European Journal of Surgical Oncology

# Non-steroidal anti-inflammatory agents and anastomotic leak rates across colorectal cancer operations and anastomotic sites: A systematic review and meta-analysis of anastomosis specific leak rate and confounding factors.

--Manuscript Draft--

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| **Manuscript Number:** | |
| **Article Type:** | Review Article (5000 words) |
| **Section/Category:** | Colorectal Cancer |
| **Keywords:** | General Surgery; Anastomotic Leak (AL); Non-steroidal Anti-inflammatory drugs (NSAIDs); Colorectal Cancer |
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| **Abstract:** | Background: Surgical intervention presents a fundamental therapeutic choice in the management of colorectal malignancies. Complications, the most serious one being anastomotic leak (AL), still have detrimental effects upon patients' morbidity and mortality. We aimed to assess whether NSAIDs, and their sub-categories, increase AL in colonic anastomoses and to identify whether this affects specific anastomotic sites.Materials and methods: A systematic search of MEDLINE, Cochrane Library, ClinicalTrials.gov, Web of Science, Science Direct, Google Scholar was conducted between 1st January 1999 till the 30th of October 2020. Cohort studies and randomized control trials examining AL events in NSAID-exposed, colorectal cancer patients were included. NSAIDs were grouped according to the 2019 NICE guidelines in non-specific (NS-NSAIDs) and specific COX-2 inhibitors. The primary outcome was AL events in NSAID-exposed patients undergoing operations with either ileocolic, colocolic or colorectal anastomoses. Secondary outcomes included NSAID category-specific AL events and demographic confounding factors increasing AL risk in this patient population.Results: Fifteen studies involving 25,395 patients were included in the systematic review and meta-analysis. Of all anastomoses, colocolic anastomoses were found to be statistically more prone to AL events in the NS-NSAID-exposed population [OR 3.24 (95% CI 0.98-10.72), p = 0.054]. Male gender was an independent confounder increasing AL rate regardless of NSAID exposure.Conclusion: The association between NSAID exposure and AL in oncology patients remains undetermined. Whilst in present work, colocolic anastomoses appear to be more sensitive to AL events, the observed association may be anastomotic site and NSAID-category dependent. |
| **Suggested Reviewers:** | |

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Word Count: 2931 (Excluding abstract: 265 words and references:1160)


## Abstract

**Background:** Surgical intervention presents a fundamental therapeutic choice in the management of colorectal malignancies. Complications, the most serious one being anastomotic leak (AL), still have detrimental effects upon patients' morbidity and mortality. We aimed to assess whether NSAIDs, and their sub-categories, increase AL in colonic anastomoses and to identify whether this affects specific anastomotic sites.

**Materials and methods:** A systematic search of MEDLINE, Cochrane Library, ClinicalTrials.gov, Web of Science, Science Direct, Google Scholar was conducted between 1st January 1999 till the 30th of October 2020. Cohort studies and randomized control trials examining AL events in NSAID-exposed, colorectal cancer patients were included. NSAIDs were grouped according to the 2019 NICE guidelines in non-specific (NS-NSAIDs) and specific COX-2 inhibitors. The primary outcome was AL events in NSAID-exposed patients undergoing operations with either ileocolic, colocolic or colorectal anastomoses. Secondary outcomes included NSAID category-specific AL events and demographic confounding factors increasing AL risk in this patient population.

**Results:** Fifteen studies involving 25,395 patients were included in the systematic review and meta-analysis. Of all anastomoses, colocolic anastomoses were found to be statistically more prone to AL events in the NS-NSAID-exposed population [OR 3.24 (95% CI 0.98-10.72), p = 0.054]. Male gender was an independent confounder increasing AL rate regardless of NSAID exposure.

**Conclusion:** The association between NSAID exposure and AL in oncology patients remains undetermined. Whilst in present work, colocolic anastomoses appear to be more sensitive to AL events, the observed association may be anastomotic site and NSAID- category dependent.


Keywords: General Surgery; Anastomotic Leak (AL); Non-steroidal Anti-inflammatory drugs (NSAIDs); Colorectal Cancer

## 1. Introduction

Surgical intervention remains the curative option for colonic malignancies. Whilst perioperative improvements have significantly decreased patient mortality and morbidity, short- and long-term complications including haemorrhage, infection, wound dehiscence, strictures and fistula formation, pose significant operative risks [1]. In procedures involving resection of colonic segments and the formation of a primary anastomosis, complications such as anastomotic

leak (AL) remain a significant issue. The definition of AL has been broadly agreed to encompass a breach of the surgical join between two hollow viscera which may lead to an observable leak of luminal contents [2]. AL rate depends upon a multitude of factors such as indication for surgery, smoking status, gender, and necessity for emergency operation among others [3]. Anastomotic sites pose varying risks of AL for example ileocolic anastomoses have a 1-4%, colocolic 2-3%, ileorectal a 3-7% while colorectal anastomoses are susceptible to a 5-19% AL rate [4]. The severity of AL represents a wide range of clinical outcomes and attempts have been made for these outcomes to be categorised for consistency according to the need for possible intervention [5].

Colonic resection can cause significant pain and discomfort in the post-operative period, with high analgesic demands. Inadequate management of pain causes multiple complications affecting various systems including cardiovascular (myocardial infarction), pulmonary (hypoventilation causing atelectasis and infection), gastrointestinal (impaired motility/ileus, nausea and vomiting), renal (urinary retention) and also impairing immune function and causing psychological distress [6]. NSAIDs offer adequate analgesia and decrease the need for opioid exposure in this patient group, as advocated by Enhanced Recovery After Surgery (ERAS) principles. Numerous meta-analyses have suggested NSAID association with AL. These studies provide conflicting evidence, leading surgeons to an empirical avoidance of NSAIDs as analgesics in all operations involving colonic anastomoses.

In this work, we sought to clarify whether NSAIDs, and their sub-categories, increase AL in colonic anastomoses in oncology patients and more specifically to identify whether this affected specific anastomotic sites.

## 2. Materials and methods

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Fig. 1, Table S5).

### 2.1. Search strategy

A systematic search of MEDLINE, Cochrane Library, ClinicalTrials.gov, Web of Science, Science Direct, Google Scholar was conducted between 1st January 1999 till the 30th October 2020. The search terms used were “Anastomosis or anastomotic leakage” AND “NSAIDs” [MesH term], adapted for each database (Table S1). No restrictions for colorectal surgery were initially placed. Upon abstract reading, manuscripts with solely upper gastrointestinal (GI) anastomoses were excluded. Unpublished data from registered clinical trials (NCT02347735, NCT03281070, NCT03771456) were sought and recorded. Contact with corresponding author was attempted and 2 weeks were allowed for response. Out of the three identified trials, we received one response but NSAID use was not recorded, and the trial was excluded.

### 2.2. Study eligibility criteria

Studies were included if: (i) they included anastomosis of the distal gastrointestinal tract; (ii) comparing postoperative NSAID use with non-use; (iii) reporting anastomotic leakage and (iv) site of anastomosis was recorded (Table S4). RCTs and both prospective and retrospective cohort studies were included examining AL events in NSAID exposed colorectal patients

(Table S4). While case reports or reports were initially collected and assessed for adequacy, our final analysis, did not include any. Restrictions included English language [excluded N=46] and human. Of the non-English manuscripts, titles in English were assessed, and none were relevant to the present review. Restrictions were not applied to participants' age, gender or ethnicity.

