Non-steroidal anti-inflammatory drugs after abdominal surgery: an umbrella review of existing evidence

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Abstract

Background: Multi-modal analgesia is recommended for enhanced recovery after colorectal and abdominal surgery. Previous reviews have reported highly discordant observations around the benefits and risks of non-steroidal anti-inflammatory drugs (NSAIDs). This umbrella review aimed to provide a recommendation based on the best available evidence.

Methods: A systematic search was performed for reviews exploring benefits and risks of NSAIDs after abdominal surgery. The quality of reviews was assessed using the AMSTAR-2 tool. Outcomes of interest comprised clinical efficacy (pain, opioid consumption, return of gut function) and safety (intestinal bleeding, anastomotic leak, acute kidney injury). The presence of discordant conclusions across reviews was investigated using the Jadad decision algorithm to determine the best available evidence.

Results: Twenty-seven reviews were included, reporting evidence for pain (n=10/27), opioid-consumption (n=11/27), gut function (n=4/27), bleeding (n=1/27), anastomotic leak (n=13/27), and acute kidney injury (n=2/27). The quality of all reviews was 'critically low'. The reviews were concordant in showing that NSAIDs reduce pain, opioid consumption, and time to gut recovery. Studies reporting anastomotic leak after colorectal surgery were highly discordant. The best available evidence showed an increased risk of anastomotic leak with non-selective NSAIDs, but not convincingly for COX-2 inhibitors.

Conclusion: NSAIDs after abdominal surgery reduce pain, opioid consumption, and the time to gut recovery. In the context of colorectal surgery, non-selective NSAIDs may increase the risk of anastomotic leak, but this is based on low quality data. Their use should be limited to selective NSAIDs until robust evidence is available to guide decision-making.

Introduction

More than 21,000 colorectal cancer resections are performed annually in the UK alone, leading to over 120,000 bed days in the National Health Service (NHS) (1). With the incidence of colorectal cancer incidence set to increase by 60% in 2030, postoperative recovery must be enhanced to improve patient outcomes and reduce healthcare burden(2). Enhanced recovery guidelines, such as those set out by the Enhanced Recovery After Surgery (ERAS) Society, outline the importance of good hydration, nutrition, analgesia, and mobility during the postoperative period to facilitate safe discharge from hospital. Optimal pain management is particularly important. If managed poorly, patients may suffer from chronic pain, long-term opioid requirements in the community, and reduced long-term quality of life (3)(4).

Multi-modal analgesia regimens target opioid and non-opioid pain pathways, seeking to reduce side effects associated with large doses of opioids such as nausea, sedation, and constipation (4). Multi-modal regimens commonly include a combination of paracetamol, non-selective or selective non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetic agents, and opioids administered as rescue analgesia (5). Together, these reduce regular morphine consumption and facilitate faster recovery (5,6). Accordingly, multi-modal analgesia is strongly recommended by ERAS guidelines across multiple fields of abdominal surgery (5).

Non-steroidal anti-inflammatory drugs are recommended for use within multi-modal regimens but their use is limited due to associations with adverse events such as gastrointestinal bleeding and acute kidney injury (AKI) (7,8). Some studies have also documented an association between NSAIDs and an increased risk of anastomotic leak after colorectal surgery (5). This has prompted a change in practice, with many clinicians opting to

avoid NSAIDs after surgery. Data from large cross-sectional studies estimate that only 28% of patients undergoing major colorectal surgery receive NSAIDs as recommended (5,9,10).

Numerous systematic reviews have investigated the benefits and risks of NSAIDs after abdominal surgery with widely conflicting conclusions. This umbrella review aimed to provide a comprehensive overview, leading to a recommendation based on the highest quality of currently available evidence. Specific objectives were to explore the impact of NSAIDs on key efficacy outcomes (postoperative pain, opioid consumption, and intestinal function) as well as safety outcomes (AKI, gastrointestinal bleeding, and anastomotic leak).

Methods

Study Design & Governance

An umbrella review was undertaken according to a prospective protocol. Umbrella reviews are a type of evidence synthesis, using systematic methods to identify systematic reviews on a broadly similar topic. Their purpose is to collate, assess, describe, and synthesise evidence from the current body of systematic review evidence, including an assessment of disparity between reports (11). Research ethics approval was not required and registration on the PROSPERO database was not applicable in this context. This report is written according to the Preferred Reporting Items for Overviews of Reviews (PRIOR) Statement (12). This review was designed to provide a systematic overview of NSAIDs after abdominal surgery, capturing data on a wide range of potential benefits and risks, leading to a comprehensive conclusion for their use.

