Association Between Glucocorticoids Treatment and Viral Clearance Delay in Patients with COVID-19: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background

Evidence of glucocorticoids on viral clearance delay of COVID-19 patients is not clear.

Methods

In this systematic review and meta-analysis, we searched studies on Medline, Embase, EBSCO, ScienceDirect, Web of Science, Cochrane Library, and ClinicalTrials.gov from 2002 to December 2, 2020. We mainly pooled the adjusted hazard ratios (HRs), mean difference (MD) or risk ratios (RRs) of viral clearance delay and did subgroup analyses by doses and the severity of illness.

Results

One trial and 38 observational studies, with a total of 7119 patients, were identified. Glucocorticoids treatment was associated with delayed viral clearance in COVID-19 (Adjusted HR 1.71, 95% CI 1.51 to 1.94, I^2=22%, PI 1.45 to 2.01), based on moderate-quality evidence. In subgroup analyses, risk of viral clearance delay was significantly higher among COVID-19 patients being mild or moderate ill (adjusted HR 1.94, 95% CI 1.39 to 2.70, I^2=52%; MD 2.59, 95% CI 1.21 to 3.97, I^2=24%), but not in those of being severe or critical ill (adjusted HR 1.85, 95% CI 1.05 to 3.26; MD 0.22, 95% CI -1.85 to 2.29, I^2=56%); taking high doses (adjusted HR 1.49, 95% CI 1.03 to 2.15; unadjusted RR 1.47, 95% CI 1.12 to 1.94) rather taking low doses (adjusted HR 1.39, 95% CI 0.93 to 2.08; unadjusted RR 1.33, 95% CI 1.00 to 1.77) or pulse (unadjusted RR 1.85, 95% CI 0.66 to 5.19).

Conclusions

Glucocorticoids treatment delayed viral clearance in COVID-19 patients of being mild or moderate ill or taking a high dose, rather in those of being severe or critical ill or taking low dose or pulse.

Introduction

Historically, glucocorticoids were widely recommended to treat SARS, but this proved to be controversial. A recent large randomized controlled trial (RCT)[1] from the United Kingdom compared 2104 hospital COVID-19 patients who were given dexamethasone with those of 4321 patients who were not. Results from this large trial showed glucocorticoid treatment cut the risk of death from 40–28% for patients on ventilators and from 25–20% for patients needing oxygen. Then, a systematic review and meta-analysis[2] involving 7 RCTs also revealed a significant association between glucocorticoids treatment and decreased mortality in COVID-19 patients of critical illness. Although these results are encouraging, glucocorticoids theoretically delay virus removal. At present, no study has systematically assessed glucocorticoids treatment effects on viral clearance for COVID-19. Thus, we conducted this systematic review and meta-analysis to evaluate this potential effect from glucocorticoids treatment for COVID-19.

Methods

Guidance and Protocol

We reported our study according to standards of the meta-analysis of observational studies in epidemiology (MOOSE)[3] and preferred reporting items for systematic reviews and meta-analyses (PRISMA)[4]. We registered our protocol for this review and meta-analysis on PROSPERO (CRD42020194225).

Eligibility criteria and definitions

We considered criteria of eligible studies as follows: participants were COVID-19 patients infected with SARS-CoV-2 confirmed through the nucleic acid test; the intervention was glucocorticoids, no matter types, and doses; the controls were COVID-19 patients receiving usual care except glucocorticoids treatment; the outcomes should involve viral clearance, no matter what kind of data was presented. Both RCTs and observational studies (including cohort studies, case-control studies, case series of more than 10 patients) were included. Viral clearance delay was defined as the opposite of SARS-CoV-2 RNA shedding at any time from illness onset (different studies were based on different time frames, usually at ≥7-day from illness onset) and the SARS-CoV-2 RNA shedding was defined as two consecutive RNA negative with at least 24-h intervals and the date of the first negative test was defined as the day of viral RNA clearance.

Literature search

Two of the authors (JB.L. and XL.L.) conducted a literature search on several databases: Medline (Ovid), Embase (Ovid), EBSCO (H.W. Wilson: OmniFile Full-Text Mega), ScienceDirect, Web of Science (All database), Cochrane Library, and ClinicalTrials.gov from 2019 to December 2, 2020. Also, we reviewed reference lists of identified studies, systematic reviews, and review articles on the same topic. Language or publication status was not restricted. Supplementary Table 1 showed the details of the search strategy.

