(8)	56/1312	58/1316	0.98(0.68-1.40)	.80
Meijvis et al [49]excluded	2369(8)	48/1184	51/1185	0.95(0.65-1.40)	.75
Blum et al [46]excluded	1888(8)	40/943	46/945	0.89(0.59-1.34)	.57
Torres et al[48] excluded	2553(8)	50/1274	50/1279	1.02(0.70-1.51)	.83
Wirz et al [52]excluded	1947(8)	41/973	46/974	0.91(0.60-1.37)	.79
Wittermans et al[41]	2272(8)	52/1132	52/1140	1.01(0.70-1.47)	.84

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excluded

Table 6. Paired Samples Statistics for secondary outcomes.LOHS=length of hospital stay;TTCS=time taken to reach clinical stability;ICU=intensive care unit

	Outcome	Mean	Std. Deviation	P value
Pair 1[41, 46-52]	LOHS in corticosteroid group	9.038	2.9947	.002
	LOHS in placebo group	11.138	5.1514	
Pair 2[41, 46, 49, 52]	ICU admission in Corticosteroid group	7.50	6.028	.041
	ICU admission in Placebo groups	11.25	7.890	
Pair 3[47, 48, 50]	TTCS corticosteroid	4.300	1.1269	.047
	TTCS placebo	5.433	1.3796	

*Table 7.*Risk of Bias Summary of included studies

Study	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Confalonieri et al[50]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Mikami et al[51]	Unclear	High risk	High risk	High risk	Low risk	Low risk	Low risk
Snijders et al[47]	Low risk	Low risk	unclear	Low risk	Low risk	Low risk	Unclear risk

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Fernandez S et al[53]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Meijvis et al[49]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Blum et al[46]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Torres et al[48]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Wirz et al[52]	Unclear	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	High risk
Wittermans et al[41]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

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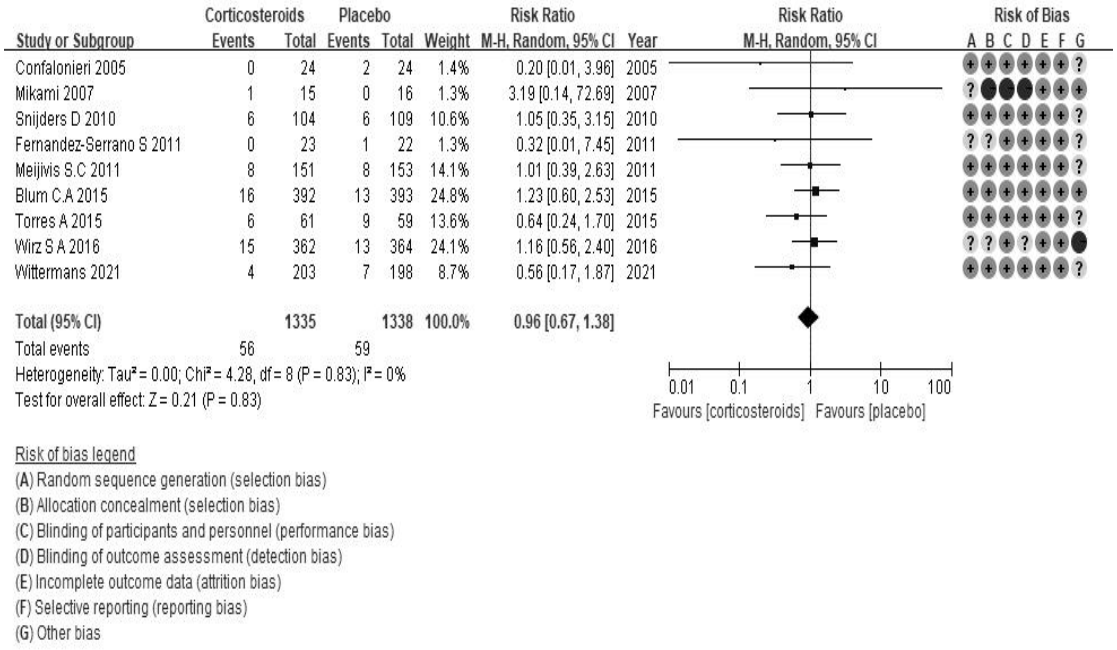

Figure 1.The Forest plot illustrates mortality of patients with CAP according to treatment arms. The sizes of the squares denoting the point estimate in each study are proportional to the weight of the study. The diamonds represent the overall findings in each plot. For all study names, see the cited references.df=degrees of freedom