Definitions

For the purpose of this umbrella review, NSAIDs were defined as pharmacological agents targeting cyclo-oxygenase enzymes (COX-1 and/or COX-2). Non-selective NSAIDs were defined as NSAIDs targeting both COX-1 and COX-2. Aspirin was included within this definition. All systemic (non-topical, non-neuraxial) routes of administration (including enteral and parenteral) were considered. Abdominal surgery was defined as any invasive instrumentation of the abdomino-pelvic cavity via open, laparoscopic, robotic, or natural orifice approaches (13).

Search Strategy

Potentially eligible reviews were identified by performing systematic searches of Embase (via Ovid), MEDLINE (via Ovid), the Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports, PROSPERO, and the Cochrane Library. Time limits for the searches were set from inception to May 2022. The search was subsequently updated to include articles up to August 2024. Two independent investigators (MK and SC) screened titles, abstracts, and full-text manuscripts for possible inclusion, with discrepancies addressed through further discussion and involvement of a third investigator (AN) to assist in reaching consensus. Reference lists of included studies were also reviewed for potentially eligible reviews. A full outline of the search strategies used are provided in Supplement Table S1.

Eligibility Criteria

To be eligible for inclusion, manuscripts had to report a systematic review, with or without meta-analysis, exploring the role of NSAIDs after abdominal surgery. Reviews comparing NSAIDs with a placebo or a non-NSAID patient group were included. Pre-specified outcomes of interest were those describing safety (including gastrointestinal bleeding, AKI, and anastomotic leak after colorectal surgery) and those describing potential clinical benefits (including pain, opioid consumption, and intestinal function). Articles published in any language were eligible, as were conference abstracts. For the purpose of this overview, reviews exploring NSAIDs and their impact on oncological outcomes were excluded.

Data Extraction & Quality Assessment

Two independent investigators (MK & AN) extracted data from reviews using a standard proforma. Variables of interest included factors relating to the review methods (such as eligibility criteria, definitions, and search strategies) and the primary studies (such as details about the population, intervention, comparator and outcomes). All reviews were assessed according to the 16-item AMSTAR-2 tool, providing an assessment of quality according to an appraisal of "critical" and "non-critical" flaws (14). After familiarisation with the tool, assessments were performed by three independent assessors (MK, AN, SC), with disagreements addressed during a consensus meeting. The output was a measure of confidence (high; moderate; low; and critically low) as described in the AMSTAR-2 guidance (14).

Discordant Reviews

Systematic reviews exploring the same outcome but with contrasting conclusions were assessed using the Jadad Decision Algorithm (15) (Figure 1). This is a tool to assist decision-makers to interpret reviews where there is discordance between the respective conclusions. The tool determines the source of discordance between systematic reviews, with consideration to differences in the clinical question, eligibility criteria, approach to data extraction, quality assessment, and statistical analysis. Three independent investigators (MK, AN, SC) applied the algorithm to all reviews in which discordance existed, with disagreements between investigators addressed during a consensus meeting. Where discordance existed, the individual studies included in each systematic review were examined to determine the percentage of overlap. The output of this assessment was to agree on a single systematic review which was considered to provide the best available evidence for each outcome.

Outcomes for which all included reviews were concordant on the same conclusion did not undergo assessment using the Jadad Decision Algorithm.

Statistical Analysis

Data are presented descriptively using rates, averages (mean and medians), and variation (standard deviation and interquartile range). Owing to a high degree of expected heterogeneity across data sets, no statistical analysis of primary studies or re-analysis of included systematic reviews or meta-analyses was undertaken. Instead, the results are presented using a narrative synthesis of findings from included systematic reviews.

Results

Summary of Reviews

The searches identified 2393 records, of which 27 full text reviews were eligible (Figure 2). Fifteen (n=15/27; 55.6%) were reviews in the context of colorectal surgery and the remainder were reviews in gynaecology (n=2/27; 7.4%) and mixed (10/27; 37.0%) abdominal procedures. Across all reviews, 10 (n=10/27; 37.0%) included only randomised controlled trials (RCT), 14 (n=14/27; 51.9%) included RCTs and non-RCTs, and two included only non-RCTs. Five reviews focussed on non-selective-NSAIDs (n=5/27; 18.5%), three focused on COX-2 inhibitors (n=3/27; 14.3%), and 19 studied both (n=19/27; 70.4%). A full outline is provided in Table 1.

Quality of Reviews

According to the AMSTAR-2 tool, all reviews were considered to be 'critically low' quality due to having at least two critical methodological flaws. The most common flaws were absence of a justified list of excluded studies (24/27, 89%), a lack of a comprehensive search strategy (23/27, 85%), and absence of a prospective protocol (18/27, 67%) (Table 2). The full results of the AMSTAR-2 quality assessment are shown in supplementary Table S3.

