Prophylactic Use of Glucocorticoids and Postoperative Delirium/Cognitive Dysfunction in Adults After Major Surgery: a Meta-Analysis of Randomized Controlled Trials

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Research

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Abstract

Objectives. To investigate whether prophylactic use of glucocorticoids (GCs) would affect the incidence of postoperative delirium (POD)/cognitive dysfunction (POCD) after major surgeries.

Methods. A systemic review of randomized controlled trials (RCTs) searched from the Pubmed, Cochrane Library, Embase, and Clinical Trials.gov was conducted. Effect of GCs on the incidence of POD/POCD and several secondary outcomes, including s100-β, mechanical ventilation time, length of ICU stay, length of postoperative hospital stay, postoperative cardiac arrhythmia, and adverse outcomes, were analyzed. The Cochrane Collaboration's risk of bias tool and the GRADE system were used to assess the risk of bias of included studies and the evidence quality of combined results, respectively.

Results. There were 726 records detected and only 11 studies were included at last. Six of the 11 RCT studies were categorized as low risk of bias, 3 studies as unclear, and 2 as high. Prophylactic use of GCs didn't show any significant effect on the incidence of POD/POCD after major surgeries, but the evidence quality of this result was very low. For the secondary outcome, GCs can significantly decrease the level of s100-β, length of ICU stay, length of postoperative hospital stay, and ventilation time, with the evidence quality varied from very low to moderate. For the rest of the secondary outcomes, no significant effect was observed.

Conclusion. Prophylactic use of GCs didn't have a significant effect on the incidence of POD and POCD. However, this result was very uncertain, and more relevant high-quality RCTs are needed.

Background

Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are common adverse cerebral outcomes of patients in surgical intensive care units (ICU). The incidence of POD and POCD varied by type of surgery and procedure risk. Previous studies reported that POD has a prevalence range from 3–62%, while the incidence of POCD is reported to be 26%-80% a few weeks after surgery [1, 2, 3]. The occurrence of POD/POCD is associated with increased mortality, reduced quality of life, and significantly increased use of healthcare resources(Sanson, et al. 2018). The precise etiologies of POD and POCD are yet to be understood, the neuroinflammatory response may play an important role. Surgical operations can elicit a stress response and induced inflammation reaction. It is believed that inflammation can cause blood-brain barrier and endothelial injury, activate the microglial cell, and furtherly lead to neurotransmitter imbalances and structural changes [1, 2].

As neuroinflammation may be critical for the development of POD and POCD, inhibiting inflammation may help to prevent the occurrence of POD and POCD. Glucocorticoids (GCs), a steroid hormone that has a strong effect of anti-inflammation and immune-modulation, may appeal as a treatment option for POD and POCD. The inflammatory response during and after major surgery can be antagonized with the administration of GCs according to multiple studies(Holte and Kehlet 2002). And three major types of GCs include dexamethasone (DEX), methylprednisolone (MP), and hydrocortisone, which have similar yet not identical pharmacological effects. It's noteworthy that the potential side effects of GCs also raise concern. For patients who underwent surgery, postoperative infection, delayed wound healing, and some other complications, may limit the value of GCs in these patients [5, 6]. Besides, neuropsychological symptoms are not rare among patients treated with long-term and/or high doses of glucocorticoids for other medical conditions. Previous studies reveal that psychiatric complications of GCs treatment can include anxiety, insomnia, delirium, and dementia [7].

A previous meta-analysis suggests that administration of GCs can decrease postoperative atrial fibrillation and mortality, and without a significant increase of side effects [8], but definitive evidence is lacking as only small trials involved. And several previous meta-studies also have assessed the effect of GCs on POD, but the results were inconsistent [9, 10]. It's still not clear whether the prophylactic administration of GCs would be beneficial or not, especially for the prevention of POD and POCD.

Therefore, we performed a systemic review and meta-analysis of random controlled trials (RCTs). The main object of our study was to investigate whether prophylactic use of glucocorticoids would affect the incidence of POD/POCD after major surgeries.

Methods

Inclusion and exclusion criteria

We included studies that met the following eligibility criteria: (1) adults (≥18 years old) who underwent major surgery; (2) pre-operative or intra-operative administration of intravenous glucocorticoids including DEX, MP or hydrocortisone in order to prevent POCD and POD regardless of the dosage; (3) randomized controlled trials; (4) primary or secondary outcome including the incidence of POCD and/or POD. Studies were excluded if: (1) full text in English not available; (2) incidence of POCD or POD not assessable; (3) GCs administered by another route.

Search strategy

Literatures collected in PubMed, EMBASE and Cochrane database were searched up to May 8, 2020. This process was finished by two reviewers (Yan X and Yang L) independently. The detailed search strategy is listed in Appendix. Reference lists of included studies and relevant reviews were hand searched to supplement the electronic search. We didn't include abstract and unpublished studies.

Endpoints

The primary outcome of this meta-analysis was the incidence of POD or POCD. Secondary outcomes included serum S100β levels, mechanical ventilation time, length of ICU stay, length of postoperative hospital stay, postoperative cardiac arrhythmia, and adverse outcomes.

