Systematic Review Article

The impact of preoperative corticosteroids on the systemic inflammatory response and postoperative complications following surgery for gastrointestinal cancer: a systematic review and meta-analysis

Disclosure/Conflict of Interest/Funding: none

Keywords: gastrointestinal cancer, corticosteroids, postoperative complications, morbidity, stress response

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Highlights

- Systematic review and meta-analysis of preoperative corticosteroids in surgery for GI cancers
- Reports significant association between preoperative corticosteroids and lower postoperative IL-6 and CRP
- The relationship between corticosteroids and lower postoperative systemic inflammatory response may underpin the impact on postoperative complications

Keywords

gastrointestinal cancer, corticosteroids, postoperative complications, morbidity, stress response

Vitae:

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Abstract

Background:

This meta-analysis examined the impact of preoperative corticosteroids on interleukin 6 (IL-6), C-reactive protein (CRP), and complications following surgery for gastrointestinal cancer.

Methods:

A systematic review was performed using appropriate keywords. Random-effects meta-analysis was performed.

Results:

11 RCTs with 474 patients, were included. Corticosteroids were significantly associated with lower IL-6 on postoperative day 1 (mean difference -148 pg/mL, 95% CI -205 to -92, p<0.001), 2 (-33 pg/mL, 95% CI -58 to -8, p=0.01), and 3 (-31 pg/mL, 95% CI -52 to -11, p=0.002), lower CRP on day 3 (-45 mg/L, 95% CI -68 to -21, p<0.001), and 7 (-14 mg/L, 95% CI -27 to -1, p=0.04), and fewer postoperative infective complications (OR 0.47, 95% CI 0.26 to 0.83, p=0.01).

Conclusion:

Corticosteroids were associated with reduction in the postoperative systemic inflammatory response and complications following surgery for gastrointestinal cancer.

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1. Introduction

Surgery leads to a predictable metabolic, neuroendocrine and immunological response [1-2]. Activation of the sympathetic nervous system leads to the release of catecholamines which induce tachycardia, hypertension and tachypnoea [3]. The cellular response to surgical trauma involves the production of pro-inflammatory cytokines including tumour necrosis factor (TNF) alpha, interleukin (IL) 1, IL-6, and IL-8 [4-5]. Such cytokines act to mobilise the innate immune system, resulting in the activation of neutrophils, macrophages and platelets, causing fever and contributing to nausea. Circulating pro-inflammatory cytokines also act on hepatocytes, altering the synthesis of the acute phase proteins, such as C-reactive protein (CRP), albumin, fibrinogen and constituents of the complement cascade [6].

Postoperative IL-6 and CRP concentrations in particular, have been found to be useful markers of the magnitude of the surgical injury [7]. The magnitude of this postoperative systemic inflammatory response, and in particular the routinely available CRP, is associated with the development of complications following colorectal surgery, oesophagectomy and liver resection [8-10]. Furthermore, threshold concentrations of CRP have been established, in the postoperative period, (190 mg/L on postoperative day 2, 170mg/L on postoperative day 3 and 145 mg/L on postoperative day 4), which predict the likelihood of developing or not developing infective complications and anastomotic leak [11-12].

The magnitude of this postoperative systemic inflammatory response and its relationship with postoperative complications is of particular interest in the context of surgery for gastrointestinal cancers. Previous studies have demonstrated an association between postoperative complications, particularly infective complications, and poorer long-term and oncologic outcomes following surgery for gastrointestinal cancer [13-14]. Indeed, it has been suggested that the magnitude of the postoperative systemic inflammatory response should

prompt further investigation to exclude the development of a postoperative infective complication [15]. Furthermore, the upcoming PRECious trial (NCT02102217) aims to randomize patients to early CT imaging or standard postoperative care if CRP rises above 140mg/L on postoperative day 3 to 5 following abdominal surgery [16].

Given the relationship between the magnitude of the postoperative systemic inflammatory response, the development of postoperative complications, and long-term outcomes, there is increasing interest in the attenuation of this postoperative stress response. Preoperative corticosteroids are a logical choice of intervention given their potential potency and duration of effect [17-18]. Indeed, preoperative corticosteroids have been used as they have been found to reduce postoperative nausea and vomiting and analgesic requirements following abdominal surgery [19-20]. A recent meta-analysis reported that preoperative corticosteroids significantly reduced postoperative day one IL-6, postoperative complications, infective complications, and length of stay following abdominal surgery [21]. Preoperative corticosteroids have also been reported to reduce postoperative IL-6 and complication rates following liver resection and oesophagectomy in meta-analyses of small numbers of studies [22-24]. To our knowledge, no prior meta-analysis has investigated comprehensively the impact of preoperative corticosteroids on the postoperative surgical stress response following surgery for gastrointestinal cancer. The present meta-analysis is the first to examine their impact on CRP. Both IL-6 and CRP are objective measures of the magnitude of the systemic inflammatory response to surgery, however CRP is more readily available in the clinical setting [7]. Furthermore, no meta-analysis has attempted to assess the dose response between preoperative corticosteroids and the magnitude of the postoperative systemic inflammatory response and postoperative complication rate.

Therefore the objective of the present systematic review and meta-analysis was to examine the impact of preoperative corticosteroids compared to placebo in the context of

randomized controlled trials, on the surgical stress response, in particular postoperative IL 6 and CRP, and their relationship with the development of infective complications, following surgery for gastrointestinal cancers.

2. Methods

The present systematic review and meta-analysis was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Digital Content 1 – PRISMA Checklist.docx) [25].

2.1 Outcomes of interest:

The primary outcome of interest was the impact of single dose preoperative corticosteroids on markers of the postoperative stress response following surgery for gastrointestinal cancer, in particular IL-6 and CRP. Those studies reporting chronic preoperative corticosteroid use or dosing at other perioperative time points were excluded. Secondary outcomes included the impact of preoperative corticosteroids on postoperative complications, infective complications, and anastomotic leak following surgery for gastrointestinal cancer, including pre-specified subgroup analysis based on surgical speciality/site. Postoperative complications were coded as categorised by the authors of the included studies where possible. Where there was doubt the authors of the present study categorised complications using a schemata described previously [26]. Post hoc meta-regression of the impact of corticosteroid dose on postoperative day 1 IL-6 was performed following completion of the pre-specified analyses. Study selection and data extraction was performed by one author (SM) and any uncertainties resolved by consensus discussion with the senior authors (PH, DM).

2.2 Literature search and study selection:

A systematic literature review was performed of the US National Library of Medicine (MEDLINE), PubMed, and the Cochrane Database of Systematic Reviews (CDSR) from inception to March 2015 inclusive. Subsequent to several pilot search strategies the following search term was used, "(cancer OR malignan* OR tumour OR tumor OR neoplasm*) AND (steroid OR corticosteroid OR glucocorticoid OR methylpredniso* OR predniso* OR dexamethasone) AND (surgery OR operati* OR perioperati* OR preoperati*) along with the Cochrane Highly Sensitive Search Strategy for RCTs [26]. Abstracts were screened for relevance and those studies which were animal and pre-clinical, those studies not published in English, and review articles were excluded. Relevant full text articles were then appraised. Randomized controlled trials of single dose preoperative corticosteroids in surgery for gastrointestinal cancer which reported on a marker of the postoperative systemic inflammatory response and postoperative complications were included in the review. Reference lists of included studies were hand searched for further relevant studies.