Pain

Ten reviews reported pain outcomes all with broadly concordant conclusions. In the setting of colorectal surgery, Burton found that movement-evoked pain (weighted mean difference (WMD): −0.28 [−0.43, −0.13]; *P*=0.0002) and pain at rest (WMD:−0.11 [–0.19, –0.02]; *P*=0.001) were significantly lower two days after surgery with the use of NSAIDs compared to controls (16). In narrative reviews of open and laparoscopic colorectal surgery, Uten and Lirk recommended the use of non-selective NSAIDs and COX-2 inhibitors as part of multi-modal

analgesia regimens, as did Lirk and Zemmel after gynaecological surgery (17,18). Amongst four reviews of mixed abdominal populations, Carter showed that intravenous Meloxicam was associated with significantly reduced pain (pain intensity difference = -6.84 [-7.00, -6.67]) over the first 24 hours compared to paracetamol (-0.650 [-1.25, -0.0617]) (19). Hyllested and Dieu provided similar recommendations for NSAIDs in combination with paracetamol (20,21).

Opioid Consumption

Eleven reviews reported opioid consumption outcomes all with broadly concordant conclusions. After colorectal surgery, Burton demonstrated reduced opioid use in the first 48 hours with NSAIDs compared to controls (WMD: -22 mg [95% CI: -28,-16] *P*<0.001]) (16). This was corroborated by Chapman and Milne, both showing reduced total morphine consumption with NSAIDs (average reduction of 12.9-30.0mg) (22,23). In gynaecological surgery, narrative reviews by Lirk and Zemmel recommended the use of NSAIDs after hysterectomy (24,25). In mixed populations, Carter showed that intravenous meloxicam was associated with lower morphine consumption within 48 hours (mean difference: -8.7 MME [95% CI: -9.1, -8.3] *P*<0.05), as did Maund with COX-2 inhibitors (mean difference: 10.9mg [95% CI: 12.8, -9.1] *P*<0.05) compared to placebo (7) Narrative syntheses by Dieu and Hyllested reported similar experiences of reduced opioid requirements in mixed populations (20,21).

Return of gut function

Four reviews reported on the role of NSAIDs for improving the return of gut function. All were in the context of colorectal surgery and all provided concordant conclusions. Chapman demonstrated significantly shorter periods until first stool (mean difference: -9.5h [95% CI -14.7, -4.8] P<0.001) and oral diet (mean difference: -12h [95% CI -18.0, -6.0] *P*<0.001) in a pooled

population of 563 participants (22). Milne similarly showed a reduction in the time to first stool (mean difference: -12.1h [95% CI: -17.2, -7.0] *P*=0.02) and oral diet (mean difference: -12.0h [95% CI: -18.7, -5.2) *P*<0.001) in a population of 515 participants (23). In keeping with these analyses, Burton reported a pooled reduction in the time to first bowel motion of 0.43 days (95% CI: -0.66, -0.21; *P*<0.001) across 505 pooled participants and Peng reported a significant reduction in the incidence of postoperative ileus (OR: 0.35 [95% CI: 0.13, 0.89] *P*=0.03) (16,26).

Bleeding Complications

Two reviews reported bleeding complications. One reported a meta-analysis of 68 studies across all types of surgery, comprising 12 types of NSAIDs, including ketorolac, diclofenac and ibuprofen. The analysis found no difference in the risk of haematoma (35 studies, risk difference (RD): 0.00 [95% CI: 0.00, 0.00] *P*=0.492), re-operation due to bleeding (19 studies, RD: 0.00 [95% CI 0.00, 0.01] *P*=0.792), or transfusion (16 studies, RD: 0.00 [95% CI 0.00, 0.00] *P*=0.492) in NSAID vs. non-NSAID groups (27). In a review relevant to pancreatic surgery, Flemming found no difference in operative blood loss (mean difference -99.4ml [95% CI -201.71 to 2.91] *P*=0.06) or postoperative haemorrhage (OR 2.35 [95% CI 0.48-11.59] *P*=0.29) with NSAIDs vs. controls (28).

Colorectal Anastomotic leak

Twelve reviews reported rates of anastomotic leak in patients receiving and not receiving NSAIDs. All were in the context of colorectal surgery and the conclusions were highly discordant.

One review reported analysis of only non-selective NSAIDs (n=1/12), whilst eleven reviews reported analysis of both non-selective NSAIDs and COX-2 inhibitors (n=11/12). Overall, the pooled rate of anastomotic leak was higher in patients receiving any type of NSAID compared to the comparator groups in six reviews (n=6/12) (26,29–33). In sub-group analyses, the rate of

leak was higher in patients receiving non-selective NSAIDs in eight reviews (n=8/12) (26,29–35) and higher in patients receiving COX-2 inhibitors in two reviews (n=2/11) (32,34). A full outline is provided in Table 3.