### 2.3. Data extraction

The studies were independently and critically assessed by three authors (SLK, LO, RJ) using a standard protocol, according to PRISMA guidelines (Table S5) and disagreements were resolved by a consensus, bias analysis was incorporated in this process (Table S2; Table S3; Fig. S1; Fig. S2). Extracted data included study design, year of study, country of study, definition of anastomotic leakage, operative diagnosis, operation, location of anastomosis, emergency vs. elective, name of NSAID (e.g. ketorolac) and type (e.g. COX-2 inhibitor) of NSAIDs used, timing of NSAID use, sample size, overall AL rate as reported in study, inclusion and exclusion criteria, and numbers of anastomotic leakage per group, patient demographics (age, gender, preoperative BMI, ASA score and TNM score (where possible), smoking status, alcohol consumption (units/week), glucocorticoid administration, diabetes mellitus status, duration of operation) (Table S4; Fig. S9).

### 2.4. Quality assessment

Quality of the included studies was assessed using the Cochrane Risk of Bias (RoB) Tool for RCTs (Table S2) and the Newcastle-Ottawa scale (NOS) for observational studies (Table S3) and (Table S2; Table S3) [7,8]. Domains were scored by SK, RJ, LO and study level RoB was defined as low risk of bias, when all domains received low bias scores unanimously. Studies were also assessed by the GRADE framework [9]. Cochrane RevMan V. 5.4 was employed for forest plots and heterogeneity assessment [10,11]. Publication bias and data asymmetry was assessed by funnel plot if at least 10 studies were included in the pooled analysis, and rank correlation test (Begg's test; RevMan V. 5.4). Adequate follow-up was set to be $\geq$ 30 days.

### 2.5. Outcome measures

The primary outcomes of this study included 1) AL in association with NSAID use in colorectal anastomoses and 2) Subgroup analysis of AL events of specific anastomotic sites upon NSAID exposure. Secondary outcomes included AL events by NSAID category (NS-NSAIDs, COX-2 inhibitors, and Ketorolac) as well as identification of demographic factors that may increase AL events in NSAID exposed patients. All outcomes were addressed in oncology patients.

### 2.6. Data handling

NICE guidelines 2019 were sought to classify NSAID categories [12]. All data including diclofenac under the COX-2 specific umbrella were re-categorised. This was not possible for one study given that the percentage of individual NSAIDs was not reported making data re-categorisation impossible [13]. Only -coxib medications (celecoxib and etoricoxib) were

classed as COX-2 specific inhibitors. Ketorolac was included in the NS-NSAIDs analysis and as a separate subgroup given its specific drug-gene interaction profile as per Drug Gene Interaction Database. Only patients with known NSAID status were included. Perioperative NSAID use refers to NSAID exposure as analgesic prior to and following the procedure in days (POD) with exposure spanning between POD -90 till POD +30. POD 0 was the day of operation. To assess rates of AL among different operations and anastomotic sites, data was adapted according to the percentage of patients undergoing a specific operation as stated in each manuscript. Manuscripts that did not clearly state either the type of operation (right hemicolectomy, left hemicolectomy, anterior resection) or the location of the anastomosis were excluded.

### 2.7. Data synthesis and meta-analysis

Only studies that were clinically and contextually homogeneous were considered for pooling for meta-analysis. The meta-analysis was conducted by computing the OR from the original data using the Cochrane-Mantel-Haenszel method. Data analysis was carried out using Review Manager (RevMan) v5.4 software (Cochrane Collaboration) using a random-effect (RE) model where applicable. Random effects model was used for sub-group analysis. Statistical heterogeneity was quantified using $I^2$ statistics and Cochrane Q tests. Inverse Variance Analysis was used to identify confounding demographic and operative factors contributing to increased AL (Fig. S9).

#### 2.7.1. Assessment of heterogeneity

Only studies that were of the same study design were included in the meta-analysis. We used the $I^2$ statistic to quantify the heterogeneity; if the $I^2$ was < 60% it was considered not substantial, if it was > 60% we used subgroups to explain the heterogeneity. Where we were not able to explain substantial heterogeneity, we raised caution with the findings.

#### 2.7.2. Subgroups to explore heterogeneity

Subgroup analysis of selective NSAIDs (COX-2), NS-NSAIDs (including ketorolac) and Ketorolac as a separate subgroup across exposed vs. control groups. Identification of demographic factors among exposed vs. control populations, that may predispose to AL, was sought. Both crude hazard ratio (HR) and adjusted HR were presented with associated 95% CIs. HR (95% CI) was adjusted for age, and gender.

#### 2.7.3. Sensitivity analysis

Asymmetry was assessed by funnel plot, and asymmetry was assessed formally by rank correlation test (Begg's test; RevMan V. 5.4). Sensitivity analyses were conducted to assess to explore heterogeneity as per GRADE framework grading [9]. Publication bias was assessed visually by funnel plot, and asymmetry was assessed formally by rank correlation test (Begg's test). Sensitivity analyses were undertaken to assess the effect of treatment duration (< 72 hours, > 72-hour, duration unspecified) (Fig. S8).

## 3. Results

### 3.1. Study selection and study characteristics

Of 4028 records screened, we identified 33 studies suitable for full-text review (Fig.1), of which a total of 15 studies were eligible for inclusion [13-27]. Three studies were RCTs [14,15,16], 3 prospective [17,18,24], and 8 retrospective cohort studies [13,19,20,22,23,25-27] and 1 retrospective case-control [21] study. Sample sizes adapted only for oncology patients undergoing colorectal procedures ranged between 44 to 10565 patients. A 46.34% of the patients were female and the mean age of the participants was 65.24 [Median: 65 years of age].

Quality assessment of observational studies (NOS scale) indicated that the majority of observational studies [n=8] were of high quality (Table S3), two were considered of moderate quality and two of poor. One RCT was considered as high risk of bias and two of low (Table S2). Characteristics of the included studies are outlined in Table S4. GRADE grading the quality of evidence as presented from the evidence of included RCTs and observational studies. Four studies were identified as of low level of certainty, of which one was an RCT. Two further studies were of moderate certainty and the remaining of high.

Only studies measuring surgical outcomes among colorectal anastomoses were included in the analysis. The indications for operation, as per data adaptation section were neoplasia. All patients included in the analysis underwent colorectal procedures. Among the included patient population, 33.95% underwent elective procedures while 4.26% emergency (Fig. S3A). Of the patients with known NSAID exposure status, 20.35% were exposed to NS-NSAIDs perioperatively, a 3.67% to ketorolac, whilst only 1.63% to COX-2 inhibitors (Fig. S3B). For 74.36% of the patients, the sub-category of perioperative NSAIDs was not stated and consequently were not included in the subgroup analyses (Fig. S3B). Overall, AL rate across studies was 5.62% (Control) and 8.27% (NSAIDs) a difference which was not statistically significant (p = 0.14) (Fig. S5).

Anastomotic leak (RE) OR between NSAID and control group was not found to be significantly different between the control vs. NSAIDs groups [Random OR: 1.07 (0.82-1.40); p = 0.62] (Fig. 2, Fig. S4). Publication bias was noticeable for 6 of the 15 included studies (Fig. S4). Subgroup analysis of observational studies [OR: 1.04 [0.79, 1.37]; $I^2$=73; p = 0.79] or RCTs [OR: 2.21 [0.64, 7.65]; p = 0.21] did not exhibit an association. Observed $I^2$ was decreased with sensitivity analysis as per GRADE scale grading ($I^2$ = 56%) (Fig. S6).