2.3 Data extraction and meta-analysis:

Data from included studies was extracted to tables and analysis was performed using Review Manager version 5.3 (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis of the impact of corticosteroids on postoperative IL 6 and CRP was performed by calculating the mean difference and 95% confidence intervals (CI) using the inverse variance method and combining study outcomes using a random effects model. Where data other than means and standard deviations were reported an attempt was made to calculate these values using published confidence intervals or p values as described by Hozo and colleagues or by the Cochrane Handbook for

Systematic Reviews of Interventions [27-28]. Results of the meta-analysis of the impact of corticosteroids on infective complications was assessed by odds ratios and 95% CIs using the Mantel-Haenzsel method and combining study outcomes using a random effects model. Peto odds ratios and their 95% CIs were combined using a fixed effects model to determine the impact of preoperative corticosteroids on anastomotic leak as there were a small number of events. Meta-regression, using a random effects model, was performed with respect to the impact of corticosteroid dose on postoperative day 1 IL-6, following conversion to hydrocortisone equivalents using a freely available Macro (Wilson, D. B. (Version 2005.05.23). Meta-analysis macros for SAS, SPSS, and Stata. Retrieved, 7th May 2015 from http://mason.gmu.edu/~dwilsonb/ma.html) with IBM SPSS version 22 for Windows (Chicago, IL, USA) [28]. Two tailed p values <0.05 were considered statistically significant.

2.4 Assessment of bias:

Assessment of the risk of bias was carried out using the Cochrane Collaboration tool provided by Review Manager version 5.3 (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Data was assessed for heterogeneity using the I^2 statistic and χ^2 test interpreted using the guidance from the Cochrane Handbook for Systematic Reviews of Interventions [27]. Assessment of potential publication bias was carried out by visual inspection of funnel plots. P values ≤ 0.05 were considered statistically significant.

3. Results

3.1 Study selection process:

The study selection process is summarised in Figure 1. Using the search protocol described, 2,428 abstracts were identified. At screening, 2,354 abstracts were excluded, of which 16 were animal or pre-clinical studies, 227 were not in the English language, 328 were review articles, 3 were duplicate publications and 1,780 were not relevant to the review. Full text articles were reviewed of the remaining 74 studies.

After assessment of full text articles 63 studies were excluded, of which 36 were not in gastrointestinal surgery patients, 6 did not include patients with malginancy, 14 did not include the intervention of interest or included corticosteroids at timings other than preoperatively, 3 did not measure either postoperative IL-6 or CRP, 2 used historical controls, 1 was a duplicate study, and 1 a co-intervention of epidural analgesia alongside preoperative corticosteroids. The remaining 11 randomised controlled trials including 474 patients were included in the review (Table 1) [30-40].

Of the included studies, 3 including 139 patients were in colorectal surgery [38-40], 4 including 156 patients were in oesophageal surgery [30, 32, 34-35], and 4 including 179 patients were in hepatic surgery [31, 33, 36-37]. Of the 474 included patients, 436 (92%) had surgery for gastrointestinal cancer while 38 (8%) from 6 studies had surgery for benign gastrointestinal disease but were included in the meta-analysis [31, 36-38, 40]. All included patients underwent open surgery, no studies of minimally invasive surgery suitable for inclusion were returned by the search strategy.

3.2 Validity assessment:

The risk of study bias is summarised using the RevMan 5.3 Risk of bias summary tool (Supplemental Digital Content 2 – Risk of bias summary.pdf). Most studies were at low risk of bias however 3 did not report outcomes for patients who dropped out following randomisation [33, 36, 38], and 6 did not adequately report allocation concealment and blinding [30-31, 33-36].

3.3 Impact of preoperative corticosteroids on IL-6:

Of the included studies, 10 including 422 patients reported the impact of preoperative corticosteroids on postoperative IL-6 following surgery for gastrointestinal cancer and were included in meta-anaysis (Figure 2) [30-38, 40]. Preoperative corticosteroids were significantly associated with lower serum concentrations of IL-6 following surgery for gastrointestinal cancer on postoperative day 1 ($p<0.001$), day 2 ($p=0.01$), and day 3 ($p=0.002$), but not postoperative day 5 ($p=0.11$) or day 7 ($p=0.69$). There was a wide variation in heterogeneity between studies with the greatest on postoperative day 1 ($I^2=86\%$, $p<0.001$) and the least on postoperative day 7 ($I^2=6\%$, $p=0.36$).

3.4 Impact of preoperative corticosteroids on C-reactive protein:

Of the included studies, 6 including 206 patients reported the impact of preoperative corticosteroids on postoperative CRP following surgery for gastrointestinal cancer and were included in meta-anaysis (Figure 3) [31, 35, 37-40]. Preoperative corticosteroids were significantly associated with lower serum concentrations of CRP following surgery for gastrointestinal cancer on postoperative day 3 ($p<0.001$), and day 7 ($p=0.04$), but not

postoperative day 1 (p=0.09) or day 2 (p=0.11). There was a wide variation in heterogeneity between studies with the greatest on postoperative day 2 (I^2=87%, p<0.001) and the least on postoperative day 7 (I^2=0%, p=0.44).

3.5 Impact of preoperative corticosteroid dose on postoperative IL-6 and CRP

Within the 10 studies reporting postoperative day 1 IL-6, there was a wide variation in preoperative corticosteroid dose in the intervention arm [30-38, 40]. Following dose conversion to hydrocortisone equivalents (HEs) of both dexamethasone (1mg = 30 HEs) and methylprednisolone (1mg = 5 HEs) [29], it was found that 2 studies gave patients 240 HEs [37,39], 3 studies gave 2,500 HEs [31, 35, 36], 3 studies gave 3,500 HEs [30, 32, 34], and 2 studies gave 10,500 HEs preoperatively [33, 37]. Meta-regression revealed no significant relationship between the corticosteroid dose as measured by HEs and effect size on postoperative day 1 IL-6 (B = -0.0065, 95% CI -0.029 to 0.016, p=0.569). No further meta-regression of the impact of preoperative corticosteroid dose on postoperative IL-6 or CRP effect size was performed as the number of studies precluded meaningful analysis.

3.6 Impact of preoperative corticosteroids on all postoperative complications

Of the included studies 10, including 434 patients with 163 complications, reported the impact of preoperative corticosteroids on postoperative complications following surgery for gastrointestinal cancer and were included in meta-analysis (Figure 4) [30-34, 36-40]. Preoperative corticosteroids were significantly associated with fewer postoperative complications following surgery for gastrointestinal cancer (OR 0.44, 95% CI 0.28 to 0.70, p<0.001) There was minimal heterogeneity between studies (I^2=2%, p=0.42). At subgroup

analysis, preoperative corticosteroids were significantly associated with fewer postoperative complications following surgery for oesophageal (p=0.01) and liver (p=0.02) but not colorectal malignancy (p=0.25).