Due to discordant conclusions, the Jadad Decision Algorithm was applied (Figure 1). A full outline of the decision-making process is provided in Supplement S1. In summary, after confirming that all reviews investigated the same question relating to anastomotic leak, it was determined that considerable variation existed in the final inclusion of primary studies as well as the respective eligibility criteria (Table 4). The full analysis of primary study overlap is shown in Supplement Table S2. Accordingly, the following characteristics were explored to determine which review provided the best available evidence: publication status of primary studies, quality of primary studies, impact of language restrictions, and analysis of individual patient data. Four reviews (n=4/12) planned to include unpublished data in their analyses but no such data were identified during the searches (16,22,29,30). Ten reviews (n=10/12) conducted a quality assessment of primary studies (16,22,26,29–31,33,35–37), but only five (n=5/10) considered these assessments within sub-analyses of high quality studies. Six reviews (n=6/12) limited their search to English language (22,29,30,32,34,37) and none (n=0/12) conducted analyses using individual patient data (Table 4). Using these criteria, the review by Jamittrong was assessed as providing the highest quality evidence available, balancing both the breadth of data and precision of statistical estimates.

Jamittrong reported a significantly higher rate of anastomotic leak in participants receiving NSAIDs (OR: 1.73 [95% CI: 1.31, 2.29] P<0.001). Discrepancy existed between sub-analyses of RCT (OR: 1.91 [95% CI: 0.69, 5.35] P=0.67) and non-RCT (OR: 1.72 [95% CI: 1.28, 2.31] P<0.001) evidence, but this was considered to represent a lack of statistical power, for the anastomotic

leak outcome, due to small sample sizes across RCTs (n=559 vs. n=31,317). More evidence to support these adverse effects was demonstrated by sub-analyses of protocolised (regular administration) and non-protocolised NSAID use. The protocolised group was associated with a higher odds of anastomotic leak (OR 4.67 [95% CI: 2.84, 7.67] *P*<0.001) compared to the non-protocolised group (OR: 1.34 [95% CI: 1.03, 1.75] *P*=0.02), raising the possibility of a dose effect. Further sub-analyses revealed that the rate of anastomotic leak in participants taking COX-2 inhibitors was not significantly higher (OR: 1.67 [95% CI: 0.90, 3.13] *P*=0.11) as it was for non-selective NSAIDs (OR: 1.80 [95% CI: 1.12, 2.91] *P*=0.02) versus controls. However, a subsequent meta-regression showed no difference in estimates of anastomotic leak for both classes of NSAID (*P*=0.85) (30).

Acute Kidney Injury

Acute kidney injury in the context of NSAID administration was explored by two reviews. Aiolfi investigated the risk of AKI in patients undergoing elective oesophagogastric surgery, finding no difference in its incidence between NSAID (0.62%) and non-NSAID groups (0.71%) according to KDIGO criteria (38). Fleming showed similar results in the setting of pancreato-duodenectomy, with no difference in the risk of AKI between NSAID and non-NSAID groups (26).

Other Outcomes

A small number of other outcomes were reported across the identified reviews. Fleming provided evidence that NSAIDs were not associated with an increased risk of clinically relevant pancreatic fistulae after pancreatic surgery (OR 1.18 [95% CI, 0.84–1.64] *P* =0.33) (28). Bukhari showed that NSAIDs were not associated with an increase in overall adverse events compared to controls after gastrointestinal surgery (RR 0.78 [95% CI 0.51 to 1.1] *P*=0.34) (41). After

oesophagogastric surgery, Aiolfi demonstrated that NSAIDs were not associated with an increase in upper gastrointestinal anastomotic leak (RR: 1.49 [95% CI 0.81-2.75] *P*=0.19) (36).

Discussion

This umbrella review provides a comprehensive assessment of the benefits and risks of NSAIDs when used as analgesia after abdominal surgery. Across multiple systematic reviews, there was wide agreement that NSAIDs are effective at reducing post-operative pain, reducing opioid consumption, and accelerating the return of gut function. A small number of reviews showed that NSAIDs do not increase the risk of bleeding-related events or AKI when used according to usual safe prescribing practice. With respect to the risk of anastomotic leak after colorectal surgery, the conclusions of all reviews were highly discordant. The best available evidence, assessed using the Jadad algorithm, demonstrated an increased risk of anastomotic leak with non-selective NSAIDs but not convincingly with COX-2 specific NSAIDs. The quality of all reviews was "critically low", representing a key limitation for this body of evidence.