Study selection

After duplicates were removed, the title and abstract of each item were browsed to screen studies with eligible participants and intervention by two independent groups of four authors (H.Y. and W.Z.; Y.Z. and LP.W.). Further screening was conducted to determine whether the item met the rest eligibility

criteria. Disagreements were resolved by consensus, and if necessary, consultation with a third author (ZW.Z.).

Data collection process

Data from included studies were extracted into standard collection forms and information tables for quality assessment were created. The quantile estimation method was applied to estimate the sample mean and standard deviation if a study presented summary statistics as median, first and third quartiles, and sample size. Note that if the study reported a hazard ratio (HR) of SARS-CoV-2 RNA shedding rather than viral clearance delay, then an HR of viral clearance delay was obtained by taking the reciprocal of the HR i.e.1/ HR and associated confidence interval (CI).

Assessment of risk of bias

The Newcastle-Ottawa-Scale (NOS)[5] for observational studies and using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) were used to assess the risk of bias by two independent groups of four authors (H.Y. and W.Z.; Y.Z. and LP.W.). Each domain of NOS was composed of 2 to 4 items of criteria, and each criterion was scored in the form of stars. A total score of 8 or 9 was assessed as low risk of bias, 6 or 7 as some concerns, and ≤5 as high risk. Each domain of RoB 2 was assessed as low risk, some concerns, or a high risk of bias. The study's overall risk of bias was determined by the highest risk of bias for any criteria. Disagreements were resolved by consensus, and if necessary, consultation with a third author (ZW.Z.).

Data synthesis

Statistical analyses were performed using the meta package in R (version 4.0.1; The R Project for Statistical Computing). We mainly used HRs and their associated 95% CI to assess outcomes, as well as a prediction interval (PI) for the effect of future studies based on the present[6]. Adjusted HRs and unadjusted HRs were separately pooled. If provided, we also pooled odds ratios (ORs), risk ratios (RRs) (for 2x2 table data) for binary data, and mean difference (MD) for continuous data. We used random-effects models to pool data. The I^2 test was used to examine heterogeneity and I^2 ≥50% was considered as significant heterogeneity. A 2-tailed P value of less than 0.05 was statistically significant. Funnel plots and the Egger test were adopted to assess the publication bias of the main results.

Subgroup analysis

We planned several subgroup analyses according to the following variables: (1) severity of illness (mild or moderate and severe or critical); (2) doses (equivalent methylprednisolone) of glucocorticoids (low dose [40 mg/day], high dose [80 mg/day], and pulse [250-500 mg/day]). The severity of illness was reported by the studies following Chinese interim guidelines for diagnosis and treatment for COVID-19 patients (version 7.0)[7,8].

Sensitivity analysis

We conducted sensitivity analyses on main results from adjusted HRs by (1) excluding the study with the largest sample, (2) excluding the study with the smallest sample, (3) excluding studies of case-control design, (4) excluding studies of retrospective cohort design, (5) excluding studies identified by influence analyses[9], (5) excluding studies with the non-low risk of bias.

Results

Eligible studies and study characteristics

Of the 6055 records, 39 studies[10-38] involving a total of 7119 patients were included in the final meta-analysis (Figure 1). Table 1 showed the characteristics of the included studies. These studies, with a size from 33 to 774 and a median age from 42 to 64, comprised 1 RCT, 11 case-control studies, and 17 retrospective cohort studies. One of the studies came from Brazil, one from Spain, and the rest from China. Most studies used a low dose of glucocorticoids, i.e.1-2 mg/kg/d (an equivalent of methylprednisolone) and only one study[29] reported pulse use of glucocorticoids, i.e. 250-500 mg/d (an equivalent of methylprednisolone). Methylprednisolone was the most common type, followed by dexamethasone, prednisone and prednisolone, and finally hydrocortisone. The median days for glucocorticoids treatment from illness onset ranged from 1 to 13 days and the median duration of treatment from 3 to 10.8 days. The studies reported different time frames of viral clearance delay, between 5- and 45-day, and the longest reported follow-up was 50 days.

Supplementary Tables 1, 2, and 3 showed the risk bias of the included studies. Seven studies were considered as low risk, 19 as some concerns, and 3 as high risk. The average score of total risk bias for case-control studies was 6.1 and the average score for retrospective cohort studies was 6.7. The only RCT was assessed as the trial with the risk bias of some concerns, due to its deviations from intended interventions.