### 3.2. AL risk per operation site in NSAID vs. control population and cofounding factors.

We sought to clarify whether a particular anastomotic site was more likely to be at risk of leak after NSAID exposure (Fig. 3) [28,29]. Among the non-exposure group, our data suggested a 4.83% [SD: 5.23] AL incidence for ileocolic, 3.23% [SD: 8.53] for colocolic and 6.32% [SD: 5.54] for colorectal anastomoses. Among these three, colocolic anastomoses were noticeably more prone to AL when patients were exposed to NSAIDs [point estimate OR 1.55 (95%CI 0.93-2.59), p = 0.10; Fig. 3B], albeit the lack of statistical significance, in comparison to ileocolic [OR 0.98, (95% CI 0.72-1.32, p = 0.87), Fig. 3A] or colorectal anastomoses [OR 0.97, (95% CI 0.76-1.23, p = 0.79), Fig. 3C]. It should be noted that the patient sample exploring

the effects of NSAIDs [N= 928] on colocolic anastomoses was significantly smaller in comparison to the ileocolic [N= 1586] and colorectal [N= 4578] subgroup analyses.

Further subgroup analysis of anastomotic site vs. COX-2 inhibitors; NS-NSAIDs and ketorolac was sought in order to clarify whether the increased AL rate observed in the NSAID exposed population was specific to a particular NSAID subclass. For ileocolic subgroup analysis did not draw any conclusions regarding NSAID category and specific AL risk (Fig. 4; Fig. S.7). For colorectal anastomoses, NS-NSAID exposed patient group was favoured with less AL events [OR 0.86, (95% CI 0.65-1.13), p = 0.27] (Fig. 4), a result that was only significant in the fixed effects OR model.

NS-NSAIDs exposure was found to increase AL rate with statistical significance in colocolic anastomoses [OR 3.25, (95% CI 0.98-10.72); p = 0.054] (Fig. 5). Subgroup analysis for COX-2 inhibitors [(OR 1.82, (95% CI 0.51-6.52)] and ketorolac [OR 2.11, (95% CI 0.28-16.14)] were not significant (p = 0.36; p = 0.47 and respectively) but nonetheless favouring control groups (Fig. 5). Sensitivity analysis of NSAID exposure duration favoured NSAID use for over 72 hours. Nonetheless this finding should be taken into clinical context and the variable “end of treatment” POD as reported by the included studies (Fig. S8). Lastly, demographic factors that might act as confounders, increasing AL % upon NSAID exposure, were male gender in the adjusted HR inverse variance analysis in agreement with previous literature (Fig. S9) [30].

## 4. Discussion

In this work, we included 15 studies, 3 RCTs and 12 observational studies, with generally low risk of bias. We found that colocolic anastomoses may be more susceptible to AL upon NS-NSAID patient exposure whilst the opposite was observed for colorectal anastomoses, albeit the lack of statistical significance.

Anastomotic leak remains a serious complication of colonic resection. In the last decade, the risk of AL has been estimated at 10% for colonic resections with a potential mortality of 2.8%-3.9% [31-32]. While NSAID use has been effective as an analgesic option in the peri-operative period, it has been under scrutiny as an AL contributing factor. Multiple meta-analyses have provided conflicting evidence regarding NSAID use and AL rates [33-38]. This is the first meta-analysis to investigate NSAID effects on site-specific AL rate in a homogenous group of patient diagnoses.

Our subgroup analysis by anastomotic site, demonstrated an increased AL rate in NSAID-exposed patients with colocolic anastomoses. The opposite held true for colorectal anastomoses albeit the lack of statistical significance. This finding is clinically important as it suggests that NSAID exposure may have variable effects upon particular anastomotic sites. This finding may favour the use of traditional analgesics in particular patient groups whilst the use of NSAIDs in others. This also may explain the outcome variability of the completed meta-analyses till today. Nonetheless, these findings remain to be corroborated by high powered RCT studies which may take into account equally NSAID category and anastomotic sites.

It should be mentioned that our results indicating the increased AL risk among NSAID-exposed patients, in the colocolic anastomosis group, are limited by the evidence base depicted by the population size [N=928]. No significant association was identified between

NSAIDs and AL in patients with ileocolic anastomoses. Colorectal anastomoses were found to have more favourable outcomes under NSAID exposure whilst no effects were observed on ileocolic anastomoses. Hence within the limits of this study we have not found evidence to discourage their use in these subgroups. Male gender was identified as an independent confounder of increased AL rate in the NSAID exposed groups. Perioperative glucocorticoid exposure, smoking and concurrent diabetes mellitus appeared to be associated with increase in point estimates of AL, albeit lack of statistical significance and this could be due to an underpowered analysis.

Previous meta-analyses have attempted to delineate the effects of NSAIDs upon AL rate with conflicting results. None have conducted an anastomotic-site specific analysis. Subgrouping for NS-NSAID was found to be significant for colocolic anastomoses, with other two sub-group analyses (COX-2 and Ketorolac) not reaching significance. This finding is in accordance with previous literature, which highlights that the large bowel is not a uniform entity with the same genetic and physiological characteristics throughout. This statement is supported by the baseline differences of genetic make-up of tumours affecting either the ascending or the descending colon [39], which may signify variable post-operative tissue behaviour upon NSAID exposure.

This study is limited by the small number of available randomised controlled trials. Large well conducted cohort studies were included but offered limited evidence, given the variability of surgical approaches and their definition, uncertainty of duration of NSAID exposure and differential study designs. Most previous studies addressing similar clinical outcomes have incorporated heterogeneous populations of upper and lower GI anastomoses, as well as patients with both benign and malignant presentations. This approach does not consider the inherent risk of AL per overall site of operation, which is significantly different between the two GI locations. Furthermore, analysing heterogenous populations as per diagnosis does not address inherent tissue friability and pathology in the overall AL outcomes [40,41]. Additionally, only two studies collected data with an exposure duration limited to under 72 hours, which made a sub-group analysis of duration (≤72, >72 hours) not feasible. Instead, we conducted a sensitivity analysis to identify potential outcome variation that may be attributed to duration of exposure, rather than the NSAID category. A strength of this study is that, in contrast to preceding meta-analyses, our search strategy identified the greatest number of papers which were reviewed and appraised prior to their inclusion in our analysis and was conducted in a clinically homogenous population. Our approach of subgroup analysis to assess the effect of NSAIDs by anastomotic site has not been performed previously and provides results which can be more easily integrated into clinical practice.

The use of NSAIDs in the perioperative care of oncology patients undergoing colonic resection may be a useful adjunct in providing optimal analgesia and reducing the opioid burden. Current literature remains conflicted on the safety of these agents in those undergoing colonic resections with the formation of a primary anastomosis.

## 5. Conclusion

The association between NSAID exposure and AL in oncological patients remains undetermined. Whilst in present work, colocolic anastomoses appear to be more sensitive to

AL events, the observed association may be anastomotic site and NSAID- category dependent.

## Author contributions

Concept conception: Kastora S. L
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Data analysis: Kastora S. L., Kounidas G.
Manuscript editing: Kastora S. L., Osborne L. L., Jardine R., Kounidas G., Carter B., Myint P.K.
Data analysis expert opinion: Carter B. Myint P.K.

Authors have nothing to disclose.
No funding was received for the present study.
All crude data available upon request.

