Journal of Endocrinology, Tropical Medicine, and Infectious Disease (JETROMI) Vol. 04, No. 4, 2022 / 148-165

JETROMI
Journal of Endocrinology, Tropical Medicine, and Infectious Disease

Effect of Nonsteroidal Anti-inflammatory Drug (NSAID) in Disease Relapse, Progression, and Development of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

Darmadi**, *Imelda Rey

Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

ABSTRACT

This systematic review and meta-analysis investigated the association between nonsteroidal anti-inflammatory drugs (NSAIDs) and inflammatory bowel disease (IDBIDBIDBIDB). Pooled analysis showed no significant association in disease relapse (OR 0.97; 95% CI 0.70–1.35; p = 0.86) and disease worsening (OR 2.06; 95% CI 0.92–4.57; p = 0.08) of existing IBD in patients receiving NSAID. In patients without prior IBD diagnosis, NSAID medication was significantly associated with the risk of new-onset IBD (OR 1.51; 95% CI 1.19–1.92; p = 0.0008).Given the varied effects of NSAIDs on IBD, careful management and consideration of dosage and frequency are essential in IBD patients. Despite these insights, the heterogeneity of study designs and small sample sizes in some cases call for further large-scale research to validate these findings.

Keywords: *Inflammatory Bowel Disease, Nonsteroidal Anti-inflammatory Drug, Systematic Review, Meta-analysis*

ABSTRAK

Studi ini mengevaluasi hubungan antara obat antiinflamasi nonsteroid (OAINS) terhadap inflammatory bowel disease (IBD). Meta-analisis menunjukkan tidak terdapat hubungan bermakna antara relapse (OR 0,97; 95% CI 0,70–1,35; p = 0,86) dan perburukan penyakit (OR 2,06; 95% CI 0.92–4.57; p = 0,08) pada pasien IBD yang mendapatkan OAINSPada pasien tanpa IBD sebelumnya, pemberian OAINS secara signifikan berkaitan dengan risiko terjadinya IBD baru (OR 1,51; 95% CI 1,19–1,92; p = 0,0008). Berkaitan dengan efek bervariasi terkait pemberian OAINS pada IBD, pertimbangan terkait dosis dan frekuensi OAINS penting dilakukan pada pasien IBD. Perlu diperhatikan terdapat heterogenitas dan jumlah sampel yang sedikit pada beberapa studi, sehingga penelitian lebih lanjut dibutuhkan untuk mengevaluasi hubungan antara OAINS dan IBD.

Kata Kunci: *Inflammatory Bowel Disease, Obat Antiinflamasi Nonsteroid, Telaah Sistematik, Meta-analisis*

*Corresponding author at: Faculty of Medicine, Universitas Sumatera Utara, Dr Mansyur 5, Medan, North Sumatera, Indonesia

E-mail address: darmadi@usu.ac.id

DOI: https://doi.org/ 10.32734/jetromi.v4i4.14473
Journal Homepage: https://jetromi.usu.ac.id

Received 28 November 2023 | Revised 28 December 2023 | Accepted 25 January 2024

1 Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder affecting the gastrointestinal tract, predominantly in the bowel. There are two subtypes of IBD, including Crohn's disease and ulcerative colitis[1]. The exact cause of IBD remains unclear, although it has been reported to result from a complex interplay between genetic, immunological, host intestinal flora, and environmental factors (e.g., smoking or medication). There were approximately 4.9 million cases of IBD globally, which mostly occurred at the age of 15–30 years with 25% having the onset during adolescence[2], [3].