Risk of viral clearance delay

A total of nine studies reported HR for risk of viral clearance delay in COVID-19 patients who received glucocorticoids treatment, of which the longest follow-up was 50 days. The overall unadjusted HR (1.58, 95% CI 1.39 to 1.80, I^2=13%, PI 1.32 to 1.90) (Figure 2B) and adjusted HR (1.71, 95% CI 1.51 to 1.94, I^2=22%, PI 1.45 to 2.01) (Figure 2A) revealed an association between glucocorticoids treatment and increased risk of viral clearance delay in COVID-19 patients. The pooled MD of days for SARS-CoV-2 RNA shedding from illness onset (2.13, 95% CI 0.83 to 3.42, I^2=73%, PI -2.66 to 6.92) (Figure 2C) and overall unadjusted RR (1.29, 95% CI 1.14 to 1.47, I^2=58%, PI 0.86 to 1.95) (Figure 3C) also confirmed the delayed viral clearance in glucocorticoids treatment patients, compared to patients revived non-glucocorticoids treatment. A few studies (four studies)[24,31,34,36] reported the ORs for risk of viral clearance delay, however, the time frames of viral clearance delay among these studies were substantially different (Li&Cao et al[24], 11-day; Xu&Chen et al[34], 15-day; Qi&Yang

et al[31], 17-day; Yan&Liu et al[36], 23-day) (Table 1). Pooled unadjusted OR (2.08, 95% CI 0.35 to 12.41, I^2=84%) (Figure 3B) and adjusted OR (1.82, 95% CI 0.70 to 4.76, I^2=57%, PI 0.04 to 81.84) (Figure 3A) of these studies showed no association between glucocorticoids treatment and risk of viral clearance delay.

Influence analyses identified four studies[15,23,26,32], with an excessive influence on the overall results, of which two studies with extreme sample size are the excluded studies of predesign in the sensitivity analyses (Supplementary Figure 8). All the sensitivity analyses based on adjusted HRs showed a similar result with that from the main analysis (Supplementary Figure 1-7). Funnel plot analysis showed no asymmetry on the HRs, RRs, and MDs (Supplementary Figure 9-12), and the Egger test detected no significant small-study effects. Due to a very limited number of studies reporting ORs, we failed to draw funnel plots and correspondingly failed to conduct Egger tests on these studies.

Subgroup analysis

Subgroup analysis revealed that risk of viral clearance delay was significantly higher in glucocorticoids-treated COVID-19 patients of being mild or moderate (adjusted HR 1.94, 95% CI 1.39 to 2.70, I^2=52%; MD 2.59, 95% CI 1.21 to 3.97, I^2=24%), but not patients of being severe or critical (adjusted HR 1.85, 95% CI 1.05 to 3.26; MD 0.22, 95% CI -1.85 to 2.29, I^2=56%) (Figure 4). Only one study[19] compared the risk of viral clearance delay between COVID-19 patients who received a low dose (40 mg/day, an equivalent of methylprednisolone) and those who received a high dose (80 mg/day), and another study[29] reported the effects of the pulse (250-500 mg/day) use of glucocorticoids. Their results indicated that a high dose of glucocorticoids increased the risk of viral clearance delay (adjusted HR 1.49, 95% CI 1.03 to 2.15; unadjusted RR 1.47, 95% CI 1.12 to 1.94), but neither low dose (adjusted HR 1.39, 95% CI 0.93 to 2.08; unadjusted RR 1.33, 95% CI 1.00 to 1.77) nor pulse use (unadjusted RR 1.85, 95% CI 0.66 to 5.19) (Figure 5).

Discussion

In this meta-analysis of 39 studies (at moderate risk of bias involving 7119 patients), glucocorticoids treatment was significantly associated with an increased risk of viral clearance delay in COVID-19 patients. Subgroup analyses demonstrated that among glucocorticoids-treated COVID-19 patients, the detrimental effect in our outcomes was associated with patients of being mild or moderate, but not patients of being severe or critical. Evidence also indicated a high dose, but not low dose or pulse use of glucocorticoids substantially lead to viral clearance delay. Though only one RCT was included, however, adjusted data from observational studies and low heterogeneity of pooled data ensured the power of conclusions.