3.7 Impact of preoperative corticosteroids on postoperative infective complications:

Of the included studies 9, including 388 patients with 68 infective complications, reported the impact of preoperative corticosteroids on postoperative infective complications following surgery for gastrointestinal cancer and were included in meta-analysis (Figure 5) [31-32, 34-40]. Preoperative corticosteroids were significantly associated with fewer postoperative infective complications following surgery for gastrointestinal cancer (OR 0.47, 95% CI 0.26 to 0.83, p=0.01). There was minimal heterogeneity between studies (I^2=0%, p=0.54). At subgroup analysis, preoperative corticosteroids were significantly associated with fewer postoperative infective complications following surgery for liver malignancy (p=0.02) but not colorectal (p=0.15) or oesophageal malignancy (p=0.58).

3.8 Impact of preoperative corticosteroids on anastomotic leak:

Of the included studies 7, including 295 patients and 19 events, reported the impact of preoperative corticosteroids on anastomotic leak following colorectal or oesophageal surgery for cancer and were included in meta-analysis (Figure 6) [30, 32, 34-35, 38-40]. The remaining 5 studies were in hepatic surgery thus did not report anastomotic leak. There was no significant association between preoperative corticosteroids and anastomotic leak (OR 1.13, 95% CI 0.44 to 2.90, p=0.79). There was minimal heterogeneity between studies (I^2=0%, p=0.61). At subgroup analysis there was no association between preoperative

corticosteroids and anastomotic leak following surgery for either colorectal (p=0.71) or oesophageal malignancy (p=1.00).

3.9 Assessment of publication bias:

Visual assessment of a funnel plot of studies reporting the impact of preoperative corticosteroids on postoperative CRP and all complications following surgery for gastrointestinal cancer (Figure 7) suggests that there may be evidence of publication bias with a positive skew amongst smaller studies.

4. Discussion

The present systematic review and meta-analysis reports that preoperative corticosteroids reduce the magnitude of the systemic inflammatory response, in particular IL-6 and CRP, and are significantly associated with fewer postoperative infective complications following surgery for gastrointestinal cancer.

The results of the present study with regard to postoperative IL-6 are consistent with recent meta-analyses of randomized controlled trials of preoperative corticosteroids in colorectal surgery, liver surgery and esophagectomy [21-24, 41]. In addition, the present meta-analysis reports a significant reduction in IL-6 on postoperative days 2, 3 and 5 in those patients given preoperative corticosteroids. The present study reports a significant reduction in CRP on postoperative days 3 and 7 in those given preoperative corticosteroids however found no significant impact of preoperative corticosteroids on postoperative day 1 or 2. As CRP is usually seen to reach its peak concentration around 48 hours after the initial surgical insult it may be that comparison on postoperative day 1 and 2 does not accurately reflect the influence of preoperative corticosteroids on the postoperative systemic inflammatory response [6]. It is of interest that even within the control groups of the studies included in the present meta-analysis, the mean data were below postoperative CRP thresholds associated with the development of postoperative complications. For example, it has recently been advocated that simple objective postoperative CRP thresholds >150mg/l on post-operative days 3-5 be used to alert clinicians to the risk of post-operative complications before clinical signs and symptoms [42]. Moreover, when examined in detail by operative site, the mean CRP concentrations reported by the studies included in the present meta-analysis were significantly lower than values reported in a comprehensive systematic review of the timing and peak magnitude of postoperative IL-6 and CRP following elective colorectal, oesophageal and liver surgery [7]. Therefore, it may be that patients recruited to previous

randomised controlled trials of preoperative corticosteroids had a lower systemic inflammatory response compared with unselected patients. If this were to be the case then this may have implications for the randomised trials that reported efficacy of pre-operative corticosteroids on complication rates. In particular, it may be that the efficacy was underestimated.

As with previous meta-analyses there was a wide variation in corticosteroid dose equivalence and timing [43]. The degree of heterogeneity between studies within each speciality in the present meta-analysis suggests that this does have an impact on the degree of attenuation of the postoperative systemic inflammatory response. Within the present meta-analysis, no significant association was found between varying corticosteroid dose equivalencies and postoperative day 1 IL-6 effect size between studies. However, this analysis was performed on a post hoc basis in response to data heterogeneity. In addition, dose timing and the differing half-life of dexamethasone and methylprednisolone were not considered and may be implicated [43]. The results of the present study do not define the ideal dose of preoperative corticosteroid to moderate the systemic inflammatory response or postoperative nausea and vomiting. For example, a recent meta-analysis of preoperative corticosteroids in the prevention of postoperative nausea and vomiting reported similar efficacy with lower doses of IV dexamethasone (4-5mg), when compared to higher doses (8-10mg) [44]. However, the efficacy of preoperative corticosteroids will depend on a number of factors including the magnitude of the systemic inflammatory response (eg. preventing patients breaching established threshold values of CRP) and the route and frequency of dose (eg. large single dose or smaller multiple doses). Further work, in the context of randomised trials examining varying corticosteroid doses with reference the magnitude of the post-operative systemic inflammatory response, is therefore required.

Postoperative IL-6 and CRP concentrations have been reported to be markers of the magnitude of the postoperative stress response [7]. In relation to short term postoperative morbidity, several recent meta-analyses have demonstrated the utility of elevated postoperative serum CRP in the early diagnosis of infective complications and anastomotic leak in gastrointestinal surgery [10, 12, 15]. In addition, the magnitude of the postoperative CRP has been reported to be associated with complication severity following colorectal surgery [45-46]. Although this inflammatory response may represent an epiphenomenon rather than a cause of infective complications, given that the presence of a systemic inflammatory response (as evidenced by IL-6 or CRP) [7] is primarily an upregulated innate immune response (with consequent suppression of adaptive immunity), it is plausible that the magnitude of the postoperative systemic inflammatory response plays a role in the development of postoperative infective complications [47]. Indeed, the results of the present review are consistent with such a causal relationship. However, further interventional studies of preoperative corticosteroids would be required to prove such a relationship.