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## Supplementary Figures

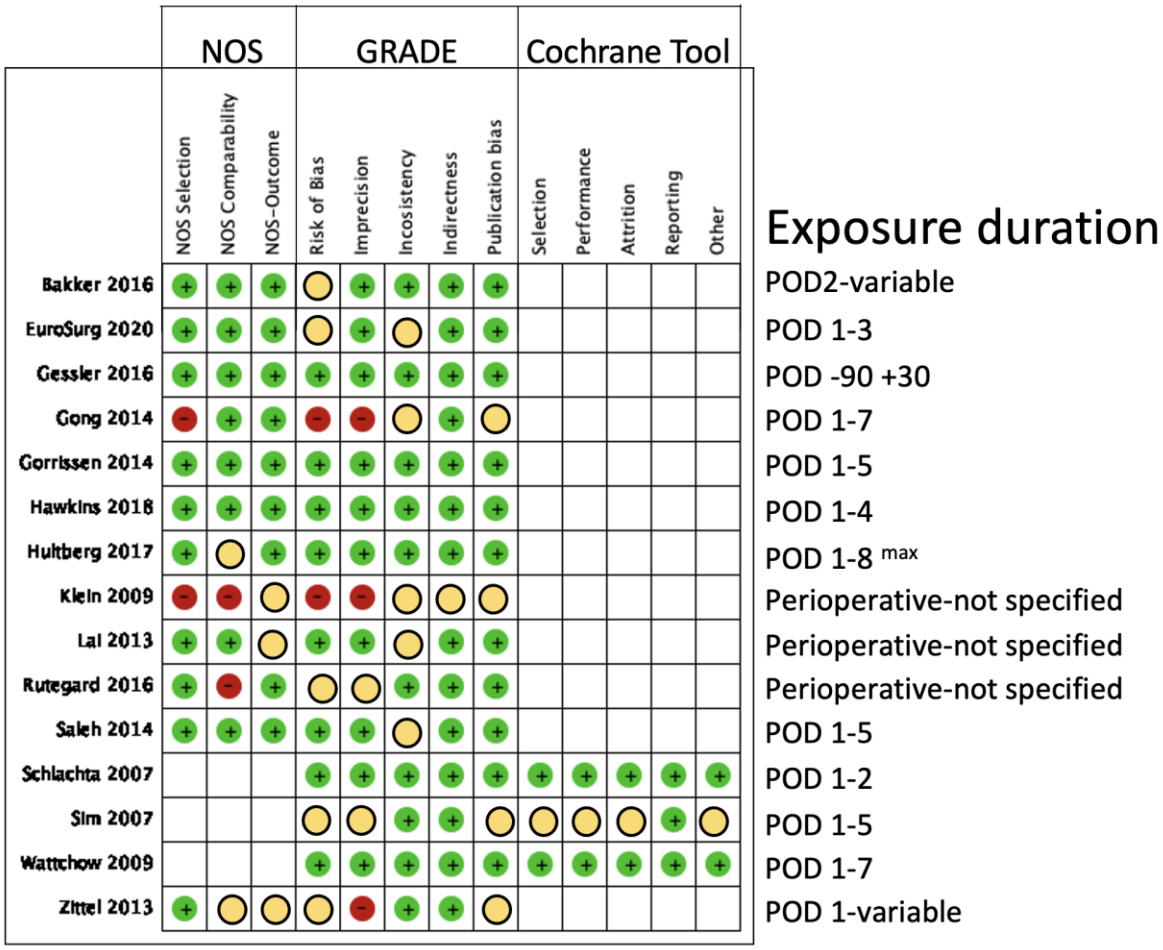



**Fig. S1.** Risk of Bias table of included studies. Newcastle-Ottawa for observational studies (NOS) Cochrane Risk of Bias Tool for RCTs; GRADE framework for recommendation.

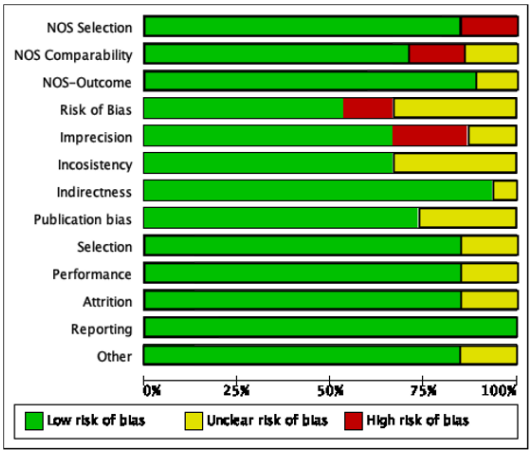



**Fig. S2**. Risk of Bias summary table of all risk of bias and level of evidence assessment.

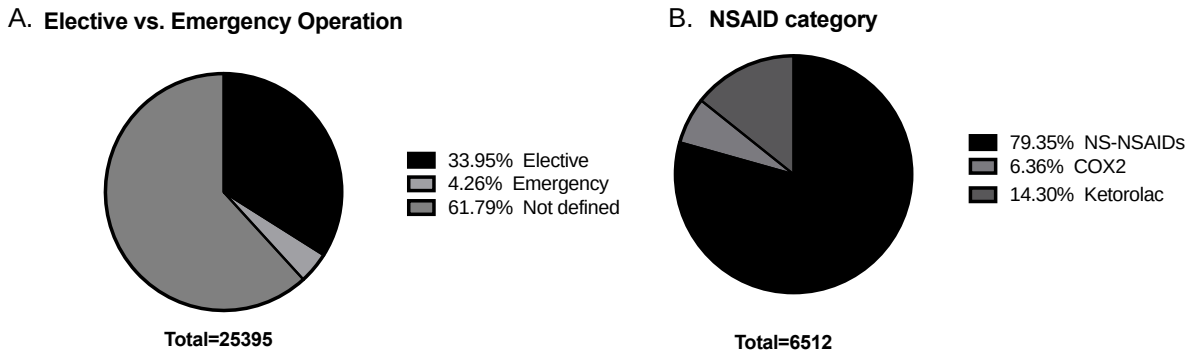



**Fig. S3. Overall study characteristics**. Urgency of operation (A), Category of NSAIDs used across studies (B). Image was generated with GraphPad Prism V.9.

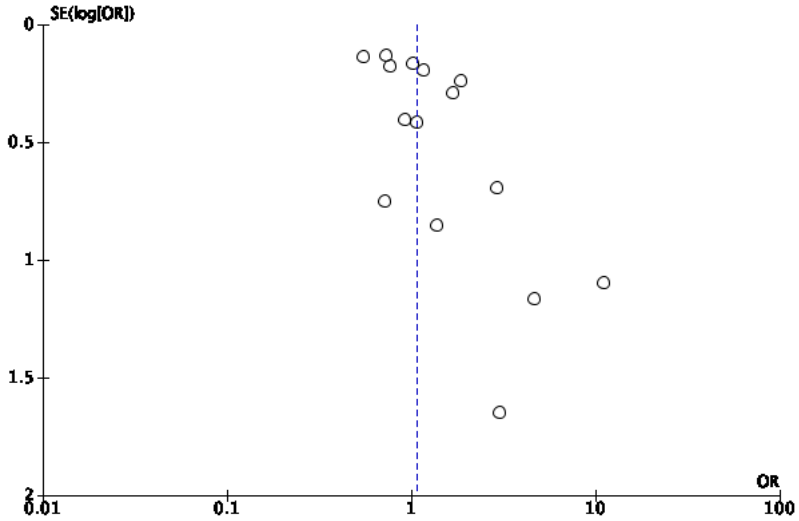
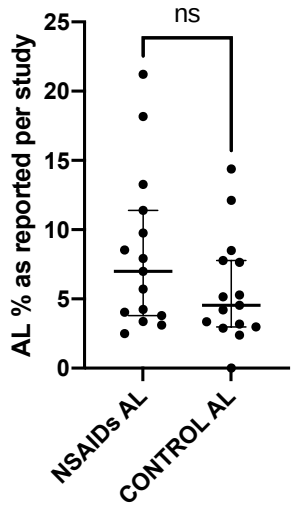