Patients with IBD may experience varying courses of disease, ranging from infrequent mild symptoms to intermittent or persistent symptoms with progressive disease. Patients may present with various gastrointestinal symptoms such as abdominal pain, diarrhea, rectal bleeding, tenesmus, or nutritional deficiencies[4]. Extra-intestinal manifestations had also been reported, including ophthalmologic (conjunctivitis, uveitis), hepatobiliary, and urologic involvement[5]. IBD is characterized by a cycle of relapse and remission, which results in a significant reduction in patient quality of life. Approximately 20% of all patients with IBD eventually develop steroid-refractory disease, while the remainder are dependent on steroids.[6]

Pain medications have been widely used in patients with IBD to alleviate their symptoms. However, the nonsteroidal anti-inflammatory drugs (NSAID) class has been thought to be associated with disease exacerbation or flare in IBD and the onset of IBD in patients without prior diagnosis of IBD[7]. However, previous meta-analyses reported inconsistent association between NSAID and exacerbation of IBD subtypes (Crohn's disease or ulcerative colitis)[8]. Also, no study has carried out a meta-analysis regarding the development of new-onset IBD in NSAIDs. Therefore, this systematic review and meta-analysis aimed to evaluate the association of NSAID and IBD regarding all aspects, including but not limited to disease relapse, progression, and development of new-onset IBD in patients without prior IBD diagnosis.

2 Methods

2.1 Eligibility criteria and data extraction

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist[9]. Inclusion criteria included (1) studies evaluating the association between any NSAID and inflammatory bowel disease and (2) comparative studies between NSAID and any other drugs. Inflammatory bowel disease (IBD) defined as the patients with established diagnosis based on clinical characteristics and examination obtained with medical records, can be either Crohn's disease or ulcerative colitis. Exclusion criteria were: (1)

review study, commentary, or viewpoint, (2) irretrievable full-text, and (3) articles in languages other than English. We sought any outcomes related to the effect of NSAID on IBD (e.g., disease relapse, worsening, progression, and NSAID as a risk factor for IBD development). Data extraction was conducted independently by two authors using Microsoft Excel software. Data extracted from each study included author name, year of publication, study design, characteristics of NSAID administration (drug name, dosing, frequency, or duration) and its comparator (control), diagnosis, number of patients, age, gender, and outcomes.

2.2 Search strategy

A literature search was conducted using available online databases, including PubMed, EMBASE, ScienceDirect, and Scopus until 1 November 2023. This review aims to evaluate the effect of NSAID administration on IBD. The following keywords were used for searching: "nonsteroidal anti-inflammatory drug", "NSAID", "inflammatory bowel disease", "Crohn's disease", and "ulcerative colitis" with their synonyms (Table 1).

Table 1 Keywords used for searching strategy

Database	Search terms
PubMed (Title/Abstract)	(Inflammatory Bowel Disease OR IBD OR Crohn's Disease OR Ulcerative Colitis) AND (Nonsteroidal Anti-Inflammatory Drugs OR Non-steroidal AntiInflammatory Drugs OR Non-steroidal Anti-Inflammatory Drugs OR nonsteroidal antiinflammatory drugs OR NSAID OR Ibuprofen OR Aspirin OR Naproxen OR Celecoxib OR Cyclo-Oxygenase Inhibitors OR cox-2 inhibitor OR cyclo-oxygenase-2 inhibitor OR cyclooxygenase-2 inhibitor OR analgesic)
EMBASE (Title/Abstract/Author Keyword)	(Inflammatory Bowel Disease OR IBD OR Crohn's Disease OR Ulcerative Colitis) AND (Nonsteroidal Anti-Inflammatory Drugs OR Non-steroidal AntiInflammatory Drugs OR Non-steroidal Anti-Inflammatory Drugs OR OR NSAID OR Ibuprofen OR Aspirin OR Naproxen OR Celecoxib OR Cyclo-Oxygenase Inhibitors OR cox-2 inhibitor OR cyclo-oxygenase-2 inhibitor OR cyclooxygenase-2 inhibitor OR analgesic)
ScienceDirect (Title, Abstract, Keyword)	(Inflammatory bowel disease OR Crohn's Disease OR Ulcerative Colitis) AND (nonsteroidal antiinflammatory drugs OR analgesia OR NSAID OR cox-2 inhibitor OR Non-steroidal Anti-Inflammatory Drugs OR cyclooxygenase-2 inhibitor)
Scopus (Title, Abstract, Keyword)	(inflammatory AND bowel AND disease OR IBD OR Crohn's OR chron AND disease OR ulcerative AND colitis) AND (nonsteroidal AND anti-inflammatory AND drugs OR non-steroidal AND anti-inflammatory AND drugs OR non-steroidal AND anti-inflammatory AND drugs OR nonsteroidal AND anti-inflammatory AND drugs OR nsaid OR ibuprofen OR aspirin OR naproxen OR celecoxib OR cyclo-oxygenase AND inhibitors OR cox-2 AND inhibitor OR cyclo-oxygenase-2 AND inhibitor OR cyclooxygenase-2 AND inhibitor OR analgesic)