Principal findings and comparison with other studies

As of writing this manuscript (early December 2020), no meta-analysis has examined the use of glucocorticoids in patients with COVID-19 regarding viral clearance delay. Most trials of glucocorticoids suspended enrollment after the RECOVERY trial which was the globally largest one and drew an encouraging conclusion of reduction in mortality of COVID-19. However, as one kind of immunosuppressant, glucocorticoids' detrimental effect-one of the most important side effects, i.e. viral clearance delay-had not been further investigated in these trials. Thus, information about its impact on the humoral immune response against the virus is in need. Most previous experience with patients infected by SARS, MERS, and H1N1 indicated that glucocorticoids delayed viral RNA clearance[39-41]. Nevertheless, one study on factors promoting the prolonged shedding of H1N1 indicated a significant association of viral clearance delay and delayed antiviral therapy, but not glucocorticoids treatment [42]. However, glucocorticoids treatment usually delayed antiviral therapy for two or more days after symptom onset and thus might have a more indirect role on the viral clearance delay [42]. Evidence is inconsistent on the viral clearance delay of glucocorticoids-treated COVID-19 patients. The most focus of the debate is the potential confounding role of doses and the severity of illness on the associations. Our meta-analysis pooled confounders-adjusted HRs and conducted subgroup analyses by doses and the severity of illness. The findings of our meta-analysis of the association of glucocorticoids administration with delayed viral RNA clearance were in line with the recently published results on COVID-19. We further discovered this association occurred in mild or moderate patients but not severe or critical patients; occurred in patients receiving a high dose, but not low dose or pulse use of glucocorticoids.

Strengths and limitations

This systematic review and meta-analysis have several methodological strengths. We pooled data in their original form and focused on the results of pooling adjusted HRs which could avoid time-varying confounding and as well as other potential confounders. Thus, the heterogeneity of main pooled results was low and the overall risk of bias was moderate. To further take the between-study variance into account, we provided prediction intervals to expect the effects of future studies to fall based on our present evidence in the meta-analysis[43]. To exam the robustness of our main results, we conducted a series of presumable sensitivity analyses, in which extreme values were detected by influence analysis and then excluded to avoid distortion of our pooled effect estimate. Moreover, we assessed potential high-risk subgroups by doses and the severity of illness, which was the main concern of glucocorticoids administration.

Our study has limitations. First, the results of this meta-analysis were main from observational studies and clinical heterogeneity was inevitable. Though the heterogeneity was low when we pooled time-effect-containing HRs, the heterogeneity of other pooled effects (MDs, ORs, RRs) was moderate-to-high. The main heterogeneity came from different time-frame among studies that reported non-time-effect-containing effects, such as ORs or RRs (2x2 table). Moreover, we failed to investigate the heterogeneity among studies that reported MDs due to limited data of confounders. Besides, the role of duration, timing, and types of glucocorticoids treatment on the viral clearance delay has not been further investigated due to insufficient accuracy of the information or lack of uniformity between studies.

Implications for practice

Through, people who have a lot of experience with glucocorticoids in the treatment of inflammatory, little information could be obtained regarding its role on the humoral immune response against the virus. Many years ago, one trial involving 29 normal adult males showed that short courses (3 or 5 days) of high dose (96 mg/d) methylprednisolone could decrease serum IgG concentration[44]. Theoretically, the reduction in antibody production might delay viral clearance and experience a high-risk of reinfection[29]. However, there was one study that demonstrated that dexamethasone treatment did not affect the formation of pneumococcal antibodies during community-acquired pneumonia[45]. Viral pneumonia should be different from bacterial pneumonia. Previous studies on H1N1, SARS, MERS has shown glucocorticoids' negative effects on viral clearance, however, the evidence is sporadic. We did the first meta-analysis to systematically investigate glucocorticoids' role on viral clearance delay of SARS-CoV-2. Our conclusion indicated glucocorticoids might delay viral clearance in mild or moderate patients and patients taking a high dose, but not severe or critical patients, and not in patients taking low dose or pulse. We believe our findings would further bring light to the current clinical practice in glucocorticoids treatment of COVID-19.

Conclusion

The findings suggest that glucocorticoids treatment delayed viral clearance in COVID-19 patients of being a mild or moderate illness, but not in those of being severe or critical. Moreover, it seems that patients taking high doses rather than taking low doses or pulse would experience a high-risk of viral clearance delay.