It is known that corticosteroids alter gene transcription and thus protein synthesis following intracellular receptor binding, however the exact mechanism by which they act to reduce inflammation is poorly understood [48]. Glucocorticoids act on the innate immune system including myeloid tissue, inhibiting the activity of neutrophils and macrophages via reduced transcription of several proinflammatory cytokines, and by increasing the transcription of lipocortins which themselves inhibit cyclo-oxygenase dependent inflammation pathways [49]. They are also recognised to have a down regulatory effect on adaptive immunity and lymphoid tissue, probably via inhibition of nuclear factor κB (NF-κB) [50]. The results of the present review taken with that of previous meta-analyses suggest that, in the postoperative period, the action of corticosteroid may at least be partly due to reduced transcription and production of IL-6 by innate immune cells, consequently reduced

synthesis of CRP by hepatocytes [21, 23-24]. Although both IL-6 and CRP are objective markers of the postoperative stress response and have both been associated with the development of complications following gastrointestinal surgery, CRP is routinely available in clinical practice [7]. Indeed, in a recent review of risk factors associated with anastomotic leak following colorectal surgery the authors advocate routine measurement of CRP on postoperative days 3 to 5, with a concentration greater than 150mg/L prompting the investigation of potentially developing complications [42]. In addition, other studies have investigated the use of other markers associated with the development of postoperative complications, for example procalcitonin, however the IMACORS study reported that CRP was more accurate in the detection of postoperative infective complications following colorectal surgery [51]. Furthermore, it has long been recognised that albumin is also a marker of the postoperative stress response [6], and is associated with postoperative complications and mortality [52]. It remains to be determined whether albumin, in terms of predicting post-operative complication, offers prognostic value in addition to that of CRP and whether albumin may be a useful therapeutic target for pre-operative corticosteroids.

There has long been a concern regarding the inhibitory effect of corticosteroids on collagen formation leading to postoperative wound dehiscence and potentially anastomotic leak. However, the present meta-analysis along with prior randomised trials and meta-analyses have failed to demonstrate a significant increase in either complication in patients given corticosteroids [21, 24, 53-54]. Much of the prior evidence regarding wound healing and infection has arisen from literature surrounding surgery for inflammatory bowel disease, in those undergoing transplant surgery, or in those with diseases of the hypothalamo-pituitary-adrenal axis [55]. Indeed, recent meta-analysis of both experimental and clinical trials suggests that receiving corticosteroids at standard therapeutic doses for 10 days or less

is unlikely to impair wound healing [56]. Lastly, as recent preliminary reports suggest that preoperative corticosteroids may have a detrimental impact on oncologic outcome, some consideration should be given to their impact on longer term outcomes, especially in surgery for gastrointestinal cancer [57-58].

The main limitation of the present systematic review and meta-analysis is the relatively small number of patients included. To maximise the number of patients within the analysis several gastrointestinal surgical specialities were considered together using a random effects model. In addition there were a small number of patients included within the present meta-analysis who had undergone surgery for benign gastrointestinal disease. Indeed these factors, to an extent, limit the generalisability of the results of the present study. However, the exclusion of the 6 studies which included a small proportion of patients without malignant disease would have significantly reduced the power of the present meta-analysis [30, 35-37, 39]. A significant degree of heterogeneity was reported in the analysis of postoperative IL-6 and CRP. This may reflect the pooling of the various surgical specialities. However, no study individually reported a statistically significant increase in either postoperative IL-6 or CRP in the corticosteroid treatment group. Thus, although there are likely to be differences in the studied patient groups or methodology, the direction of the treatment effect at least, is very likely to be similar across the included studies. There was a wide variability in concentrations of IL 6 and CRP amongst studies within the same postoperative day. Both the biological variability of IL 6 and CRP, alongside the variety of surgical specialties included in the present study may account for this [59]. Other potential confounders include the use of a variety of preoperative corticosteroids, their dose and timing, although a random effects model was used as an attempt to minimise this, alongside meta-regression techniques. In addition, there may be a degree of publication bias toward positive results amongst the smaller studies included in the meta-analysis. In the present study, despite a broad and

inclusive search strategy, there were no trials conducted in the USA included in the analysis. Therefore, it would appear that although preoperative corticosteroids are used in routine clinical practice in the USA, no formal RCTs have been undertaken there. Finally, all of those studies included in the present meta-analysis were published prior to 2009. A single study in liver surgery, published in 2010, was excluded due to the use of postoperative corticosteroids in the treatment group, however it interestingly reported reduced concentrations of IL-6 and CRP in the treatment group with a trend toward fewer complications [60]. The lack of more recent studies may relate to the rapid uptake of enhanced recovery or fast-track postoperative protocols in gastrointestinal surgery which often include preoperative corticosteroids for the prevention of postoperative nausea and vomiting [61]. Nevertheless, the results of the present review with regard to the effect of preoperative corticosteroids on IL-6 and CRP provide important new information since they suggest that the efficacy of such interventions may be dependent on the magnitude of the postoperative systemic inflammatory response.

The results of the present systematic review and meta-analysis suggest that preoperative corticosteroids are associated with a reduction in the magnitude of the postoperative stress response and , within some subgroups, the likelihood of postoperative complications following surgery for gastrointestinal cancer. Although the magnitude of this postoperative systemic inflammatory response, especially CRP, has been associated with the development of complications following surgery, relatively few studies, have examined whether the attenuation of the systemic inflammatory response with preoperative corticosteroids may indeed reduce infective complication rates. Clearly, given the significant heterogeneity in the small number of studies included in the present meta-analysis, further work is warranted.

5. Acknowledgements/Conflict of interest statement: No financial or competing interests

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7. Tables and footnotes

7.1 Table 1: Clinical trials investigating the impact of preoperative steroids on the postoperative stress response following surgery for gastrointestinal cancer