Data extraction and risk of bias assessment

Two authors (Yan X and Yang L) evaluated the quality of all included studies by examining patient selection, comparability of interventions and control groups, and assessment of outcomes. All data were extracted from article texts, tables, and figures. The quality of included trials was evaluated based on the Cochrane Risk of Bias Methods according to the following criteria: random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For each item, the answer of “yes” indicates low risk of bias, “no” indicates high risk of bias, and “unclear” indicates unknown risk of bias [11].

Overall assessment of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to assess the evidence grade of the main and secondary outcomes. GRADE pro software(version3.6) was used to conduct this procedure. The GRADE system classifies the quality of evidence into four levels: (1) High quality, which means that further research is very unlikely to change the confidence in the estimate of effect; (2) Moderate quality, which means further research is likely to have significant effect on the confidence and may change the estimate; (3)Low quality, which means further research is very likely to have an important effect on the confidence in the estimate of effect and is likely to change the effect;(4) Very low quality, which means that any estimate of effect is very uncertain. Evidence quality based on RCTs begins with high-quality, but several reasons, including study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias, may decrease the confidence in the evidence. The GRADE system also offers two grades of recommendations, including “strong” and “weak”, which is based on the quality of evidence [12].

Assessment of heterogeneity and data synthesis

We used Mantel-Haenszel fixed or random-effects models to produce across-study summary relative risk (RR) with a 95% confidence interval (95% CI). The pooled effects were calculated using a fixed effect model when there was no significant heterogeneity, while the random effects model was chosen when significant heterogeneity was observed. The Chi-square test was used to evaluate heterogeneity between trials, and the I^2 statistic was used to estimate the percentage of total variation across studies. I^2 value greater than 50% was considered as having significant heterogeneity. When there was significant heterogeneity, subgroup analysis would be conducted trying to explain the source of heterogeneity. Egger’s and Begg’s statistical tests were used to assess the publication bias. And sensitivity analysis was used to test the stability of the results. The Review Manager (version 5.3) software would be used to finish relevant statistical analysis.

Results

Study selection and characteristics

There were 726 records identified from database searches. After removing duplicates and articles that obviously not related to our topic, 31 studies were full-text reviewed for potential exclusion in the review. At last, 11 eligible studies [13-23], all of which were placebo-controlled trials, were included in the meta-analysis after full-text reviewing (Figure 1.). Three of the 11 studies were multicentric, while the rest 8 studies were mono-centric. The years of publication were between 2012 and 2018, the samples sizes were 30-7507, and mean ages ranged from 48.0-80.0. Surgery types consisted of cardiac (CABG, and/or valve surgery), orthopedic, thoracic, neurosurgery, and other non-cardiac and non-neurological surgeries under general anesthesia. GCs used in these trials included DEX (n=7), MP (n=3) and hydrocortisone (n=1). Three studies compared GCs therapy with no intervention and the other studies compared GCs therapy with placebo. Ten studies evaluated the incidence of main outcomes, while 8 studies provided the results of secondary outcomes. Detailed characteristics of each study were shown in Table 1.

Risk of Bias in the included trials

As Figure 2. shows, six of the 11 RCT studies were categorized as low risk of bias, 3 studies as unclear, and 2 as high. Double-blinding was implemented in 8 studies, and 3 had no information of masking. The high risk of bias was mainly caused by inadequate allocation concealment, incomplete outcome data, and selective reporting. Random sequence generation was adequate in 9 studies, while the rest studies reported no information of it. Allocation concealment was adequate in 8 studies, inadequate in one study, and could not be assessed 2 studies. Double-blinding was implemented in 8 studies, and 3 had no information of masking.

Incidence of POD/POCD

Ten RCTs reported data to explore whether prophylactic use of glucocorticoids would affect the incidence of POD/POCD after major surgeries. As shown in Figure 3, POD occurred in 524 of 6148 (8.5%) patients randomized to intravenous GCs and 595 of 6162 (9.7%) patients randomized to placebo or without GCs. And no significant difference was observed between the two groups (RR=0.80; 95%CI, 0.61-1.04; P=0.09; I^2=64%), which indicated that the use of GCs failed to affect the incidence of POD after major surgeries. When considering the incidence of POCD, 208 of 938 (22.2%) patients randomized to intravenous GCs and 140 of 625 (22.4%) patients randomized to placebo or without GCs were defined to have POCD. Pooled random effect (RR=0.77; 95%CI, 0.41-1.46; P=0.42; I^2=81%) revealed that prophylactic use of GCs failed to show a significant effect on POCD. Results

of the GRADE system (Table 2) revealed that the evidence quality of these results was very low, indicating that our estimates of effect were very uncertain.

Considering the high level of heterogeneity, random-effects model was chosen to show the results. To explore the source of heterogeneity, subgroup analysis was carried out according to type and dose of GCs, medication time, surgery type, the average age of patients, and risk of bias. When the datasets were categorized by medication time (Figure 4a), we found that prophylactic use of GCs before induction of anesthesia had a clear protective effect on POD (RR=0.57; 95%CI, 0.35-0.95; P=0.03; I^2=17%). For patients average-aged larger than 65 years (Figure 4b), prophylactic use of GCs also had protective effect on POCD (RR=0.42; 95%CI, 0.25-0.69; P=0.0007; I^2=0%).Besides, P-value for subgroup difference of age was less than 0.05, indicating that the average age of patients may partly explain the source of heterogeneity in the POCD result. However, the results of other subgroup analyses failed to explain the source of heterogeneity.