2.3 Risk of bias assessment

Risk of bias assessment was conducted using the NIH quality assessment tool for each study design (e.g. controlled intervention study, observational cohort, case-control studies)[10]. Domain addressed in controlled intervention study includes randomization, treatment allocation, blinding, similarity of groups at baseline, dropout, adherence, avoiding other interventions, outcomes measures assessment, power calculation, prespecified outcomes, and intention-to-treat analysis. Domain addressed in observational cohort studies includes research question, study population, groups recruited from the same population and uniform eligibility criteria, sample size justification, exposure assessed before outcome measurement, sufficient timeframe to see an effect, different levels of the exposure of interest, exposure measures and assessment, repeated exposure assessment, outcome measures, blinding of outcome assessors, follow-up rate, and statistical analyses. Domain addressed in case-control studies include the research question, study population, target population and case representation, sample size justification, groups recruited from the same population, inclusion and exclusion criteria prespecified and applied uniformly, case and control definitions, a random selection of study participants, concurrent controls, exposure assessed before outcome measurement, exposure measures, and assessment, blinding of outcome assessors, and statistical analyses. The assessment of the study was independently performed by two authors and determined by the third author. Included studies were categorized into “good”, “fair”, or “poor”.

2.4 Statistical analysis

Data were presented in tables and figures. Data syntheses were performed using Review Manager 5.4 (Cochrane Collaboration, Oxford, England). Meta-analysis was performed to quantitatively assess the effect of non-steroidal anti-inflammatory drugs (NSAID) in inflammatory bowel disease (IBD). A random-effect model was used as there may be diverse interventions regarding of types of NSAID used between studies, which may potentiate the presence of heterogeneity in treatment effect. The effect size was calculated using the Mantel-Haenszel odds ratio (OR) and the number of events in treatment and control groups. Several events in treatment and control groups will be manually extracted from each study. Heterogeneity analyses were conducted using the Q test and I2 statistics. Subgroup analysis was performed in the study with heterogeneity.

3 Results

3.1 Study characteristics

This review included a total of 14 studies[11]–[24] for quantitative review, which consisted of 1 RCT, 4 prospective cohorts, 3 retrospective cohorts, and 6 case-control studies (**Figure 1**). Outcomes reported were disease relapse, disease worsening (emergency admission to hospital and IBD-related *Clostridium difficile* infection), progression to colorectal cancer, and risk of

development of IBD in patients receiving NSAID. Characteristics of the included study and risk of bias can be seen in **Table 2**.