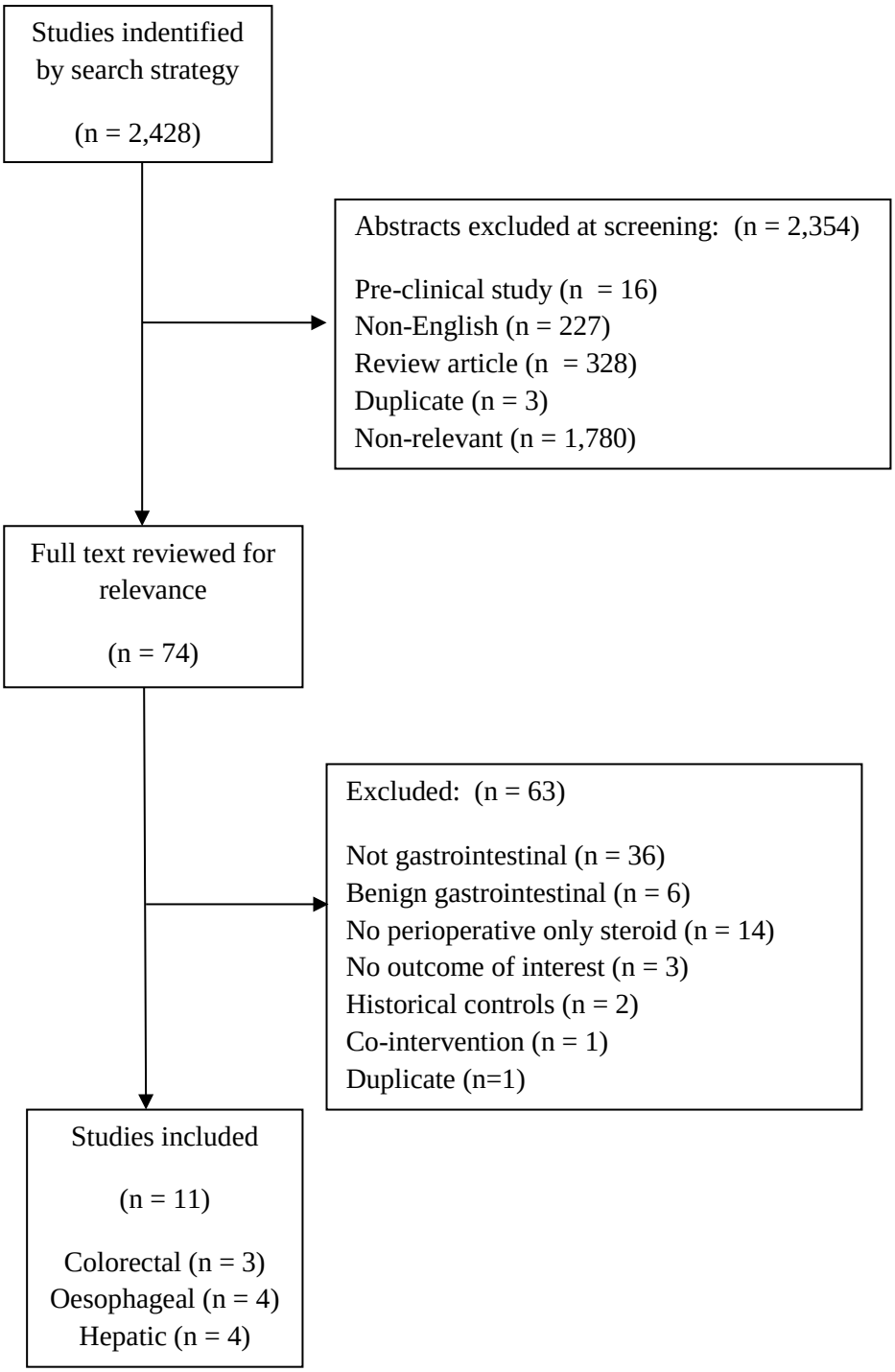
Author	Year	Journal	Country	n	Speciality	Steroid/dose/route /timing	Surgical stress response	Period	Significant outcomes
Kirdak et al.	2008	Am Surg	Turkey	27	Colorectal	Dexamethasone 8mg IV at induction	Pain, nausea, IL 6, CRP	POD 1-3	None
Zargar-Shoshtari et al.	2009	Br J Surg	New Zealand	60	Colorectal	Dexamethasone 8mg IV, at induction	Pain, nausea, WCC, Neutrophils, CRP, IL 1β, IL 6, IL 8, IL 10, IL 13, TNFα, (serum and peritoneal cytokines), fatigue	Pain and nausea POD 1-3, Fatigue POD 1-60, CRP and cytokines POD 1	Higher WCC, neutrophils and lower pain, nausea, serum IL 6, serum IL 8, peritoneal IL 6, peritoneal IL 13 in steroid group
Vignali et al.	2009	Dis Colon Rectum	Italy	52	Colorectal	Methylprednisolone 30mg/kg IV, 60 mins preop	Pain, FVC, FEV1, CRP, IL 6, IL 8, TNFα	POD 1-5	Higher FVC, FEV1 and lower pain, CRP, IL 6, IL 8 in steroid group
Matsutani et al.	1998	J Surg Res	Japan	33	Oesophageal	Methylprednisolone 10mg/kg at induction	TNFα, IL 6, PT, APTT, AT III	POD 1-7	Higher AT III and lower TNFα, IL 6 in steroid group
Sato et al.	2002	Ann Surg	Japan	66	Oesophageal	Methylprednisolone 10mg/kg at induction	IL 1, IL 6, IL 8, IL 10, cortisol, lymphocytes, neutrophils	POD 1-7	Higher IL 10 and lower IL 1, IL 6, and IL 8 in steroid group
Takeda et al.	2003	J Nippon Med Sch	Japan	17	Oesophageal	Methylprednisolone 10mg/kg IV at induction	Serum and broncheoalveolar IL 6 and IL 8	POD 1	Lower serum IL 6 and IL 8, and lower broncheoalveolar IL 8 in steroid group
Yano et al.	2005	Hepatogastroenterol	Japan	40	Oesophageal	Methylprednisolone 500mg IV 2hrs preop	IL 6, IL 8, IL 10, WCC, rectal pHi, body weight	POD 1-3	Lower IL 6, IL 8 and CRP

		ogy							
Yamashita et al.	2001	Arch Surg	Japan	33	Liver	Methylprednisolone 500mg IV 2hrs preop	IL 6, IL 10, CRP, Bil, AST, ALT	POD 1-7	Higher IL 10 and lower Bil, IL 6, CRP in steroid group
Muratore et al.	2003	Br J Surg	Italy	53	Liver	Methylprednisolone 30mg/kg IV at induction	IL 6, Bil, AST, ALT, PT	POD 1	Lower IL 6 in steroid group
Aldrighetti et al.	2006	Liver Transpl	Italy	73	Liver	Methylprednisolone 500mg IV at induction	IL 6, TNFα, Bil, AST, ALT, PT, platelets, AT III, D-dimer	POD 1-5	Higher AT III, platelets, and lower IL 6, TNFα in steroid group
Schmidt et al.	2007	J Hepatobiliary Pancreat Surgery	Germany	20	Liver	Methylprednisolone 30mg/kg IV 90 mins preop	IL 6, IL 8, IL 10, CRP, TNFα, HLA-DR, Bil		Lower IL 6, IL 8, CRP, TNFα, Bil in steroid group