The use of NSAIDs after colorectal surgery is controversial. In 2012, Klein and colleagues raised concerns about NSAIDs, demonstrating a greater associated risk of anastomotic leak with diclofenac (OR: 7.2 [95% CI: 3.8-13.4] $P<0.001$) but not with ibuprofen (OR: 1.5 [95% CI: 0.8-2.9] $P<0.18$) when used as post-operative analgesia after colorectal resection (39). Since then, numerous randomised and non-randomised studies have reported highly conflicting observations. Some randomised trials have echoed similar concerns about the risk of anastomotic leak but these were seldom powered definitively to evaluate differences in postoperative adverse events, particularly a relatively rare outcome of anastomotic leak. In other non-randomised evidence, large international cohort studies have demonstrated no difference in the rates of anastomotic leak with or without NSAIDs but these were limited by bias inherent to observational studies (8). Despite successive iterations of ERAS guidelines recommending that NSAIDs can be used after colorectal surgery, recent evidence suggests that

they are administered to only 28% of patients during the early postoperative period (5,10,40). The reasons for this observation remain unclear, although anxieties around anastomotic leak and the serious impact that it can have on patients are likely to be key factors. In keeping with the present data, the most recent iteration of ERAS guidelines recommend the use of selective NSAIDs after colonic surgery, but recommend against the use of non-selective NSAIDs.

As well as uncertainty about a causal association between NSAIDs and anastomotic leak, the underlying mechanism of action and how this might vary between different sub-classes of drugs is unclear. Some studies have revealed associations between anastomotic leak and cyclo-oxygenase (COX) inhibition, leading to poorer anastomotic healing. The current evidence suggests that inhibition of COX affects leucocyte function, reduces vascular endothelial growth factor and angiogenesis, and disrupts the formation of collagen (38). Some data have also shown that biliary excretion of NSAID metabolites, as is the case with diclofenac, may further compound the risk of anastomotic leak, particularly in the setting of a small bowel anastomosis. Other studies have proposed cardiovascular mechanisms leading to NSAID-induced anastomotic leak, such as micro-thrombosis and micro-emboli causing a reduction in anastomotic perfusion (33). The role of these mechanisms and their inter-relationship is still to be fully elucidated, making it difficult to select the most appropriate NSAID to be studied.

The insights put forward by this umbrella review must be balanced against its strengths and limitations. The breadth of data presented is a strength, enabling a comprehensive assessment of safety and efficacy endpoints across multiple types of surgery. Another strength is the use of the Jadad Decision Algorithm, providing a systematic approach to address discordance across reviews. This is important owing to the challenge of interpreting multiple conflicting reports, which may drive the known uncertainty around implementing existing guidelines in favour of

NSAIDs. Limitations are also recognised. Firstly, the results of this study are limited by the quality of primary evidence. Whilst the Jadad Decision Algorithm enabled a decision to be made about the best current evidence, it is acknowledged that the quality of all included reviews was "critically low" according to the AMSTAR-2 tool. The Jadad Decision Algorithm also does not prioritise between randomised and non-randomised evidence, although in this case all evidence quality was deemed critically low. Higher quality studies will need to recruit a sufficiently large sample to enable statistically-powered assessments of NSAIDs on relatively uncommon safety outcomes. Unclear equipoise, particularly around the issue of anastomotic leak after colorectal surgery, may be a key challenge to address in future work. Secondly, as a review of quantitative data, it is likely that other qualitative observations were missed. Such data may help to explain the underlying factors and anxieties leading clinicians to avoid the use of NSAIDs. Future work should aim to examine these factors with a view to developing a strategy for future research.

In summary, the best available evidence suggests that NSAIDs after abdominal surgery confer multiple potential benefits, including reduced pain, faster return of gut function, and an opioid-sparing effect. In the specific context of colorectal surgery, non-selective NSAIDs may increase the risk of anastomotic leak, but this is based on lower quality data. This umbrella review brings together the findings of multiple conflicting reviews in an effort to reduce uncertainty and guide decision-making on this topic. The recommendation of this review based on the best available evidence is that the use of NSAIDs after non-colorectal abdominal surgery should be readily encouraged. After colorectal surgery, the use of selective NSAIDs should continue as long as they remain supported by enhanced recovery guidelines, but non-selective NSAIDs should be avoided. Definitive evidence for the safety of NSAIDs after colorectal surgery is still lacking. Further research should continue until robust evidence is available to better inform risk-benefit decisions.