Secondary outcome

S100-β Four studies documented the level of S100-β. As the result shown in Figure 5a, there was no significant difference on the level (MD=-0.01; 95%CI, -0.02-0.00; P=0.06; I^2=48%), indicating that GCs can't change the level of S100-β significantly. And the evidence quality of S100-β was ranked as moderate (Table 2).

Length of postoperative ICU stay and length of postoperative hospital stay There were 6 and 5 studies with data of postoperative ICU stay and hospital stay, respectively. As Figure 5b and 5c show, prophylactic use of GCs can significantly reduce the length of postoperative ICU stay by an average of 4.73 hours (MD=-4.73; 95%CI, -8.71–0.74; P=0.02; I^2=81%) and the length of postoperative hospital stay by an average of 0.16 days(MD=-0.16; 95%CI, -0.31--0.01; P=0.04; I^2=50%). However, results of the GRADE system revealed that the evidence quality of postoperative ICU stay was very low, while the evidence quality for postoperative hospital stay was moderate (Table 2).

Length of postoperative mechanical ventilation Five studies reported the length of postoperative mechanical ventilation (Figure 5d). A significant difference between the two groups was observed (MD=-0.49; 95%CI, -0.72–0.26; P<0.0001; I^2=0%), which shows a significant effect of GCs on mechanical ventilation time. The evidence quality of this result was ranked as low (Table 2).

30-day mortality Only three studies reported 30-day mortality (Figure 5e). The fixed combined results revealed that prophylactic use of GCs had no significant effect on 30-day mortality (RR=0.88; 95%CI, 0.73-1.06; P=0.19; I^2=0%). The evidence quality of this result was ranked as moderate (Table 2).

Postoperative cardiac arrhythmia Most of the studies involved were related to cardiac surgery. For patients who underwent cardiac surgery, 4 studies reported the event of cardiac arrhythmia (Figure 5f). Prophylactic use of GCs wouldn't increase nor decrease the risk of postoperative cardiac arrhythmia (RR=0.96; 95%CI, 0.90-1.01; P=0.13; I^2=33%). For this result, the evidence quality was categorized as moderate (Table 2).

Adverse effect We also explored the adverse effect of GCs. The incidence of postoperative infection was evaluated and 5 studies reported relevant data. As shown in Figure 6, prophylactic use of GCs wouldn't increase the risk of postoperative infection significantly (RR=0.81; 95%CI, 0.60-1.09; P=0.16; I^2=78%). Evidence quality of postoperative infection was ranked as very low (Table 2).

Table 1
Main characteristics of included studies.

Author, year	Country	Age (mean,SD, years)	Surgery type	No. of Participants		Main outcome and method for accessing	main outcome incidence, No. (%)	
				intervention	control		intervention	control
Clemmesen, 2018	Denmark	80.0 ± 8.5	hip fracture surgery	59 (MP, 125 mg iv, preoperative)	58 (NS, equal volume, iv, preoperative)	POD (CAM-S)	10(16.9)	19(32.8)
Dieleman, 2012	Netherlands	66.1 ± 10.8	cardiac surgery	2235(DEX, 1 mg/kg iv, maximum100mg intraoperative)	2247(NS, equal volume, iv, intraoperative)	POD (indication for treatment with neuroleptic drugs)	205(9.2)	262(11.7)
Danielson, 2018	Sweden	69.8 ± 9.1	cardiac surgery	15(MP,15 mg/kg iv, intraoperative)	15(NS,equal volume iv, intraoperative)	POCD (unknown)	1(6.7)	2(13.3)
Fang, 2014	China	48.3 ± 5.7	microvascular decompression	635(DEX, 0.1or 0.2 mg/kg iv, preoperative)	319(NS, equal volume, iv, preoperative)	POCD (test battery composed of 7 tests)	165(26.0)	71(22.2)
Glumac, 2017	Croatia	64.0 ± 9.2	cardiac surgery	80(DEX, 0.1 mg/kg iv, preoperative)	81(NS, equal volume, iv, preoperative)	POCD (test battery composed of 5 tests)	9(11.3)	21(25.9)
Hauer, 2012	Germany	68.7 ± 8.6	cardiac surgery	56(Hydro, 100 mg iv preoperative→10 mg/h iv for 24 h, POD1→5 mg/h iv for 24 h, POD2→20 mg tid iv, POD3→10 mg tid iv, POD4)	55(without Hydro)	POD(DSM-IV)	7(12.5)	6(10.9)
Mardani, 2013	Iran	62.1 ± 11.8	Cardiac surgery	43(DEX,8 mg iv preoperative and 8 mg q8h iv. for the first three postoperative days)	50(NS,8 mg iv preoperative and 8 mg q8h iv. for the first three postoperative days)	POD (MMSE and DSM-IV)	7(16.3)	19 (38.0)
Ottens, 2014	Netherlands	64.4 ± 11.9	cardiac surgery	140(DEX, 1 mg/kg iv,maximum 100 mg, intraoperative)	138(NS, equal volume, iv, intraoperative)	POCD (test battery composed of 5tests)	19(13.6)	10(7.2)
Qiao, 2015	China	68.5 ± 3	resection of esophageal carcinoma	30(MP,10 mg/kg, preoperative)	30(without MP)	POCD (MMSE and MoCA)	/	/
Valentin, 2016	Hungary	68.2 ± 6.1	noncardiac and non-neurologic surgery	68(DEX,8 mg iv, preoperative)	72(without DEX)	POCD (TICS)	14(20.5)	36(50)