**Fig. S4.** Funnel plot of Fig. 2. Publication bias of included studies.




| | |
|---|---|
| Unpaired t test | |
| P value | 0.1459 |
| P value summary | ns |
| Significantly different (P < 0.05)? | No |
| One- or two-tailed P value? | Two-tailed |
| t, df | t=1.496, df=28 |

**Figure S5.** Collective AL % and unpaired t-test of statistical significance.

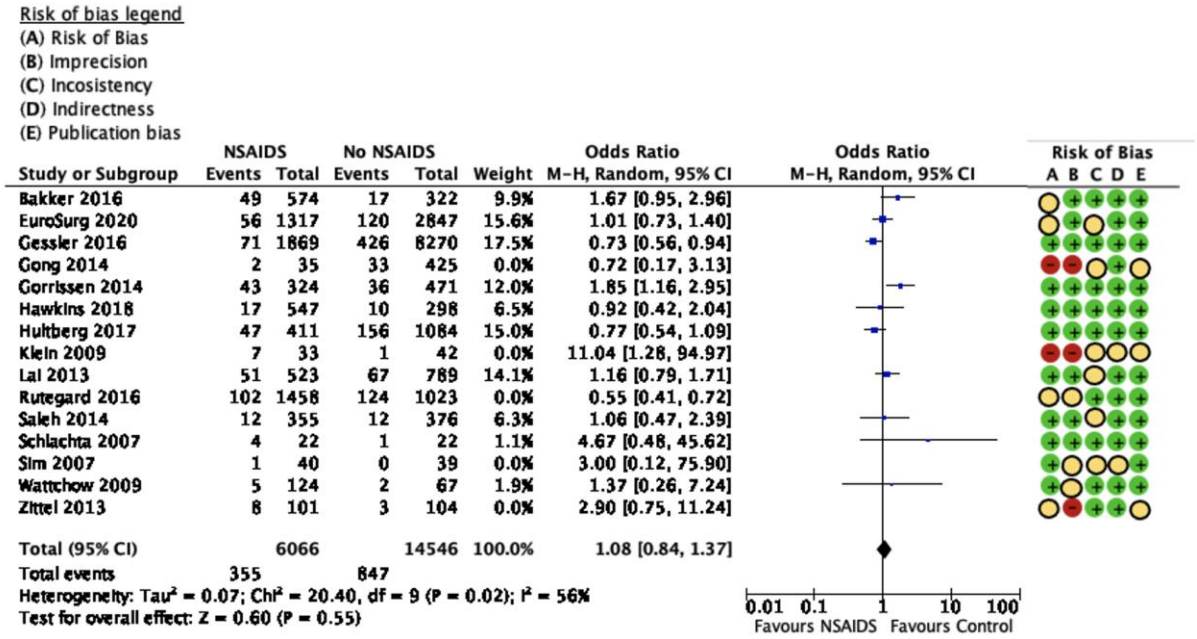



**Figure S6.** Sensitivity analysis to explore heterogeneity as per GRADE framework grading.

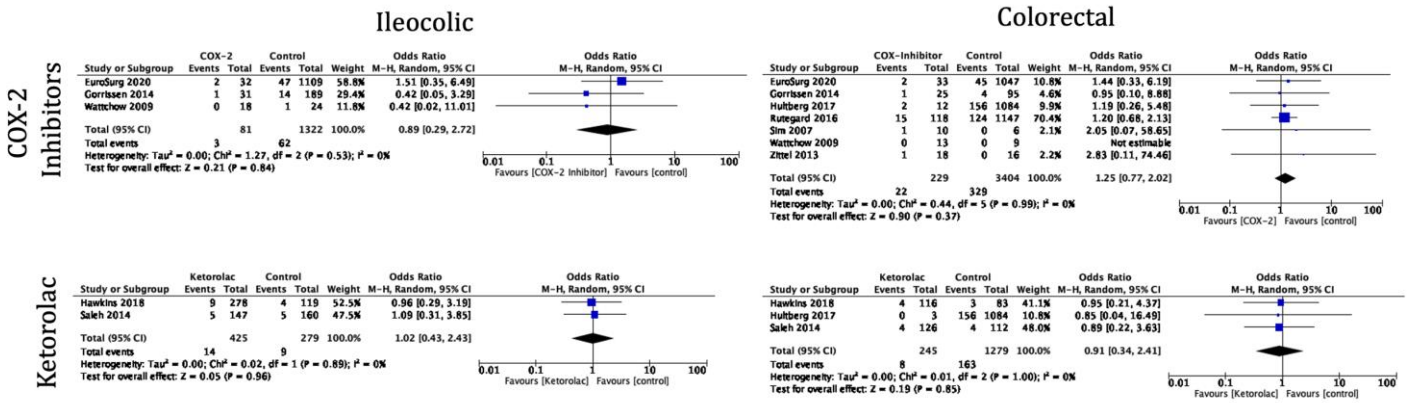



**Figure S7.** Mantel-Haensel statistical method with random effects analysis model and odds ratio as output only for extracted data from included studies for postoperative NSAID exposed patients undergoing operations involving ileocolic (left-side forest plots) or colorectal anastomoses (right-sided forest plots) NSAIDS. NSAIDs have been categorized according to NICE 2019 guidelines into selective e.g COX-2 inhibitors (-coxib) and ketorolac given its higher specificity. Image was generated with Cochrave RevMan V.5.4