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Tables and figures

Table 1: Characteristics of included systematic reviews

	Author (Year)	Search Limit	Studies (n=)	Study Types	Study Outcomes	NSAIDs
Colorectal	Rushfeldt (2011) (34)	Dec-10	13	Mixed	AL	NS and COX2
	Burton (2013) (16)	May-11	6	RCT	AL, Ileus, Opioids, Pain	NS and COX2
	Bhangu (2014) (33)	Feb-13	20	Mixed	AL	NS and COX2
	Peng (2016) (26)	Dec-15	12	RCT	AL, Ileus	NS and COX2
	Cata (2017) (37)	Jan-17	21	Mixed	AL	NS and COX2
	Huang (2018) (32)	Jun-17	17	Mixed	AL	NS and COX2
	Milne (2018) (23)	Apr-17	5	RCT	Ileus, Opioids	NS and COX2
	Chapman (2019) (22)	Jan-18	6	RCT	AL, Ileus, Opioids	NS and COX2
	Modasi (2019) (31)	Nov-16	7	Non-RCT	AL	NS and COX2
	Arron (2020) (41)	Apr-20	9	Non-RCT	AL	NS and COX2
	Jamjittrong (2020) (30)	Aug-18	24	Mixed	AL	NS and COX2
	Kastora (2021) (29)	Oct-20	15	Mixed	AL	NS and COX2
	Chen (2022) (35)	May-20	7	Mixed	AL	NS
	Bukhari (2024) (42)	Jan-24	138	Mixed	AL, Adverse events	NS and COX2
	Lirk (2024) (18)	Jan-22	72	RCT	Pain	NS and COX2
	Uten (2024) (17)	Jan-22	13	Mixed	Pain	NS and COX2
Gynaecology	Zemmel (2006) (25)	Unknown	4	Unknown	Opioids, Pain	NS and COX2
	Lirk (2019) (24)	May-18	56	RCT	Opioids, Pain	NS
Mixed/ Abdominal	Hyllested (2002) (20)	Jan-01	6	RCT	Opioids, Pain	NS
	Romsing (2005) (43)	Jun-04	19	RCT	Opioids	COX2
	Maund (2010) (7)	Feb-09	60	RCT	Opioids	NS and COX2
	Carter (2020) (19)	Dec-19	27	RCT	Opioids, Pain	COX2
	Bongiovanni (2021) (27)	Aug-19	68	Mixed	Bleeding	NS
	Dieu (2021) (21)	Oct-19	34	Mixed	Opioids, Pain	COX2
	Flemming (2024) (28)	Jun-21	7	Mixed	Bleeding, Opioids, Pain	NS and COX2
	Albarrak (2024) (44)	Jan-23	6	Mixed	Pain, PONV	NS and COX2
	Aiolfi (2023) (38)	Nov-22	6	Mixed	AL	NS

RCT: Randomised controlled trials; NSAID: non-steroidal anti-inflammatory drug; NS-NSAID: Non-selective NSAID; COX2: Cyclooxygenase-2 inhibitor; AL: Anastomotic Leak; PONV: post-operative nausea and vomiting

Table 2: AMSTAR-2 tool critical flaw outcomes* for all included reviews

Critical methodological flaw	Number of manuscripts (n=27)
Absence of prospective protocol	18/27 (67%)
Lack of comprehensive search strategy	No strategy = 2/27 (7%) Partial strategy according to AMSTAR-2 criteria (14) = 21/27 (78%)
Absence of justifications for exclusions of individual studies	24/27 (89%)
Lack of appropriate risk of bias assessment	8/27 (30%)
Inappropriate methods for meta-analysis	8/27 (30%)
Not accounting for risk of bias when interpreting results	9/27 (33%)
No assessment of publication bias where applicable	9/27 (33%)

**The overall confidence rating using the AMSTAR-2 tool is based on the presence of specific weaknesses from the checklist. If a study is considered to involve more than one critical flaw, the overall confidence is deemed to be critically low.*

Table 3: Summary of reported colorectal anastomotic leak rates with NSAID compared to comparator