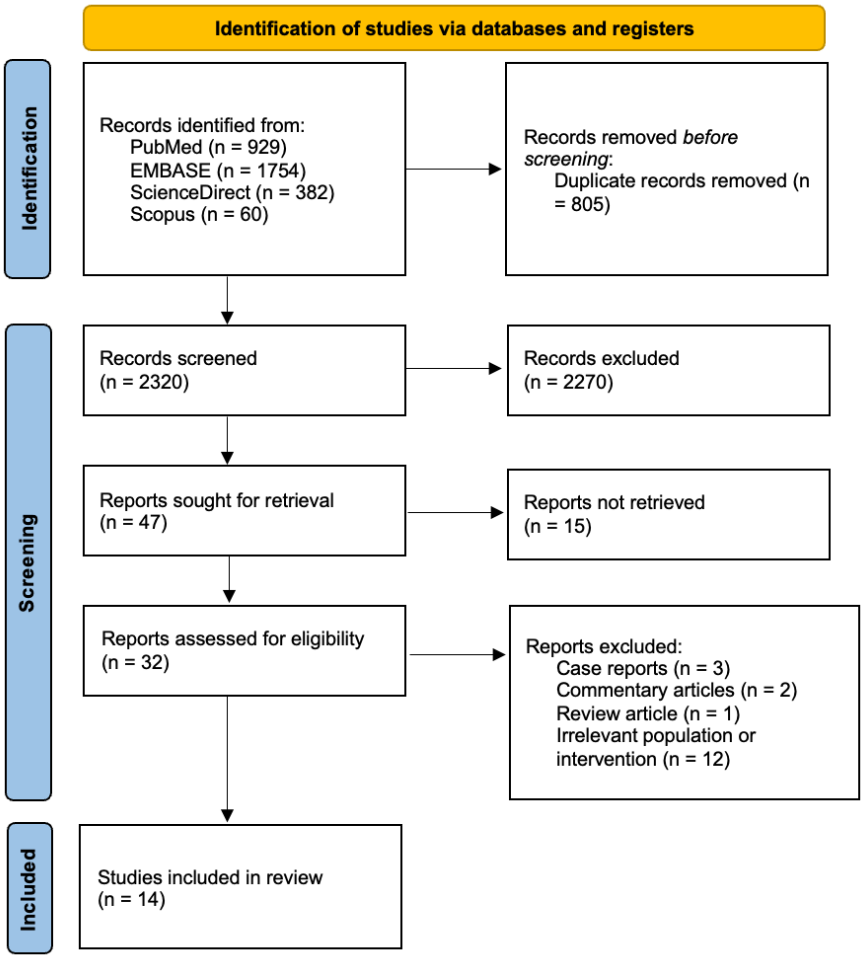

Figure 1 Flow chart of searching strategy.

Table 2 Characteristics of included study.

No	Study ID	Design	NSAID	Comparator/ Control	Dose (g)/ frequency/ duration	Diagnosis	No. of patients	Age (year)	Male/Female	Rob
1	Rampton 1983	Case-control	Aspirin, mefenamic acid	Acetaminophen	Aspirin: 1.2 (0.3–2.4) gram Mefenamic acid: 5 gram	Ulcerative colitis	83 (21 relapse; 62 remission)	Relapse = 42 (22-79) Remission = 43 (19-80)	Relapse: 9/12 Remission: 26/36	Fair
2	Evans 1997	Case-control	Any NSAID	No NSAID	(a) current exposure, within 45 days before the index date; (b) recent exposure, between 45 and 180 days before the index date; and (c) past exposure more than 180 days before the index date	IBD	400 (case = 200; control = 200)	Case = 46 (9-96) Control = matched	N/A	Fair
3	Sandborn 2006	RCT	Celecoxib (COX-2 inhibitor)	Placebo	Celecoxib 200 mg twice daily for 14 days	Ulcerative colitis	217 (110 celecoxib group; 107 placebo group)	Celecoxib group = 47.2±12.15; Placebo group = 48.3±13.41 p = 0.512	Celecoxib group = 45% male; Placebo group = 46% male p = 0.778	Poor
4	Velayos 2006	Case-control	Any NSAID	No NSAID	Use of non-prescription NSAID or aspirin	Ulcerative colitis	376 (Cases = 188; control = 188)	N/A	Case = 71% male Control = 71% male	Good