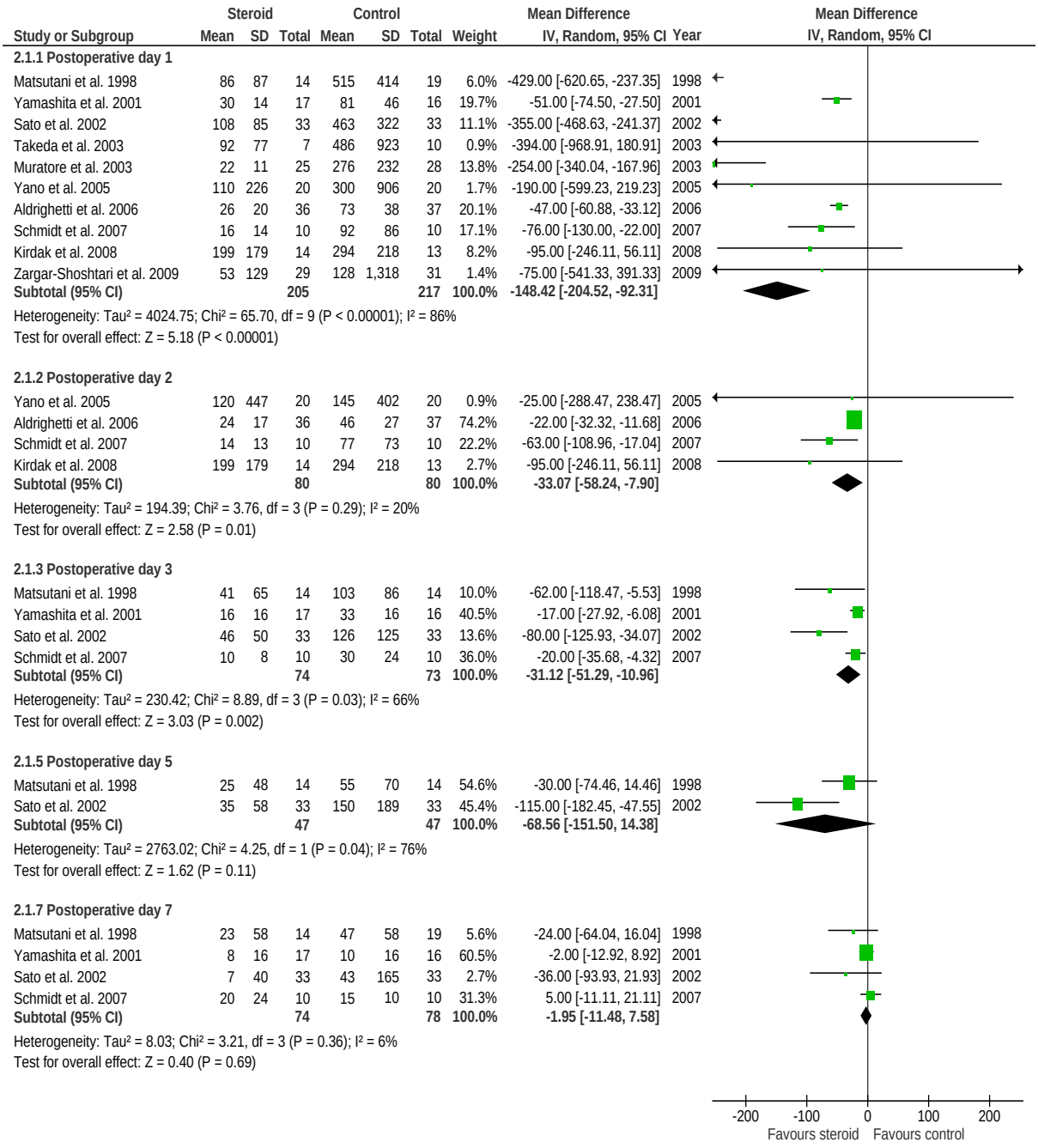
POD postoperative day, *IV* intravenous, *IL* interleukin, *CRP* C-reactive protein, *TNF* tumour necrosis factor, *WCC* white cell count, *FVC* forced vital capacity, *FEV* forced expiratory volume, *ADH* anti-diuretic hormone, *AT* antithrombin, *Bil* bilirubin, *AST* aspartate transaminase, *ALT* alanine transaminase, *PT* prothrombin time, *HLA* human leukocyte antigen

8. Figures and Legends

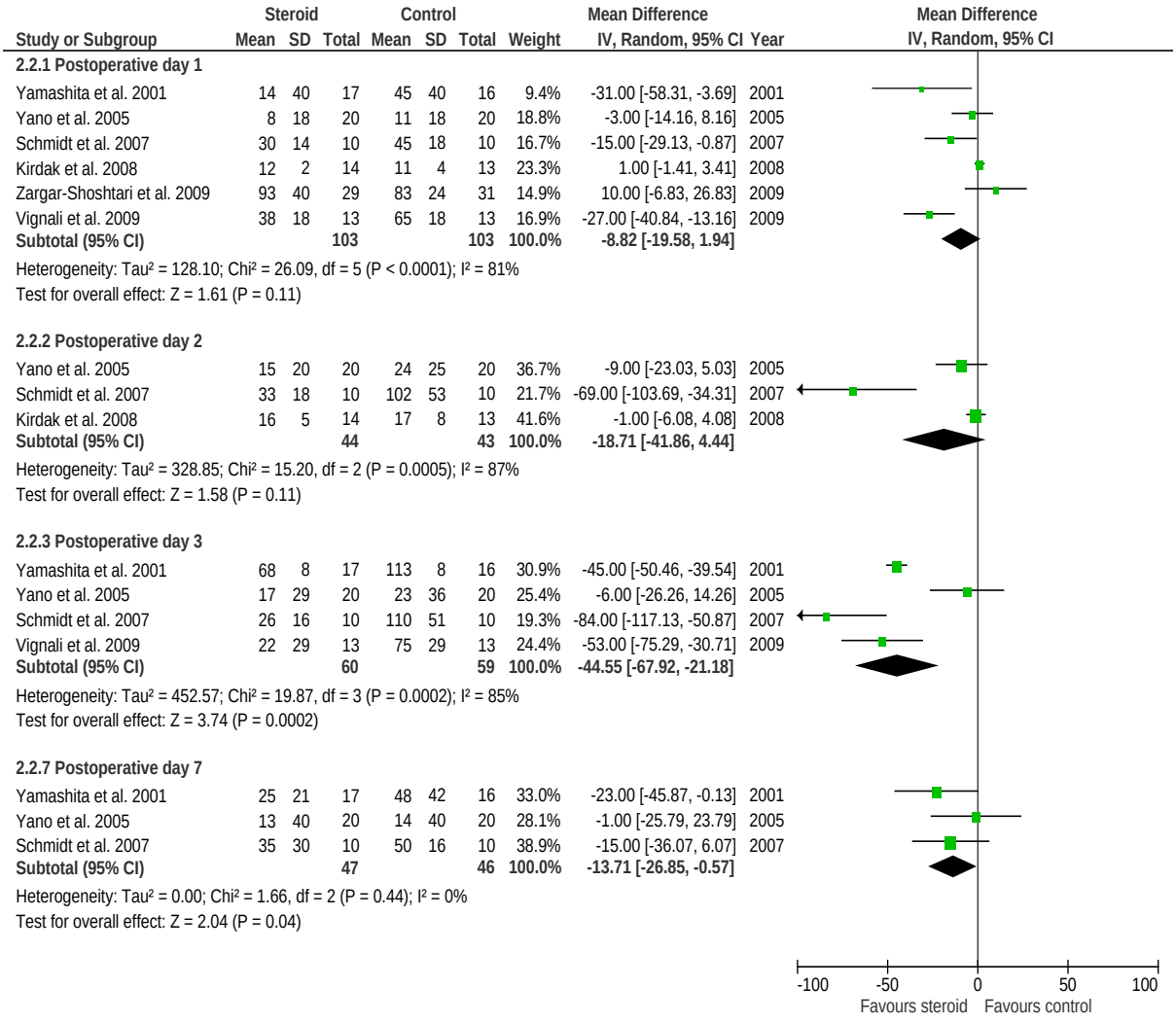
8.1 Figure 1: PRISMA flowchart demonstrating study selection