Abbreviations

COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome; RCT, randomized controlled trial; MOOSE, meta-analysis of observational studies in epidemiology; PRISMA, preferred reporting items for systematic reviews and meta-analyses; NOS, Newcastle-Ottawa-Scale; HRs, hazard ratios; ORs, odds ratios; RRs, risk ratios; MD, mean difference; CI, confidence interval; PI, prediction interval.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Additional data are available from the corresponding author on reasonable request at kangyan@scu.edu.cn.

Competing interests

All the authors declared no competing interests.

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Authors' contributions

JB.L., ZW.Z., and YK conceived the study and designed the protocol. JB.L. and XL.L. performed the literature search. HY, WZ, YZ, and LP.W. selected the studies, exacted the relevant information, and assessed the risk of bias of included studies. JB.L. synthesized the data and wrote the first draft of the paper. All authors contributed to critically revising successive drafts and approved the final version. JB.L., ZW.Z., and Y.K. are guarantors. The corresponding authors avouch that all listed authors meet authorship criteria and that no other qualified authors have been omitted.

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Tables

Table1. Characteristics of Included Studies

Author	Country	Design	Size	Age (Median/median range, years)	Glucocorticoids dose (Equivalent of MP)	Glucocorticoids type	Treatment timing (From illness onset, median days)	Treatment duration (Median/range, days)	Time frame of viral clearance delay (Follow-up)
Chang&Zhao et al	China	CC	67	14-59	NA	NA	NA	NA	16-day (≥ 16 days)
Chen&Song et al	China	RC	371	63-65	49.5* mg/d	DM, MP, PN	14.1*	9.1*	NA
Chen&Zhu et al	China	RC	267	49	NA	NA	NA	NA	45-day
Ding&Feng et al	China	RC	82	49	NA	NA	NA	NA	NA
Fang&Mei et al	China	RC	78	39.9-60.6	38† mg/d	MP	NA	7	NA
Feng&Li et al	China	CC	564	47	NA	NA	NA	NA	NA (50 days)
Fu&Luo et al	China	RC	33	41-65	1 mg/kg/d	MP	NA	NA	NA (≥22 days)
Gong&Guan et al	China	RC	34	33.8-38.2	1-2 mg/kg/d	MP	NA	5-10	NA
Hu&Li et al	China	CC	206	53.7*	40/80 mg/d	MP	NA	NA	30-day
Hu&Yin et al	China	CC	183	49	43.3† mg/d	NA	NA	4	20-day
Huang&Zhu et al	China	RC	309	45	40-160 mg/d	MP	NA	NA	NA (40 days)
Jeronimo&Farias et al	Brazil	RCT	393	55	1 mg/kg/d	MP	NA	5	5-, 7-day
Ji&Zhang et al	China	RC	684	61	1-2 mg/kg/d	DM, MP, PN	NA	3-5	14-, 28-day
Li&Cao et al	China	CC	66	47.5	NA	MP	NA	NA	11-day
Li&Li et al	China	RC	475	42	20/40 mg/d	MP, PS	2 (from admission)	NA	NA (50 days)
Ling&Xu et al	China	RC	66	44	NA	DM, PN	NA	NA	NA
Liu&Li et al	China	RC	646	57	80† mg/d	DM, MP, PN	13	NA	NA
Liu&Zhang et al	China	RC	774	64	40† mg/d	MP, PS	1	6	30-day
Ma&Zeng et al	China	RC	450	46.2*	56.6†	MP, PS	9	5	NA
Masia&Fernandez-Gonzalez et al	Spain	RC	77	63.5-71	250-500 mg/d	MP	NA	3	NA
Ni&Ding et al	China	RC	72	46-52	0.75-1.5 mg/kg/d	MP	NA	NA	NA
Qi&Yang et al	China	CC	147	42	NA	NA	NA	NA	17-day
Shi&Wu et al	China	CC	99	54	60† mg/d	NA	8	NA	28-day
Wu&Hou et al	China	RC	382	60.7*	NA	DM, HC, PN	NA	NA	NA
Xu&Chen et al	China	CC	113	52	0.5-1 mg/kg/d	MP	NA	NA	15-day
Xue&Zheng et al	China	CC	48	47	NA	NA	NA	NA	20-day
Yan&Liu et al	China	CC	120	52	NA	NA	NA	NA	23-day
Yuan&Xu et al	China	RC	132	43.7-52	52.2†	MP	8.3	10.8	NA
Zuo&Liu et al	China	CC	181	44.3*	NA	NA	NA	NA	21-day

Abbreviations: CC, case control; RC, retrospective cohort; RCT, randomized controlled trial; DM, dexamethasone; MP, methylprednisolone; PN, prednisone; PS, prednisolone; HC, hydrocortisone; NA, not available; * mean; † median.