5	Meyer 2006	Retrospective cohort	Any NSAID	No NSAID	At least once daily dosing of any COX inhibitor in the month before relapse or, if the patient's IBD was in remission, in the month before the patient's last clinic visit.	IBD	60 (relapse = 22; remission = 38)	Relapse = 44.6 ± 18.2 Remission = 52.3 ± 18.5	Relapse = 8/14 Remission = 16/22	Fair
6	Takeuchi 2006	Retrospective cohort	Naproxen, diclofenac, Indomethacin	Acetaminophen	Naproxen (500 mg twice a day), 29 on diclofenac (75 mg twice a day), and 22 on indomethacin (75 mg twice a day)	IBD	109 (32 NSAID, 26 non-NSAID)	Naproxen = 40 (20–70) Diclofenac = 33 (20–68) Indomethacin = 38 (24–70) Acetaminophen = 37 (24–62)	Naproxen = 14/18 Diclofenac = 19/10 Indomethacin = 9/13 Acetaminophen = 12/14	Fair
7	Bernstein 2010	Prospective cohort	Any NSAID	No NSAID	Any use of NSAID	IBD	383 (Flare = 174; Non-flare = 209)	52.1±13.0 years	Flare 37.2% male; Non-flare 46.4% male	Good
8	Chan 2011	Prospective cohort	Aspirin	No aspirin	Any aspirin recorded ranged from 1 month to 1 year	Ulcerative colitis; Chron's disease	CD = 35 UC = 84	CD = 52.7 (37.6–75.8) UC = 56.8 (35.8–77.0)	CD = 10/25 UC = 47/37	Fair
9	Ananthakrishnan 2012	Prospective cohort	Any NSAID	No NSAID	0 tablets/week (n = 52), 0.5–1.5 tablets/week (n = 22),	Ulcerative colitis; Chron's disease	76,795	56.7 (43.5-76.7)	All female	Good

					2–5 tablets/week (n = 21), and >5 tablets/week (n = 28)					
10	Wang 2013	Case-control	Any NSAID	No NSAID	At least twice per week for at least one month.	Ulcerative colitis	2616 (1308 UC; 1308 control)	UC = 41.6 ± 12.3 Control = 41.4 ± 13.5	UC = 1.23:1 Control =1.23:1	Good
11	Feagins 2014	Case-control	Any NSAID	No NSAID	Any use of NSAID	IBD	134 (flares = 66; control = 68)	Case = 49.0 ± 14.3 Control = 53.1 ± 15.7 p = 0.09	Flare: 59/7 Control: 63/5 p = 0.56	Fair
12	Regnault 2014	Retrospective cohort	Any NSAID	No NSAID	Taking NSAID within the two months before hospitalization	IBD	*C. difficile* infection (n = 34); No *C. difficile* infection (n = 449)	CD infection = 33 (22–46) No-CD infection = 32 (25–44) p = 0.85	CD infection = 17 (50%) male No-CD infection = 246 (55.1%) male p = 0.58	Fair
13	Hensley 2015	Case-control	All NSAIDs, Non-selective NSAIDs, Selective COX-2 inhibitors, Aspirin	Paracetamol	3 months before the assessment	IBD	158 (Stable = 99; relapse = 59)	Stable = 53.3 ± 15.4 Relapse = 47.6 ± 16.4 p = 0.03	Stable = 53.5% male Relapse = 44.1% male p = 0.25	Fair
14	Long 2016	Prospective cohort	Any NSAID	No NSAID	Exposure definitions were determined a priori and included categories of any/none and ≥5 times/monthly	IBD	791 (336 any NSAID; 455 no NSAID)	Any NSAID = 43.8±14.8; No NSAID = 44.8±15.4	Any NSAID = 28.9% male No NSAID = 32.7% male	Fair

					versus <5 times/monthly.					

3.2 Disease Relapse

A total of 8 studies[11], [13], [15]–[17], [19]–[21] were included for analysis of relapse in IBD patients with NSAID medication, as seen in **Figure 2**. There was no significant difference in the occurrence of relapse between patients receiving NSAID and not (OR 0.97; 95% CI 0.70–1.35; p = 0.86). Heterogeneity between studies was moderate (I^2 = 34%).