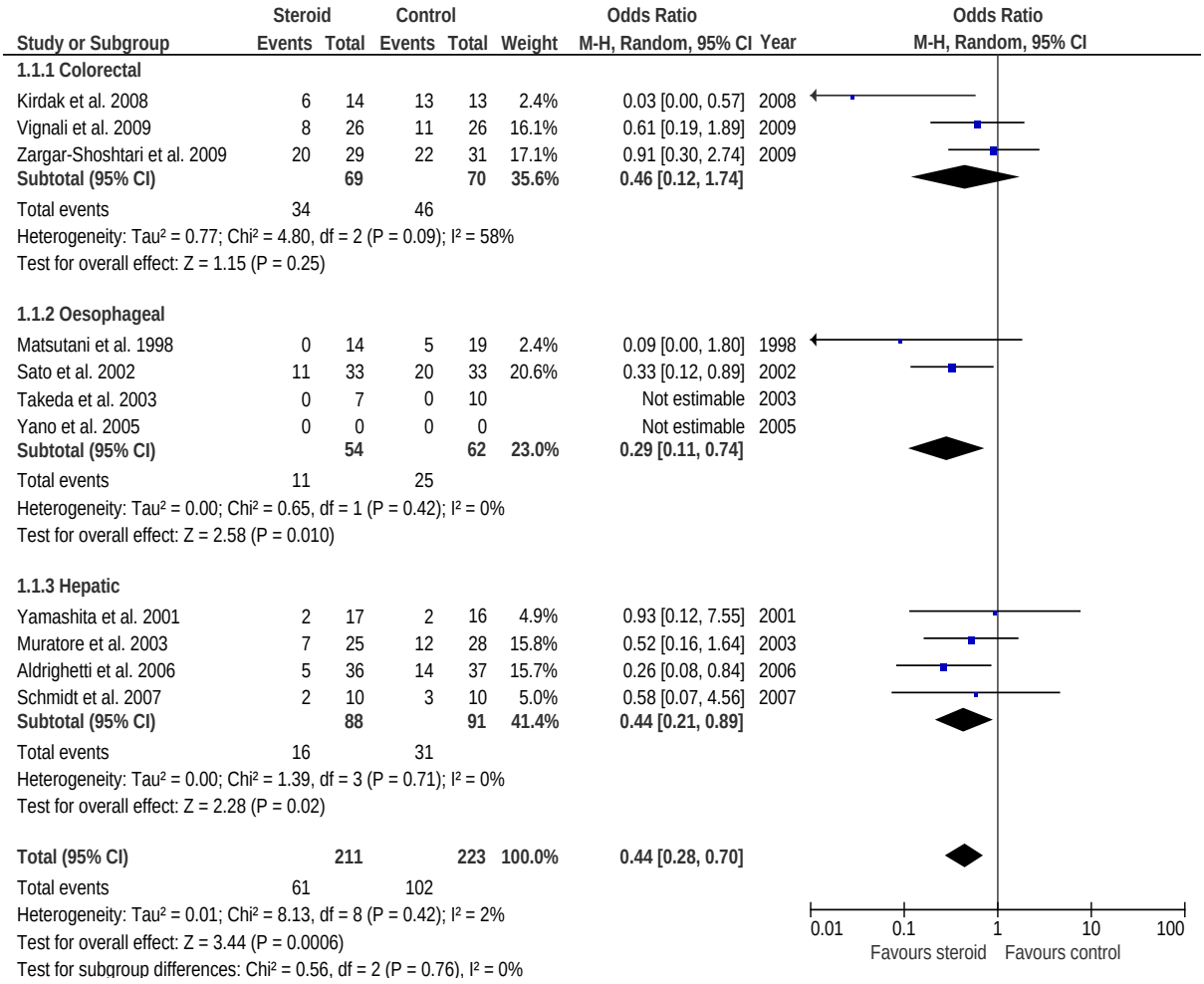
8.2 Figure 2: Impact of preoperative corticosteroids on serum interleukin 6 following surgery for gastrointestinal cancer



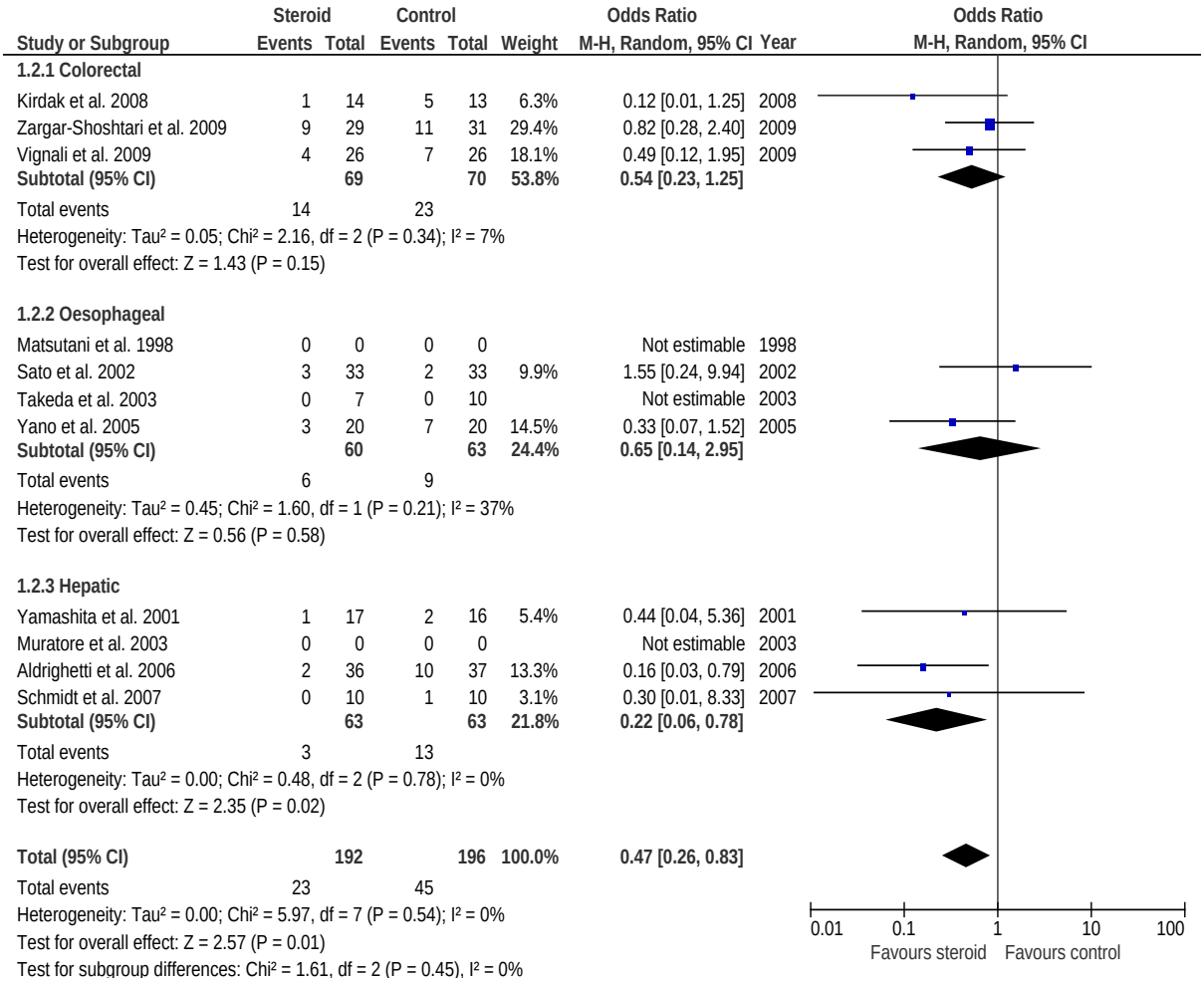
8.3 Figure 3: Impact of preoperative corticosteroids on serum C-reactive protein following surgery for gastrointestinal cancer