CAM, Confusion Assessment Method; DEX, Dexamethasone; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; Hydro, Hydrocortisone; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; MP, Methylprednisolone; NS, normal saline; POCD, Postoperative Cognitive Deficit; POD, Postoperative delirium; TICS, Telephone Interview for Cognitive Status;

Author, year	Country	Age (mean,SD, years)	Surgery type	No. of Participants		Main outcome and method for accessing	main outcome incidence, No. (%)	
				intervention	control		intervention	control
Whitlock, 2015	Canada	67.4 ± 13.7	cardiac surgery	3755(MP,250mg + 250 mg iv, intraoperative)	3752(NS, equal volume, iv, intraoperative)	POD(CAM)	295(7.9)	289(7.7)

CAM, Confusion Assessment Method; DEX, Dexamethasone; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; Hydro, Hydrocortisone; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; MP, Methylprednisolone; NS, normal saline; POCD, Postoperative Cognitive Deficit; POD, Postoperative delirium; TICS, Telephone Interview for Cognitive Status;

Discussions

In this meta-analysis, our main goal was to assess whether prophylactic use of GCs would affect the incidence of POD/POCD after major surgeries. The results of our study including 10 RCTs showed that GCs did not significantly change the incidence of POD and POCD. However, prophylactic use of GCs can significantly reduce the length of postoperative ICU stay, the length of postoperative hospital stay, and the mechanical ventilation time, while it also failed to show a significant reduction in s100-β and 30-day mortality.

Two previous meta-studies, conducted by Liu *et al* [10] and Tao *et al* [9], have reported the effect of GCs on POD. In Liu's study, both MP and DEX were found to have no significant effect on POD. Consistent with Liu's results, our results also revealed that GCs didn't show the ability to prevent POD after major surgery. However, a significant effect of DEX on POD was found in Tao's meta-analysis. This inconsistency may be caused by the difference in included studies. In Tao's study, only 3 RCTs were included. Among the three studies, the study conducted by Sauer *et al* [24] was the substudy of another study conducted by Dieleman *et al* [13]. It's inappropriate to involve both of the two studies in one meta-analysis, which may cause the imprecision of the combined results. This problem also existed in Liu's study when assessing the effect of MP on POD [19, 25]. For meta-analysis, checking the duplication of data and involving articles properly are both important to get an accurate and valid result.

POD and POCD are common complications of major surgery, especially for elderly people [1, 2]. And we found that GCs can significantly reduce the incidence of POCD on patients average-aged larger than 65 and a significant difference between age subgroups was observed, indicating that age may be an important factor affecting the result. We also found that administration of GCs before induction of anesthesia showed a positive result, thus medication time may also affect the result. This may remind that the timing of GCs administration might be of critical importance, and administration GCs after induction of anesthesia may be too late to benefit because the onset of GCs action needs generally 1to 2 hours, and the inflammation is activated immediately after the incision [5]. It's noteworthy that both the two positive results were combined by 2 or 3 small sample size studies and 2 studies involved even showed a high risk of bias, thus the validities of the two results were very limited.

S100-β, which is considered as a biomarker of acute brain injury, may have an association with POCD [26]. Our result showed that prophylactic use of GCs had no significant effect on the serum level of s100-β, which is consistent with the result of POCD. This consistence may provide support for the validity of the POCD result. POD and POCD can impact patient health and are always associated with prolonged ICU and hospital stay, greater mortality and morbidity, and delays in functional recovery. Although we didn't find the significant effect of GCs on the incidence of POD and POCD, we did find the positive effect of GCs on the length of postoperative ICU stay, the length of postoperative hospital stay, and the mechanical ventilation time. As POD and POCD are not the only risk factor of these outcomes, GCs may positively affect these results through some other mechanisms. For the results of 30-day mortality and postoperative cardiac arrhythmia, both showed no significant effect. The difference between our results reminds us that, for patients who underwent major surgery, whether GCs are beneficial, ineffective, or even detrimental, are not clear and need more study to solve this problem. Besides, our results of secondary outcome also had some inconsistence with a previous meta-analysis conducted by Whitelock *et al* [8]. Only small trials were included in Whitelock's study, which may cause the inconsistence.