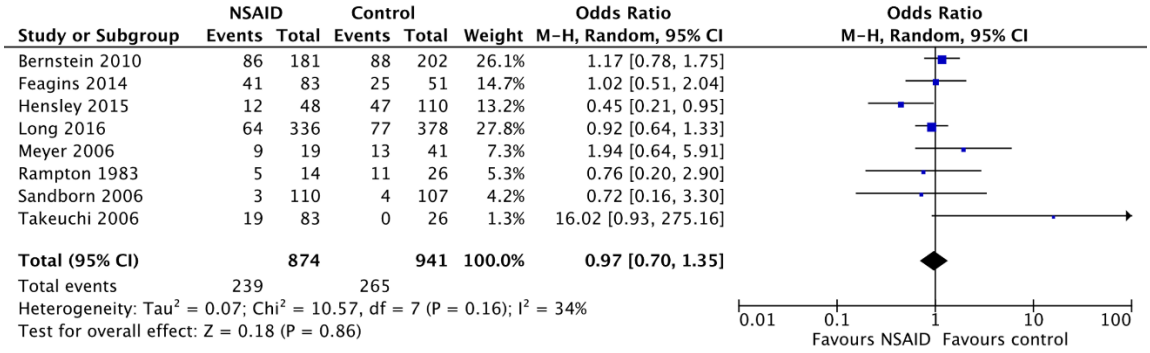

Figure 2 Forest plot of relapse between NSAID and control.

Subgroup analysis was performed to explore the source of heterogeneity, by categorizing studies based on their comparator to NSAID. Two studies specifically used acetaminophen as a comparator to NSAID medication, which is shown in Figure 3. No significant difference in the occurrence of relapse in patients receiving NSAID in both subgroups.

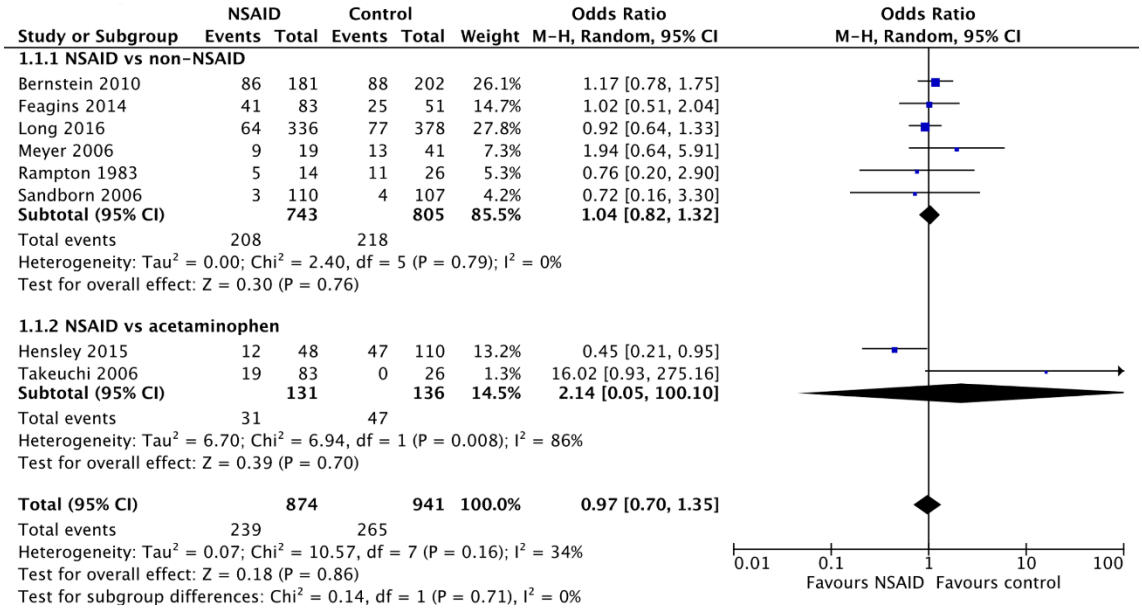

Figure 3 Subgroup analysis between NSAID and control.

3.3 Disease worsening

A total of 2 studies[12], [14] were included for analysis of disease worsening in IBD patients with NSAID medication, as seen in Figure 4. NSAID was associated with a higher rate of disease

worsening compared to patients not receiving NSAID, despite not being statistically significant (OR 2.06; 95% CI 0.92–4.57; p = 0.08). There was moderate heterogeneity between studies. This may be explained as each study uses different outcomes regarding disease worsening. Evans et al. used emergency admission to hospital in IBD patients as the outcome, while Regnault et al. used IBD-associated Clostridium infection as the outcome. Subgroup analysis cannot be performed as there were only two studies included.