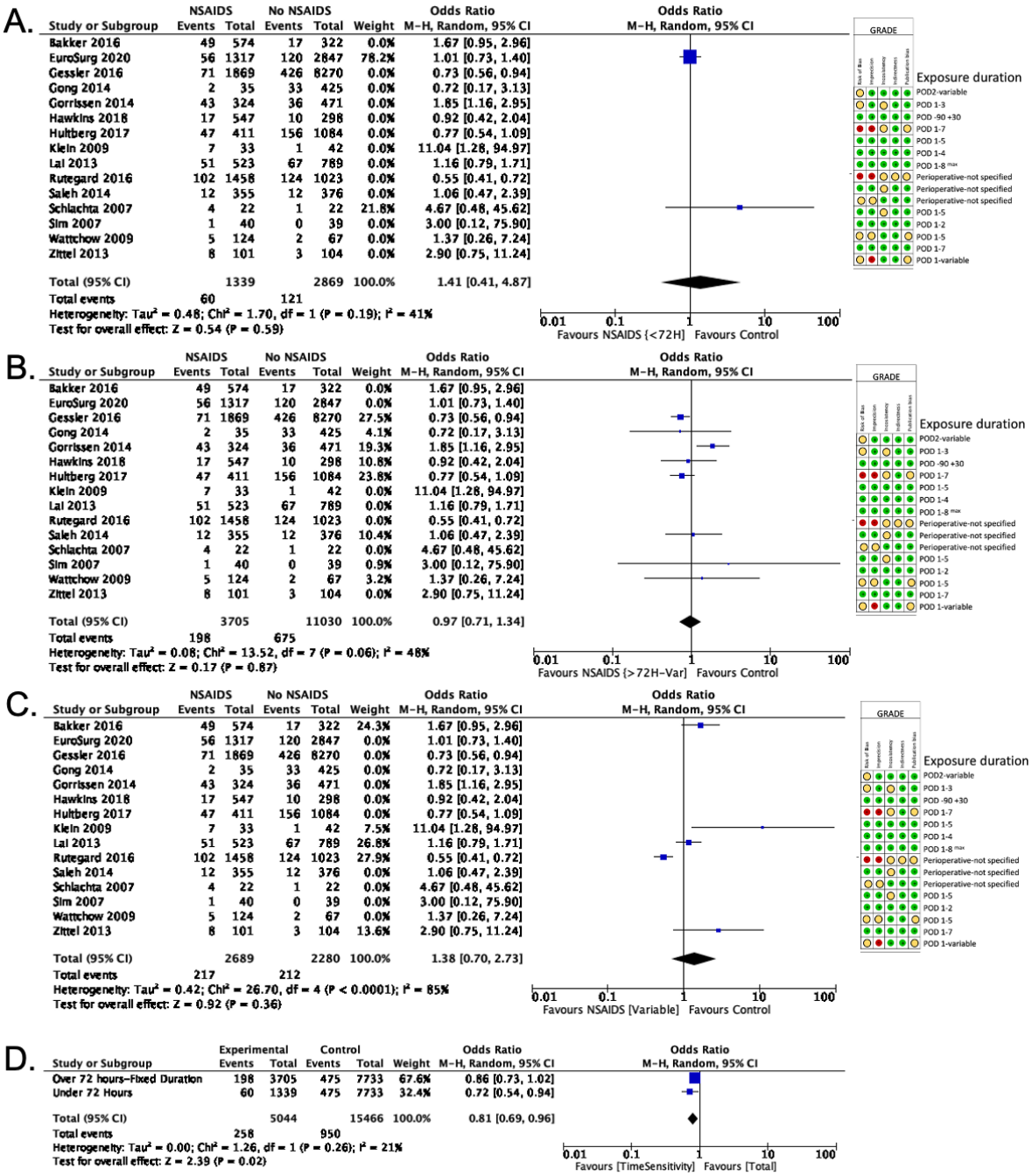



Fig S8. Sensitivity analysis of NSAID exposure [≤ 72 hours] OR 0.72 [0.54, 0.94], p-value: 0.02 (A), >72 hours with duration specified OR 0.86 [0.73, 1.02], p = 0.09 (B), duration not-specified (C), Comparison of collective results (Fig. 2) with sensitivity outcomes (D). Image was generated with Review Manager V. 5.4 Cochrane Tool for meta-analysis.

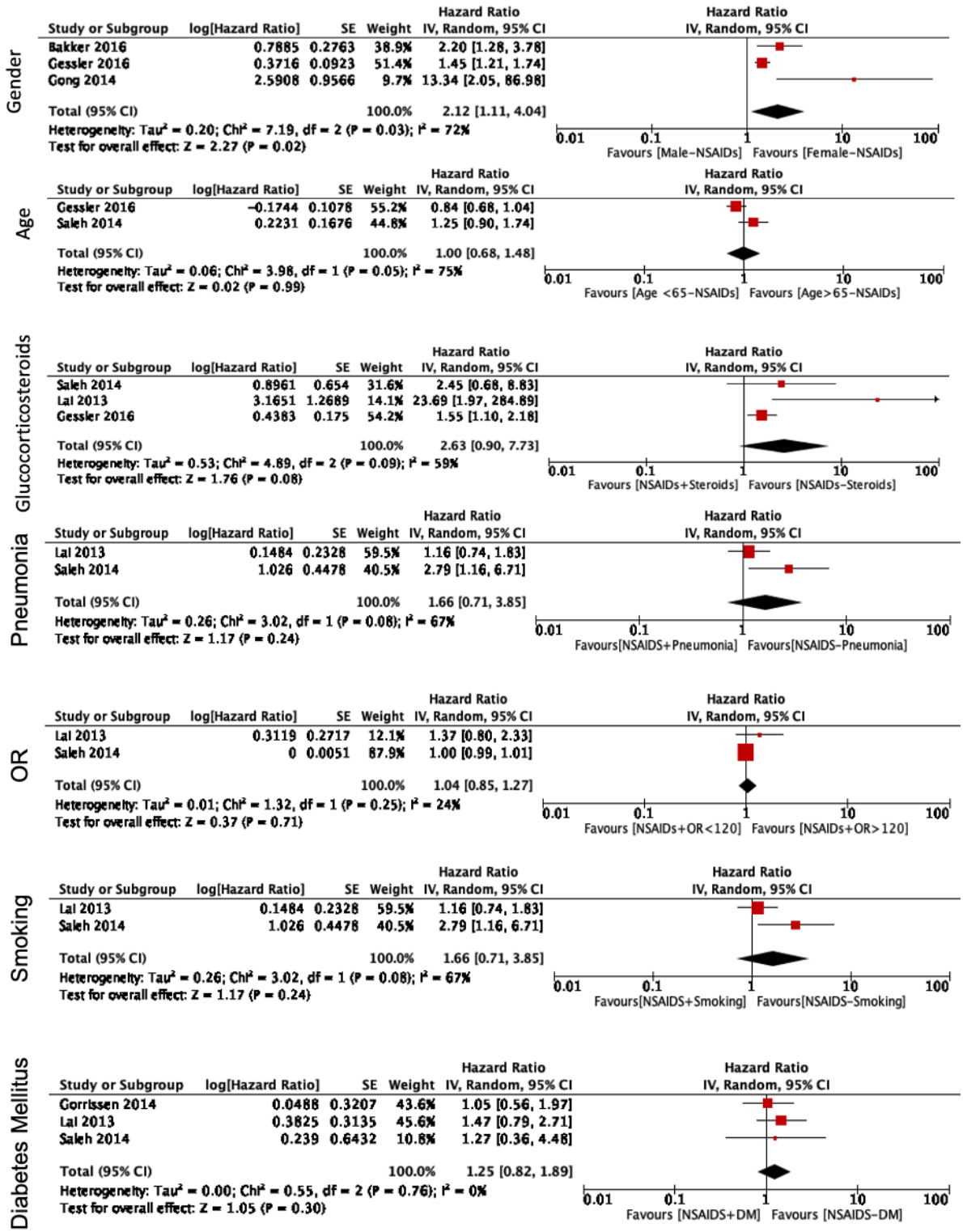



Fig. S9. Generic Inverse Variance analysis of adjusted hazard ratio (95% CI) as per study. Adjusted HR for Age, Gender, Glucocorticosteroids, Pneumonia. Crude HR analysis for OR, Smoking, Diabetes Mellitus. Image was generated with Review Manager V. 5.4 Cochrane Tool for meta-analysis.