GCs has a strong effect on inflammation inhibition and immunosuppression, which may increase worrying about the risk of infection. Our result revealed that prophylactic use of GCs would not increase the risk of postoperative infection and this result is consistent with Whitelock's study [8]. However, the evidence quality of this result was very low, limiting the value of our result.

Notably, substantial heterogeneity was detected in this meta-analysis and subgroup analysis failed to find the source of heterogeneity. As stated above, patient's age may be the source of heterogeneity to some extent. Besides, we found that the cognitive tests used and the time of postoperative assessment varied in studies involved in our study. As the incidence of POD and POCD varies depending on the cognitive performance tests, time of postoperative assessment, and the limitations of specificity and sensitivity of the current cognitive tests, the variance may partly explain the source of heterogeneity. However, subgroup analysis based on different cognitive tests and time of assessment can't be achieved to confirm our conjecture.

Some other limitations also existed in our study. First, the evaluation of POD and POCD are varied and have subjectivity, which may cause deviation of the real situation. Second, most of the studies involved had small sample sizes, especially for the result of POCD, which furtherly limited the value of our study. Third, the number of involved studies for each main outcome was small, thus we didn't analyze sensitivity and publication bias. Besides, some secondary outcomes, like postoperative infection and cardiac arrhythmia, didn't have clear definitions in most of the included studies, making the track of events risks under-reporting. Even we rigorously involved RCTs only in our study, the value of our study was still limited. GRADE system

revealed that our results of the main outcome and several results of secondary outcome showed low or very low-quality evidence, thus we can't make a definitive conclusion due to the lack of high-quality evidence. More high-quality RCTs are needed to elucidate relevant problems.

Conclusions

In conclusion, prophylactic use of GCs didn't have a significant effect on the incidence of POD and POCD. However, this result was very uncertain, and more relevant high-quality RCTs are needed.

List Of Abbreviations

CAM, Confusion Assessment Method; DEX, Dexamethasone；DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; MP, Methylprednisolone; Hydro, Hydrocortisone; GCs, Glucocorticoids; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICU, Intensive Care Unit; MD, Mean Difference; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; NS, normal saline; POCD, Postoperative Cognitive Dysfunction; POD, Postoperative Delirium; RCTs, Randomized Controlled Trials; TICS, Telephone Interview for Cognitive Status.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

All relevant data in this study are freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality. And relevant data can be obtained by contacting the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yan X contributed to study design, literature search, data extraction and combination, study quality and evidence quality assessment, and drafting and revisions of the manuscript.

Yang L contributed to literature search, data extraction and study quality and evidence quality assessment.

Yi L contributed to consensus making, drafting and revision of the manuscript.