Figures

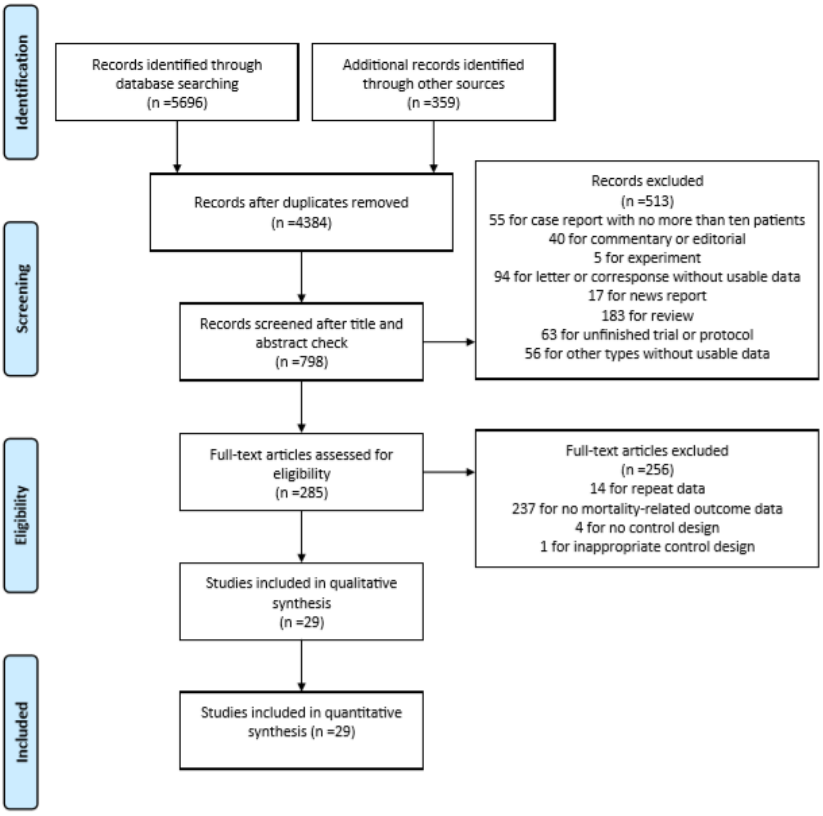

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the Article Selection Process

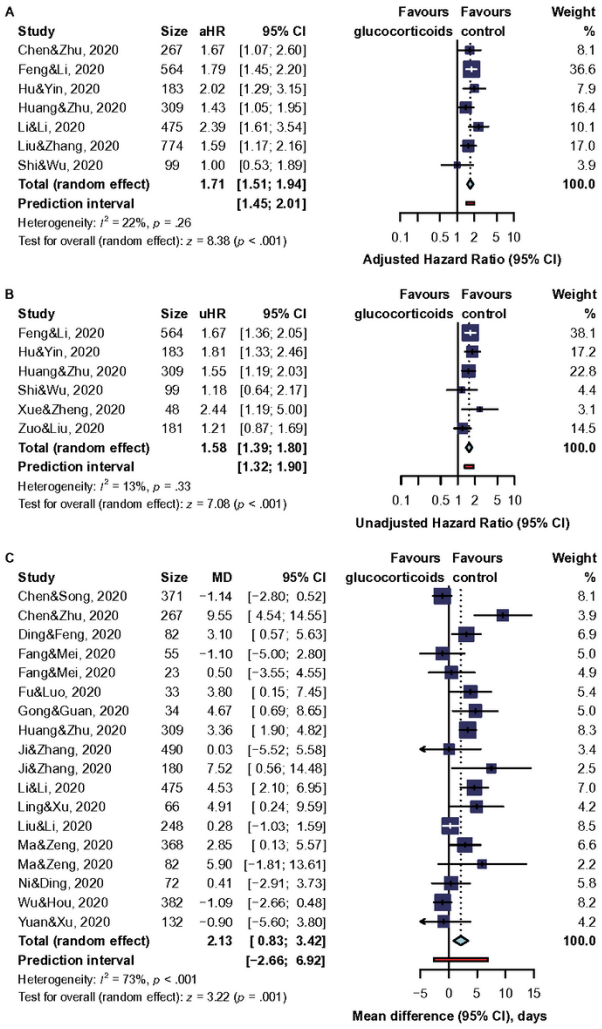

Figure 2

Forest Plot of Hazard Ratios and Mean Differences for Risk of Viral Clearance Delay