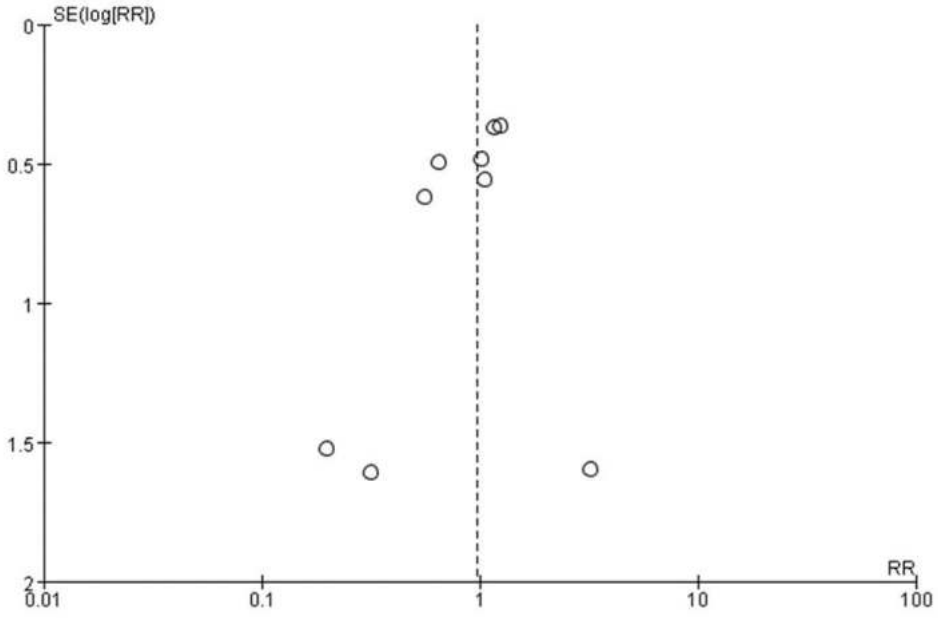

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Figure 2.Funnel plot of comparison: Mortality of patients with CAP. The dashed lines indicate the 95% CI. Each open circle represents a separate study. The middle-dashed line indicates the overall effect.The unequal scatter indicates bias which might be due to a small number of included studies.There are no clustered studies at the bottom which indicates small sample size.

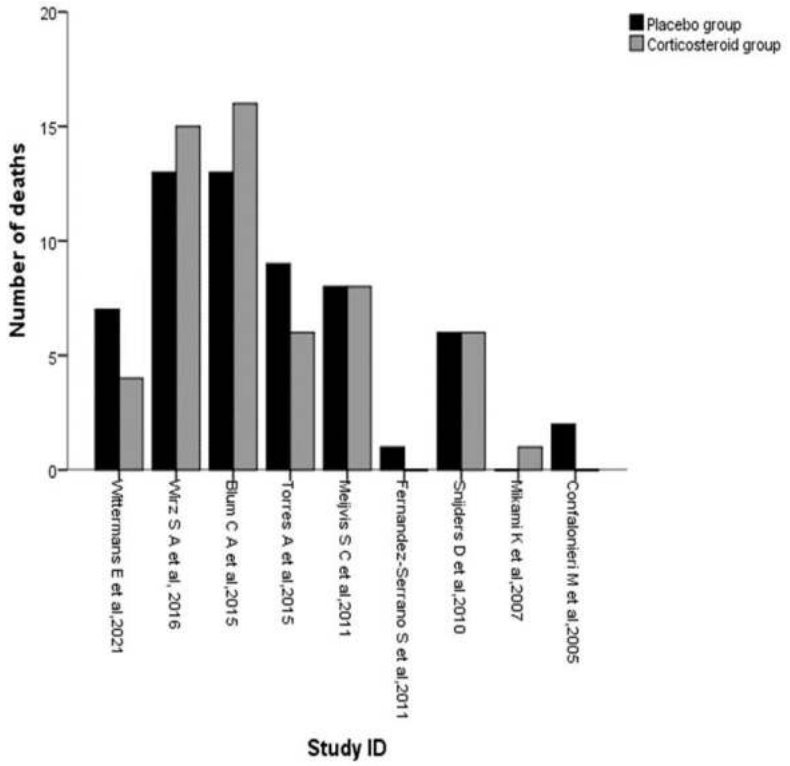

Figure 3 The bar chart illustrates how many people died in each study (both corticosteroid and placebo groups)