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Tables

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

Figures

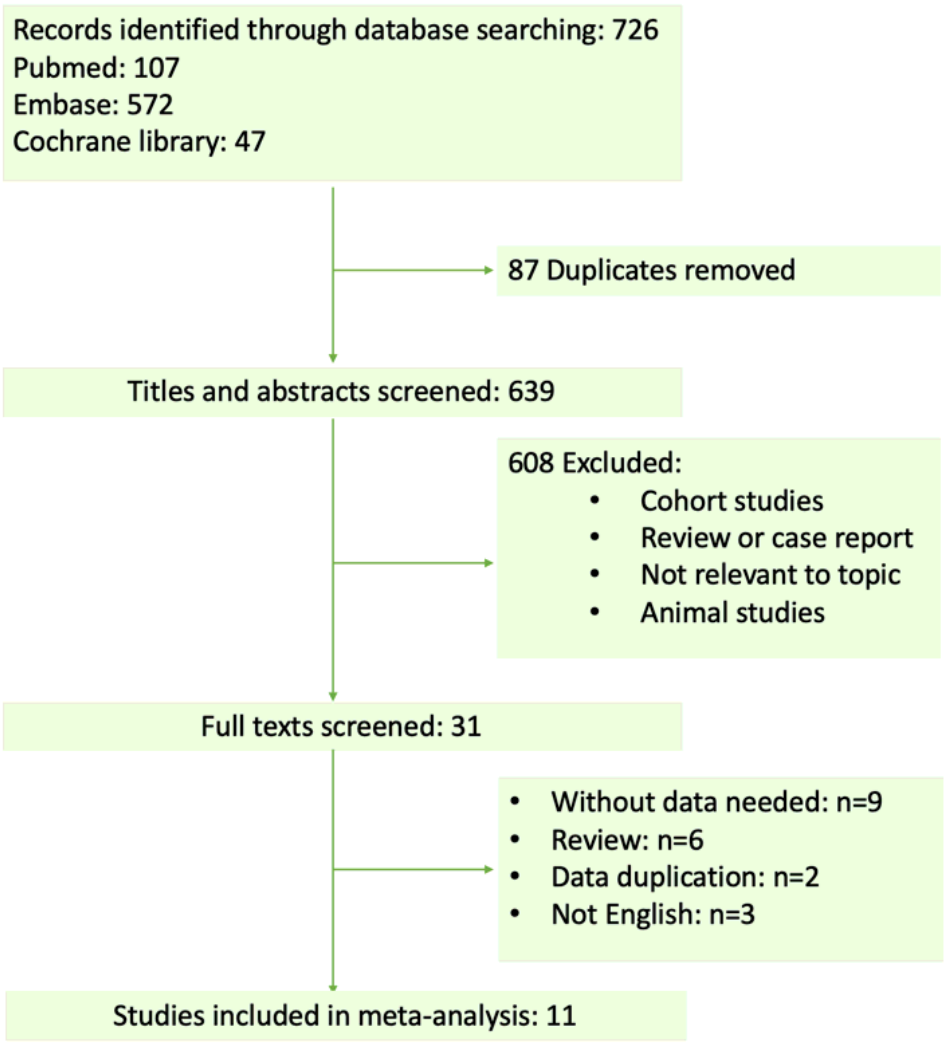


Figure 1

Flow chart of study selection

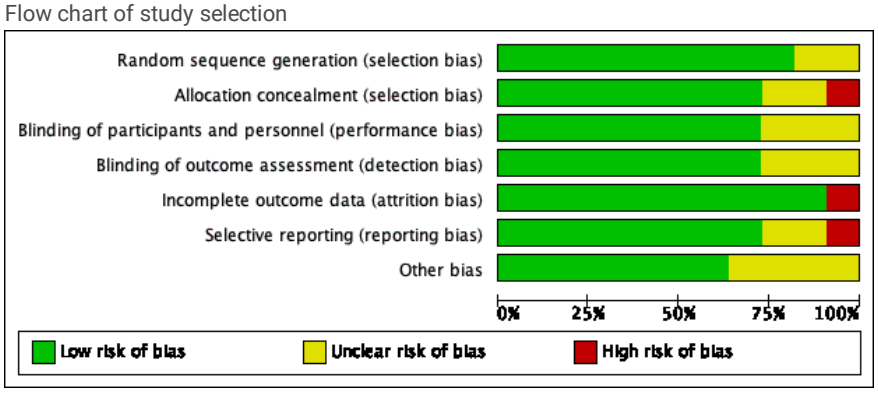


Figure 2

Risk of bias summary of included RCTs

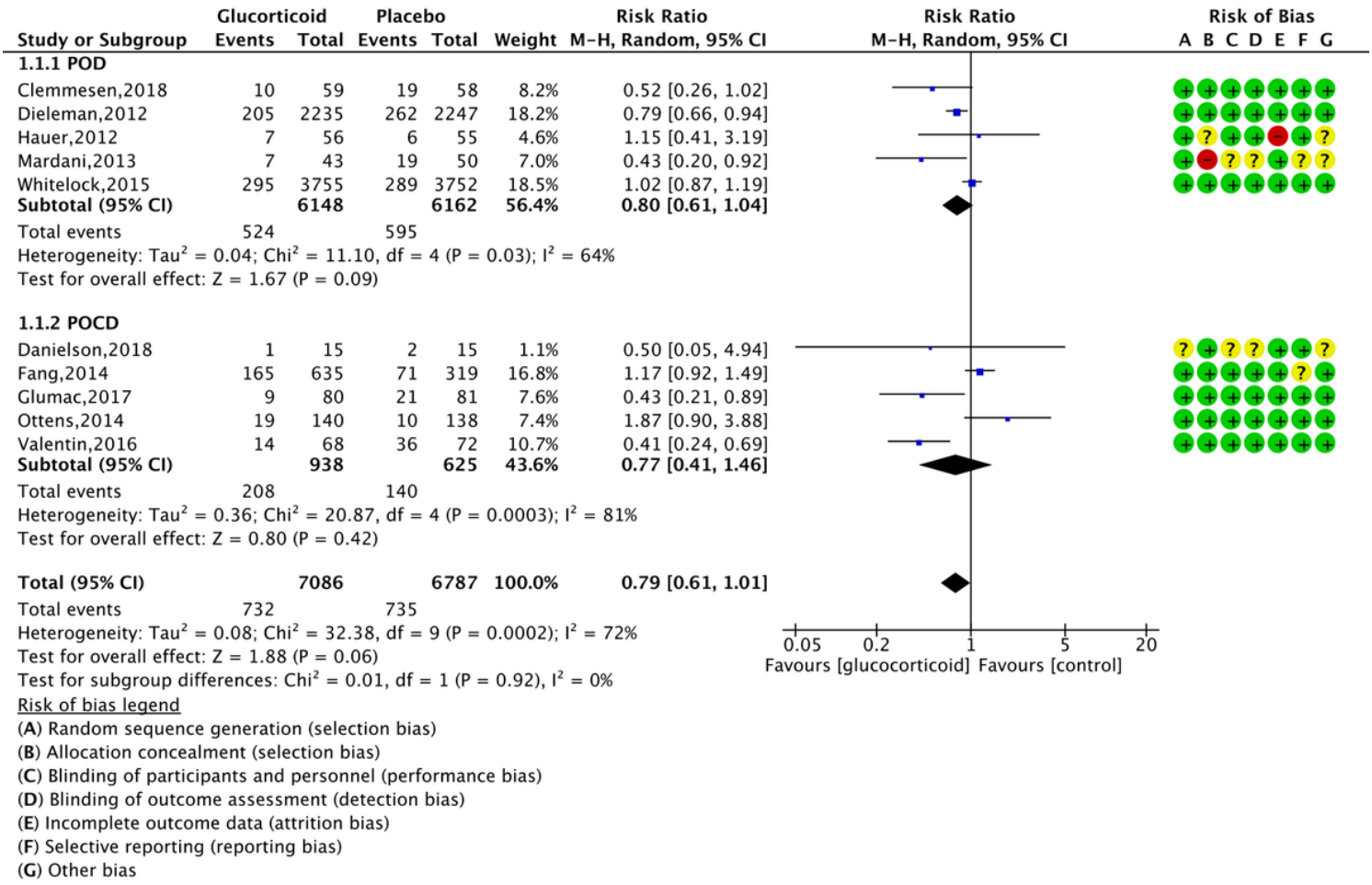