Author (Year)	Study Population (n)	NS-NSAID AL rate	COX2 AL rate	Overall AL rate
Kastora, (2021)	Colorectal cancer (n=25,395)	Increased with colo-colic site [OR 3.25 (CI 0.98-10.72); p=0.054]	No difference [OR 1.82(CI 0.51-6.52); p=0.36]	No difference overall [OR 1.07 (CI 0.82-1.40); p=0.62) Trend towards increased risk with colo-colic site [OR 1.55 (CI 0.93-2.59); p=0.10]
Arron (2020)	Colorectal cancer (n=10,868)	No difference [RR 1.05 (CI 0.56-1.99); p=0.87]	No difference [RR 1.75 (CI 0.67-4.57); p=0.26]	No difference [RR 1.23 (CI 0.81-1.86); p=0.34]
Jamjittrong (2020)	Mixed (n=31,877)	Increased [OR 1.80 (CI 1.12-2.91); p=0.02)	No difference [OR 1.67 (CI 0.90-3.13); p=0.11]	Increased [OR 1.73 (CI 1.31-2.29); p <0.001]
Chapman (2019)	Mixed (n=563)	No sub-group analysis done	No sub-group analysis done	AL rate similar between groups in 4/5 studies reporting AL.
Modasi (2019)	Mixed (n=9835)	Increased [OR 1.77 (CI 1.43-2.20); p<0.00001]	No difference [OR 1.17 (0.50, 2.74); p=0.700]	Increased [OR 1.58 (CI 1.23, 2.03); p=0.0003]
Huang (2018)	Mixed (n=26,098)	Increased [OR = 2.02 (CI = 1.62–2.50); p< 0.0001)	No difference (OR = 2.59 (CI 1.02-6.59); p=0.05)	Increased [OR 2.00 (CI 1.48–2.71); p< 0.00001)]
Cata (2017)	Mixed cancer population (n=NA)	Evidence conflicting, Diclofenac may be associated with AL	Evidence conflicting, Celecoxib may be associated with AL	Evidence conflicting, may be associated with AL
Peng (2016)	Mixed (n=3829)	Increased [OR 2.96 (CI 1.99-1.99); p<0.00001]	No difference [OR 2.27 (CI: 0.68-0.68); p=0.18)	Increased [OR 3.02 (CI 2.16-2.16); p=0.00001)
Bhangu (2014)	Mixed (n=4464)	Increased [OR 2.37; p=0.001)	No difference [OR 2.32; p=0.170]	Increased [OR 2.14; p=0.001)
Burton (2013)	Mixed (n=40,210)	No difference [OR 2.14 (0.78-5.84; p=0.14]	No difference [OR 1.46 (0.25-8.60); p=0.67]	No difference [OR 2.16 (CI 0.85-5.53; p=0.11]
Rushfeldt (2011)	Mixed (n=887)	Increased with Diclofenac	Increased with Celecoxib	Not reported
Chen (2022)	Mixed (n=400,822)	Increased with Keterolac [OR 1.23 (CI = 1.09-1.39); p=0.0007]	Not reported	Not reported

RCT: Randomised controlled trials; NSAID: non-steroidal anti-inflammatory drug; NS-NSAID: Non-selective NSAID; COX2: Cyclooxygenase-2 inhibitor; AL: Anastomotic Leak; CI: 95% Confidence Interval; OR: Odds ratio; RR: Risk ratio.

Table 4: Jadad decision algorithm for reviews reporting anastomotic leak after colorectal surgery

Author (Year)	Jadad A – Same question?	Jadad C – Same trials?	Jadad G – Same selection criteria?	Jadad I – Assessment of publication status, quality of included studies, language restrictions, individual patient analysis
Kastora, (2021)	Yes	No, n=15 Mixed	No, cancer population	Unpublished studies: Yes Quality assessment: Yes Language Restriction: English Data on individual patients: No
Arron (2020)	Yes	No, n=9 NRS	No, mixed population	Unpublished studies: No Quality assessment: Yes** Language Restriction: None Data on individual patients: No
Jamjittrong (2020)	Yes	No, n=24 Mixed	No, mixed population	Unpublished studies: Yes Quality assessment: Yes** Language Restriction: English Data on individual patients: No
Chapman (2019)	Yes	No, n= 6 RCTs	No, mixed population	Unpublished studies: Yes Quality assessment: Yes Language Restriction: English Data on individual patients: No
Modasi (2019)	Yes	No, n=7 NRS	No, mixed population	Unpublished studies: No Quality assessment: Yes Language Restriction: None Data on individual patients: No
Huang (2018)	Yes	No, n=17 Mixed	No, mixed population	Unpublished studies: No Quality assessment: No Language Restriction: English Data on individual patients: No
Cata (2017)	Yes	No, n=21 Mixed	No, mixed population	Unpublished studies: No Quality assessment: Yes** Language Restriction: English Data on individual patients: No
Peng (2016)	Yes	No, n=12 RCTs	No, mixed population	Unpublished studies: No Quality assessment: Yes Language Restriction: None Data on individual patients: No
Bhangu (2014)	Yes	No, n=8 Mixed	No, mixed population	Unpublished studies: No Quality assessment: Yes** Language Restriction: None Data on individual patients: No
Burton (2013)	Yes	No, n=6 RCTs	No, mixed population	Unpublished studies: Yes Quality assessment: Yes** Language Restriction: None Data on individual patients: No

Rushfeldt (2011)	Yes	No, n=3 NRS	No, mixed population	Unpublished studies: No Quality assessment: No Language Restriction: English Data on individual patients: No
Chen (2022)	Yes	No, n=7 mixed	No, cancer population	Unpublished studies: No Quality assessment: Yes Language Restriction: None Data on individual patients: No

NRS: Non-randomised studies; RCT: Randomised controlled trials; NSAID: non-steroidal anti-inflammatory drug; NS-NSAID: Non-selective NSAID; COX2: Cyclooxygenase-2 inhibitor;

*** indicates where sub-analyses were performed comprising only high-quality studies*

Figure 1: Jadad tool decision algorithm for anastomotic leak after colorectal surgery.