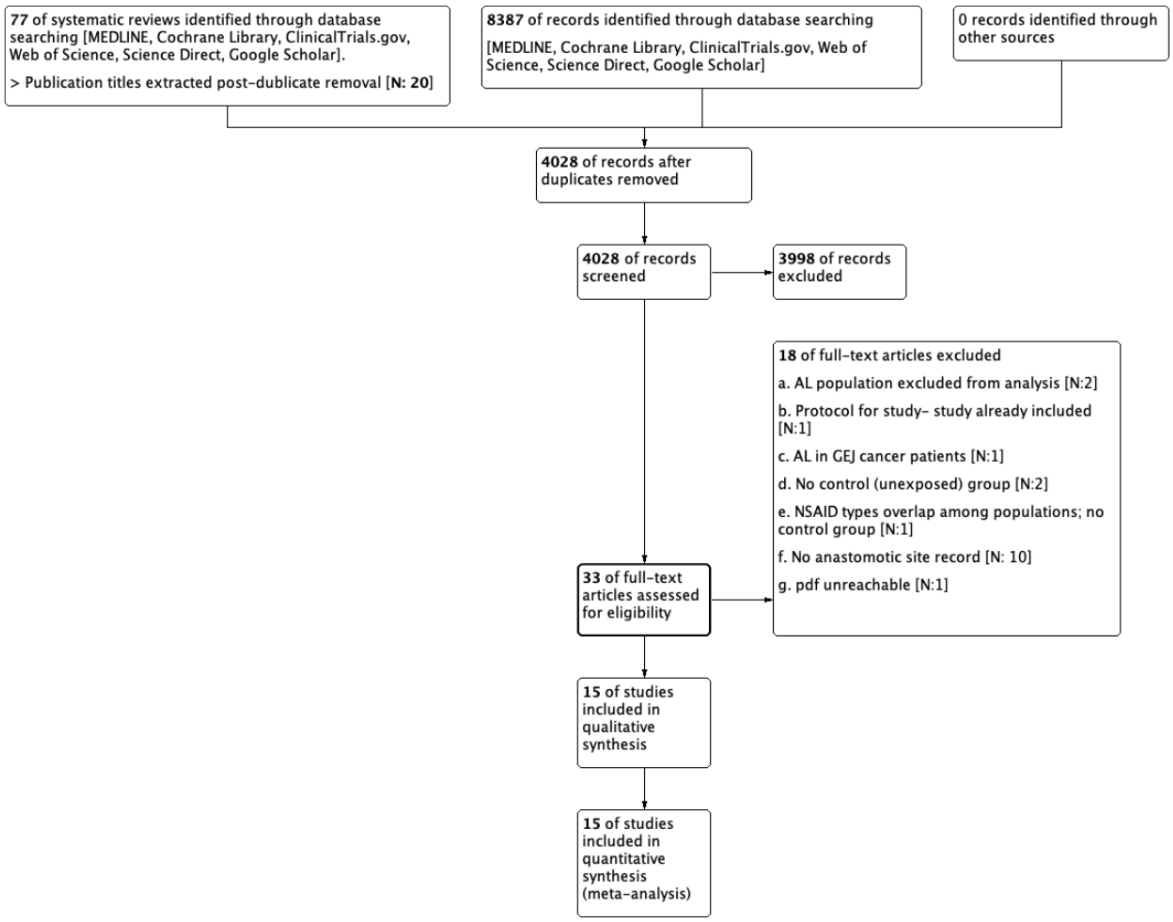



**Fig. 1** PRISMA Flow diagram of search strategy.

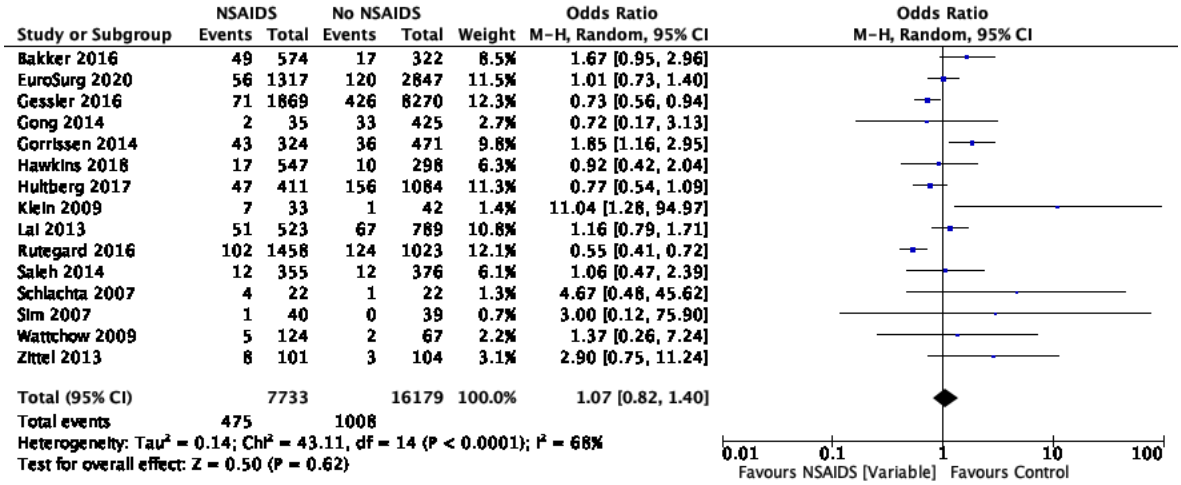



**Fig. 2.** Mantel-Haensel statistical method with random effects analysis model and odds ratio as output only for included observational studies and for RCTs and funnel plot assessing respective variance (Fig. S4). NSAID group contains both non-selective and selective NSAIDS. Subgroup for observational studies 1.04 [0.79, 1.37], 73%, Test for overall effect: Z = 0.27 (P = 0.79); Subgroup RCTs OR 2.21 [0.64, 7.65], 0%, Test for overall effect: Z = 1.25 (P = 0.21).

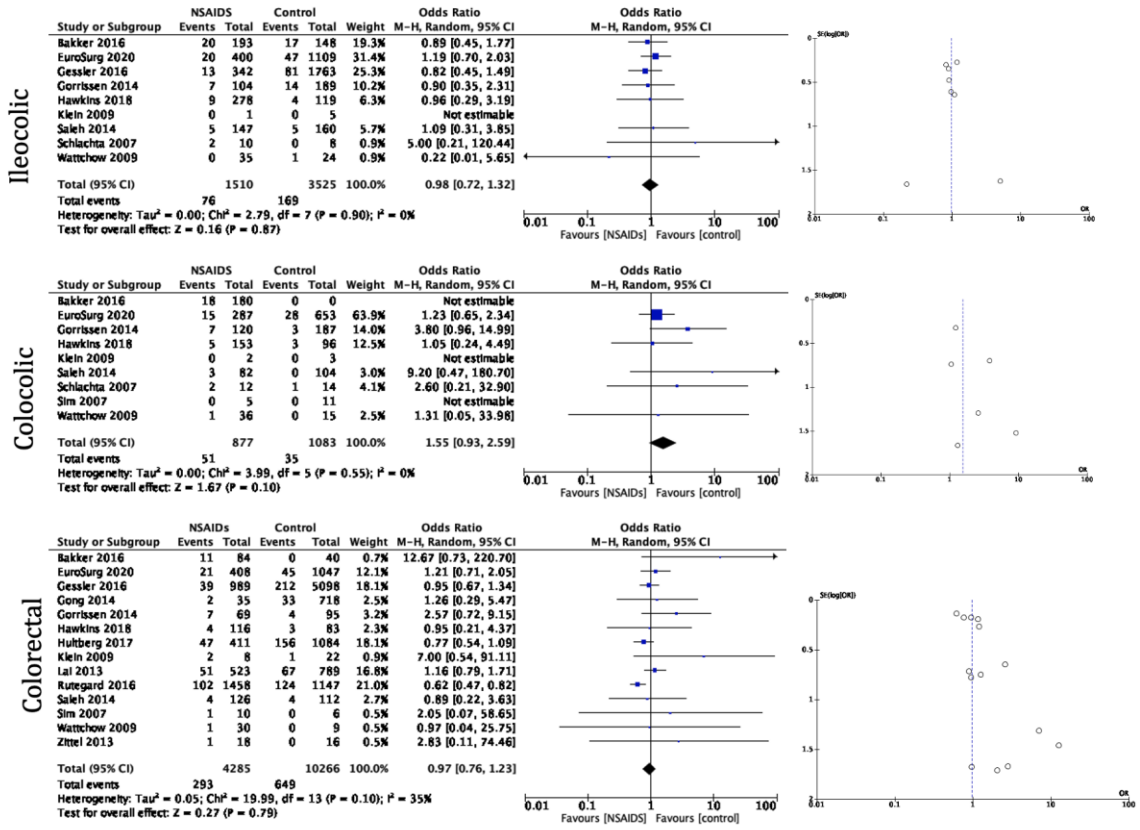



**Figure 3.** M-H statistical method with random effects analysis model and odds ratio as output only for extracted data from included studies for postoperative NSAID (all categories) exposed patients undergoing operations involving ileocolic (A) colocolic (B) and colorectal anastomoses (C) and associated funnel plots assessing respective data variance.