Figure 3

Forest plot for the meat-analysis of GCs' impacts on the incidence of POD and POCD

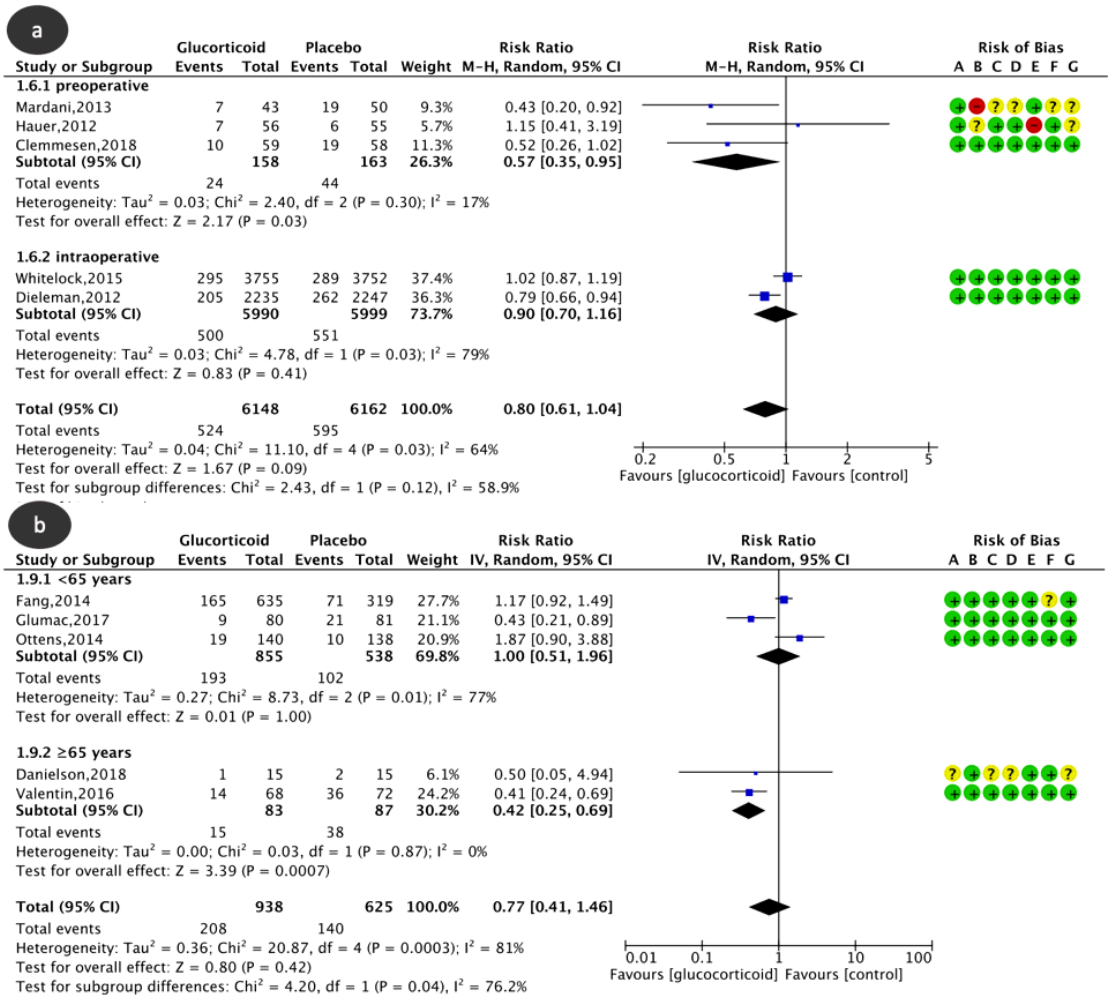


Figure 4

Forest plot of subgroup analysis (a) The incidence of POD stratified according to medication time; (b) The incidence of POCD stratified according to average age of patients.