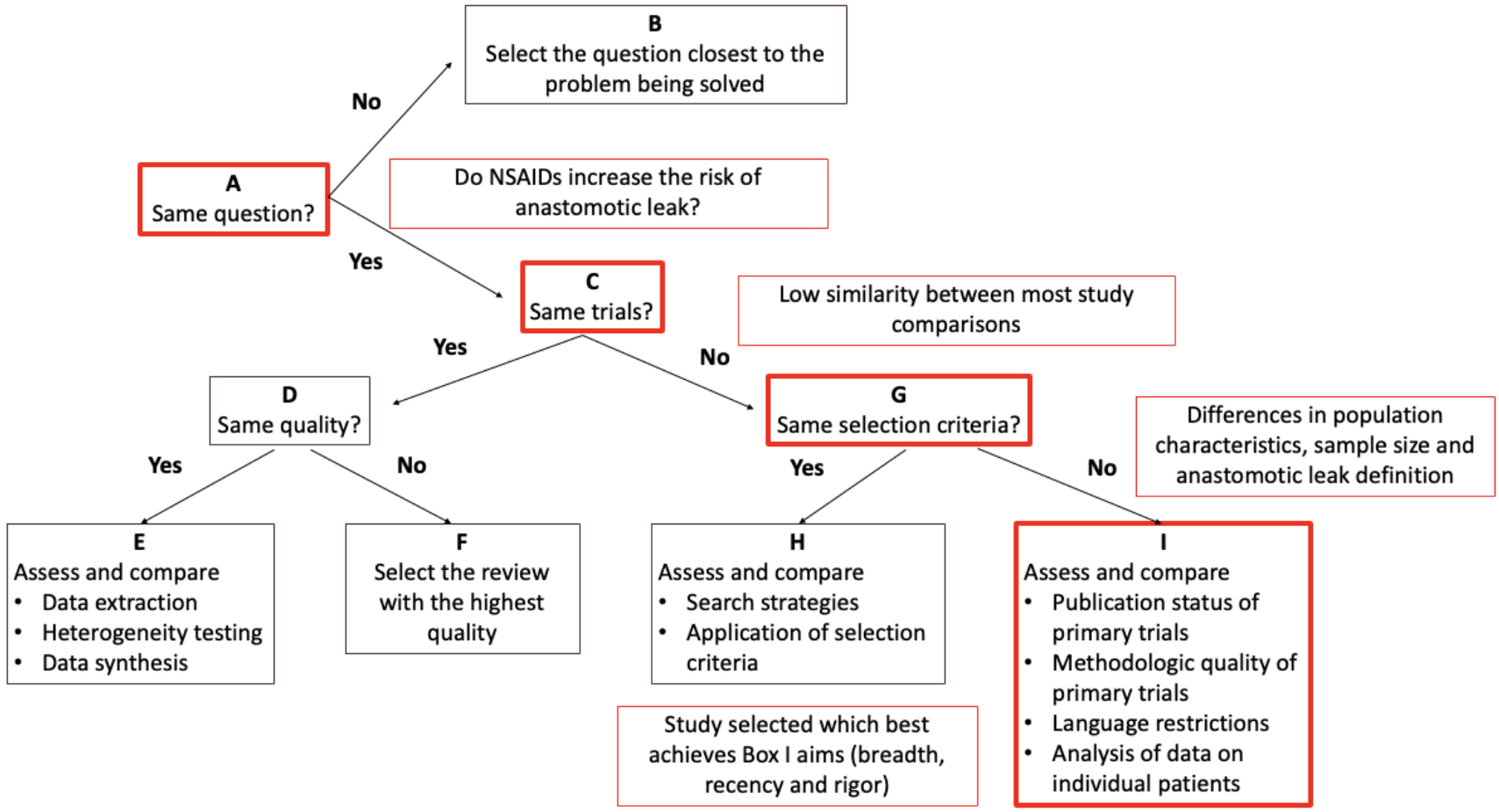

Figure 2: PRISMA Diagram