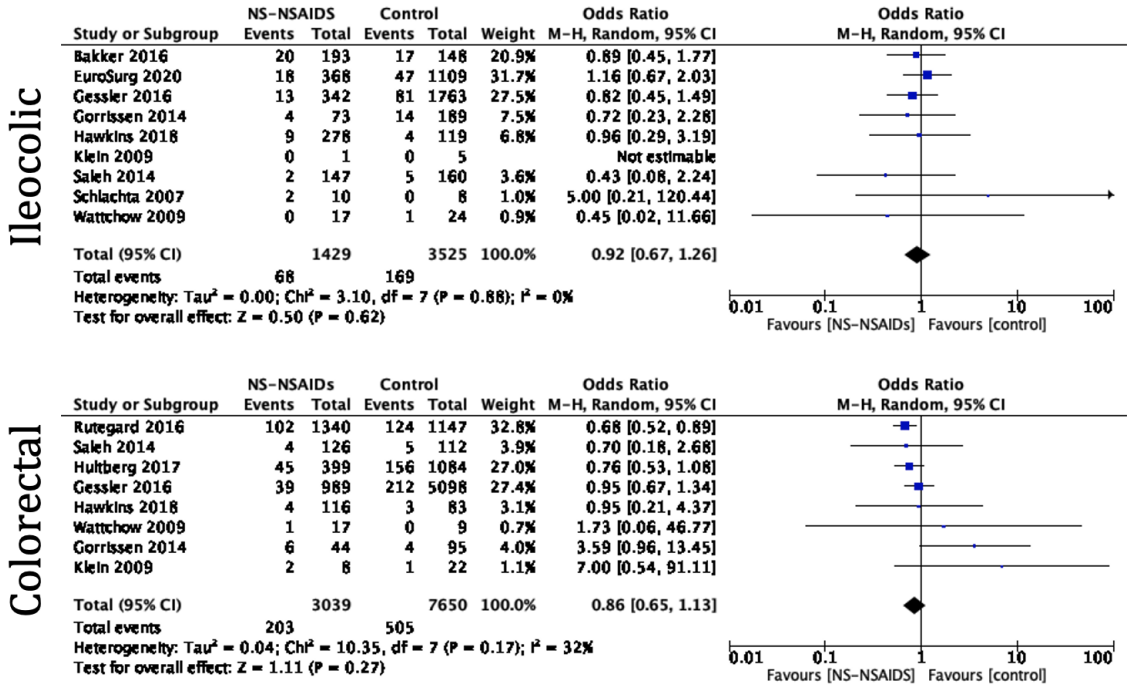



**Fig 4.** M-H statistical method with random effects analysis model and odds ratio as output only for extracted data from included studies for postoperative NSAID exposed patients undergoing operations involving ileocolic or colorectal anastomoses. NSAIDs have been categorized according to NICE 2019 guidelines into non- selective (NS) (diclofenac, ketorolac, ibuprofen), selective e.g COX-2 inhibitors (-coxib) and a subgroup analysis for ketorolac given its higher specificity.

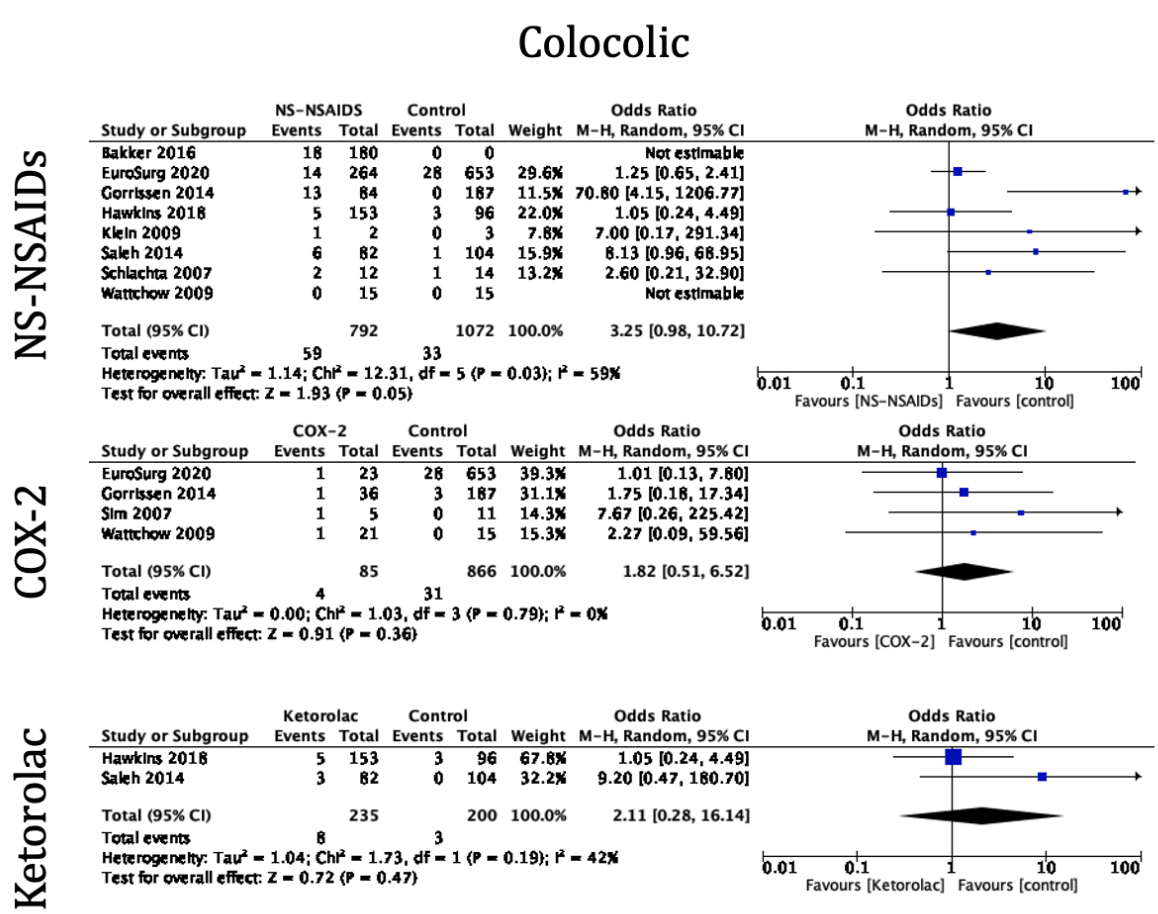



**Figure 5.** M-H statistical method with random effects analysis model and odds Ratio as output only for extracted data from included studies for postoperative NSAID exposed patients undergoing operations involving colocolic anastomoses. NSAIDs have been categorized according to NICE 2019 guidelines into non- selective (NS) (diclofenac, ketorolac, ibuprofen), selective e.g., COX-2 inhibitors (-coxib) and a subgroup analysis for ketorolac given its higher specificity.