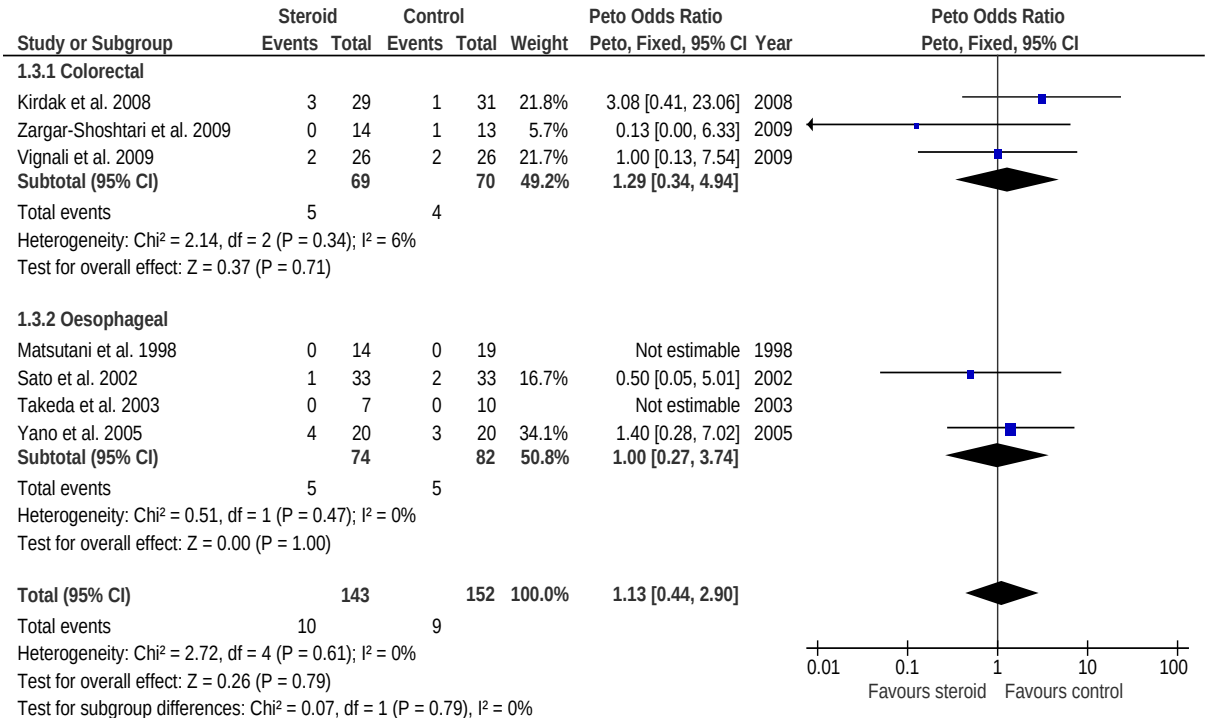
8.4 Figure 4: Impact of preoperative corticosteroids on all postoperative complications following surgery for gastrointestinal cancer



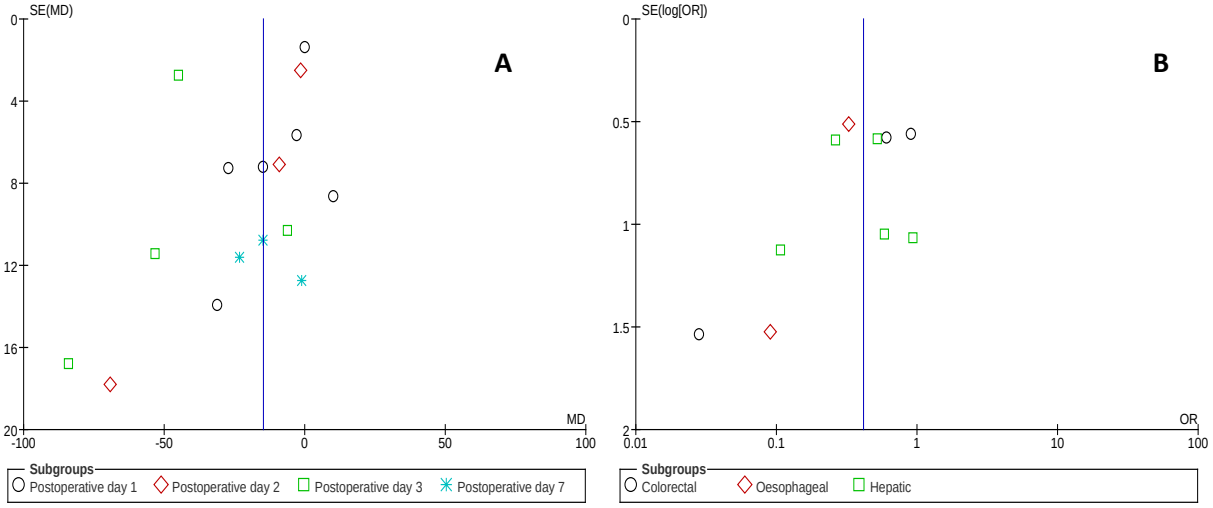
8.5 Figure 5: Impact of preoperative corticosteroids on infective postoperative complications following surgery for gastrointestinal cancer



8.6 Figure 6: Impact of preoperative corticosteroids on anastomotic leak following surgery for gastrointestinal cancer



8.7 Figure 7: Funnel plots of the impact of preoperative corticosteroids on **A**: postoperative C-reactive protein and **B**: all postoperative complications following surgery for gastrointestinal cancer



9. Supplementary Digital Content:

9.1 Supplementary Digital Content 1 – PRISMA Checklist.docx

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9-11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9-11
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9-11

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9-11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12-16 (Fig 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	(Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-16 (Suppl file 2)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	(Fig 3-5)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-16and (Fig 3-5)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13 and

			(Fig 6)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-16and (Fig 3-5)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10

9.2 Supplemental Digital Content 2 - Risk of bias summary.pdf: green symbol = low risk, red symbol = high risk, no symbol = unclear risk