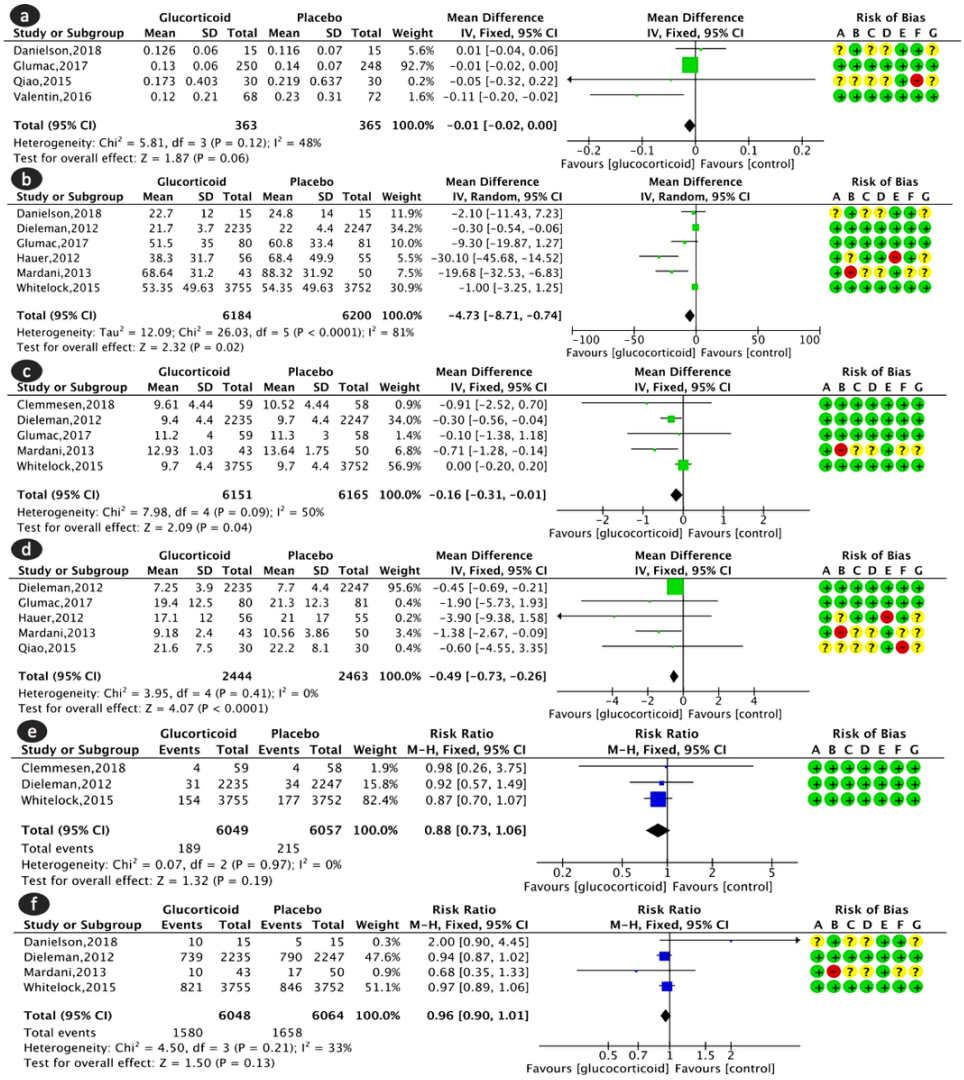
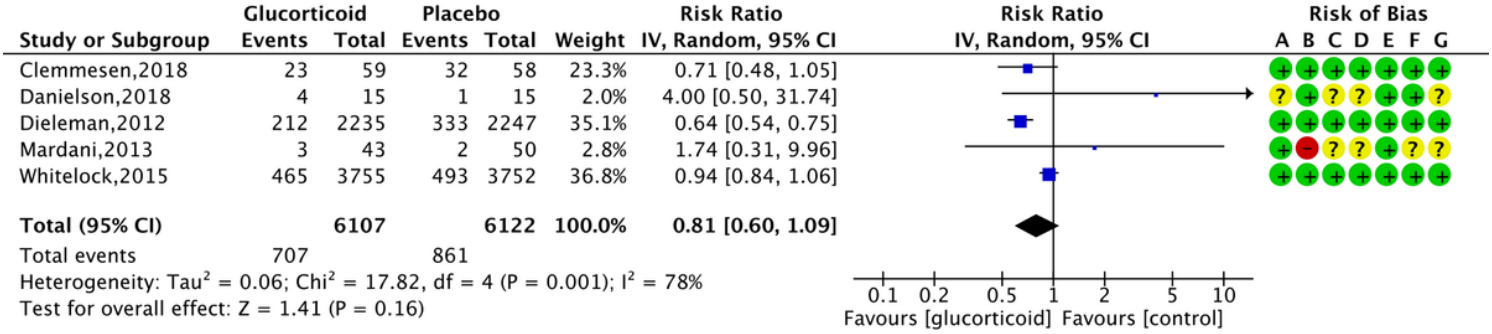


Figure 5

Forest plot for the meat-analysis of GCs' impacts on secondary outcomes (a) S100-β; (b) Length of postoperative ICU stay; (c) Length of postoperative hospital stay; (d) Length of postoperative mechanical ventilation;(e) 30-day mortality; (f) Incidence of postoperative cardiac arrhythmia



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 6

Forest plot for the meat-analysis of GCs' impacts on the incidence of postoperative infection

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.JPG
- Table2.JPG