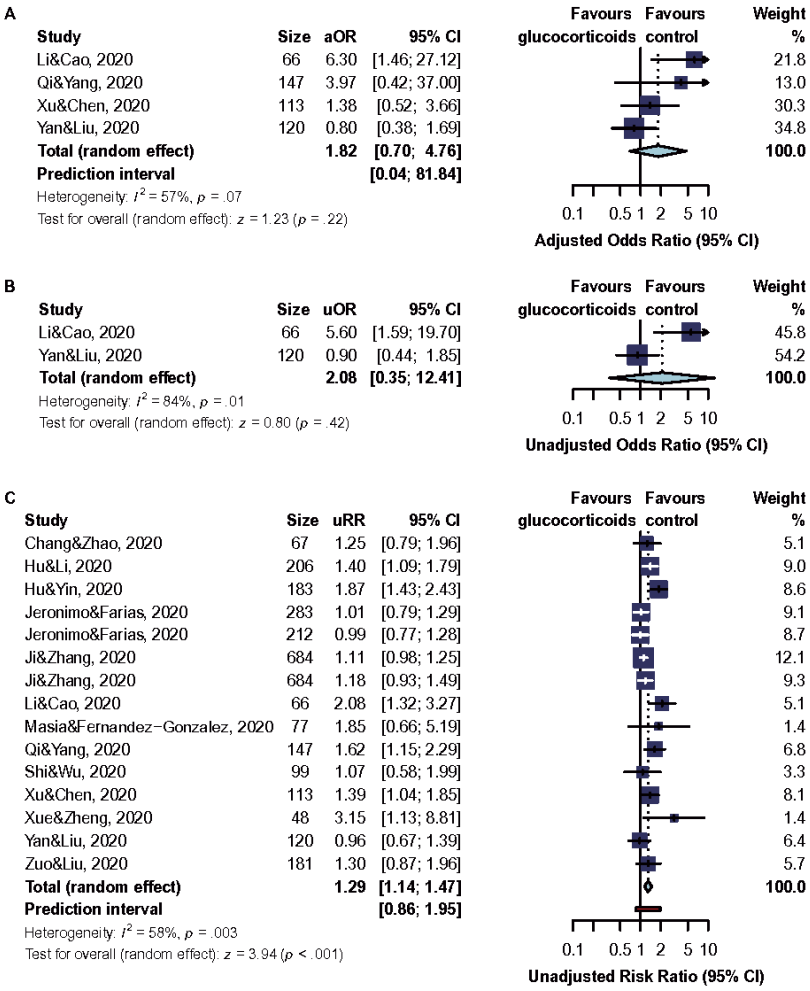

Figure 3

Forest Plot of Odds Ratios and Risk Ratios for Risk of Viral Clearance Delay

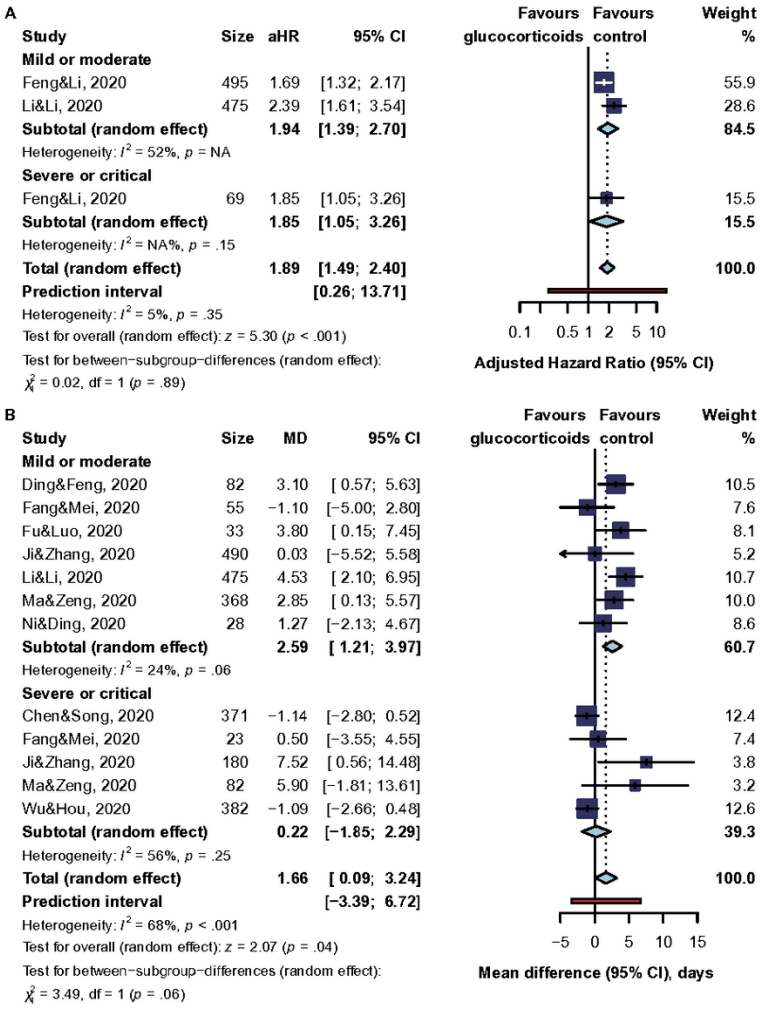

Figure 4

Subgroup Analysis by Severity of Illness

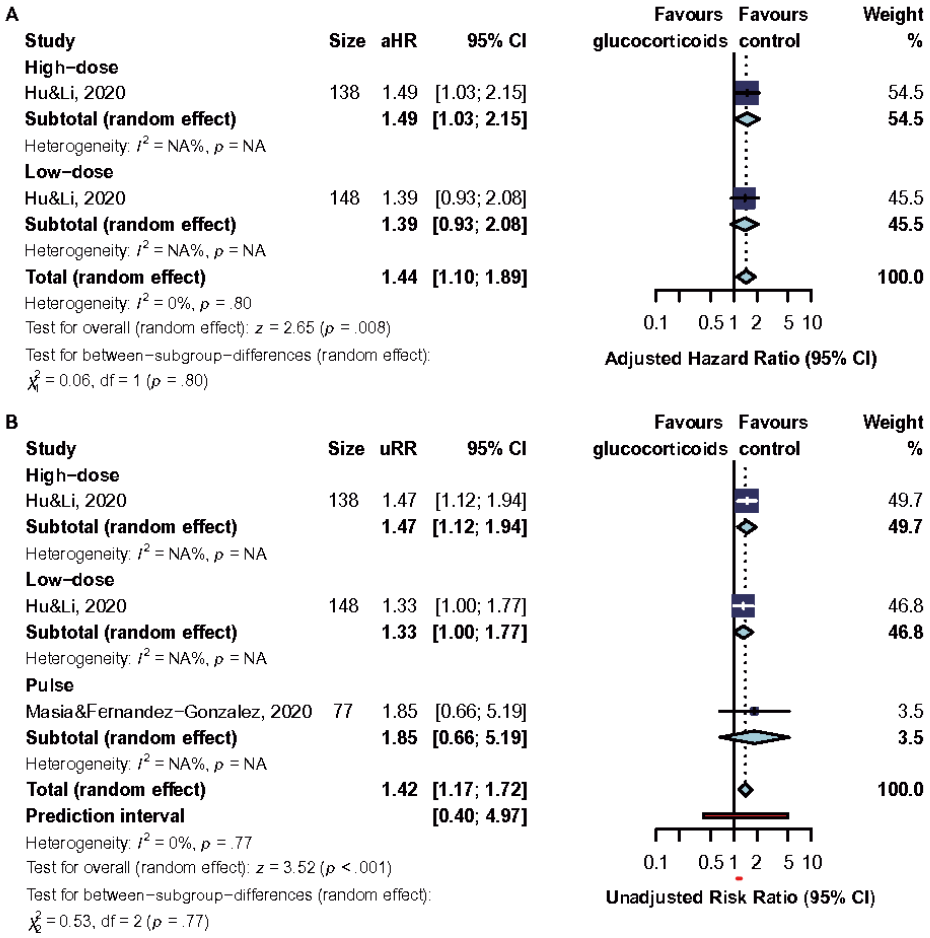

Figure 5

Subgroup Analysis by Doses of Glucocorticoids

Supplementary Files

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- SFig2.SensitivityAnalysesExcludingSmallestSample.pdf
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