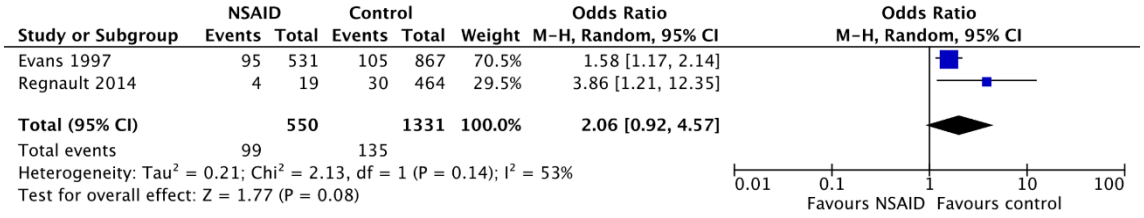

Figure 4 Forest plot of disease worsening between NSAID and control.

3.4 Progression to colorectal cancer

One study, Velayos et al.[18] reported the association between NSAID and progression to colorectal cancer in IBD patients. NSAID may have protective effects in the progression of colorectal cancer in IBD patients (OR 0.1; 95% CI 0.03–0.5; p <0.05).

3.5 Risk of development of IBD

A total of 3 studies [22]–[24] evaluated the role of NSAID in the development of new-onset IBD from patients previously not diagnosed with either Crohn's disease or ulcerative colitis, as seen in Figure 5. NSAID medication was significantly associated with the development of IBD (OR 1.51; 95% CI 1.19–1.92; p = 0.0008). There was no clinically important heterogeneity between studies (I2 = 25%).

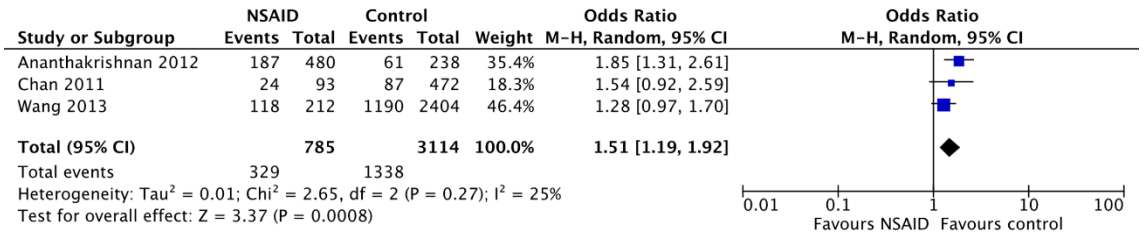

Figure 5 Forest plot of development of IBD between NSAID and control.

4 Discussion

IBD is a chronic inflammatory disorder affecting the gastrointestinal tract with two known subtypes: Crohn's disease and ulcerative colitis. IBD is thought to be multifactorial in origin, involving genetic, immunological, host intestinal flora, and environmental factors (e.g., smoking and medication) [1], [16]. IBD is characterized by a cycle of remission and relapse, which is

associated with significant morbidity to the patient. IBD is generally more common in Western and developed countries, but prevalence has slowly arisen in Asian countries such as Taiwan, with a prevalence of Crohn's disease and ulcerative colitis being 2.1 per 100,000 and 12.8 per 100,000 people respectively[25].

Management of patients should focus on risk modification associated with relapse in IBD to improve patient quality of life, such as medication history of the patient. NSAIDs are among the most commonly used drugs, with approximately 60 million Americans using NSAIDs regularly[26]. It accounts for 5–10% of all prescribed medication annually[27]. It has anti-inflammatory, antipyretic, and analgesic properties, making the drugs suitable for many health conditions affecting patients of all ages[28].

Aside from its therapeutic effects, NSAID has been linked to multiple other gastrointestinal toxicities at the level of the mucosa, such as ulcers, erosions, gastrointestinal bleeding, strictures, and perforation of the bowel[28]. Histologically, NSAID-induced injury in the bowel was seen as patchy inflammation with abundant lymphoplasmacytic and neutrophil cells with slight disarray in the crypt and focal erosion[29]. It has been proposed that gastrointestinal toxicity in patients receiving NSAID was related to its inhibitory effect on prostaglandin synthesis through cyclooxygenase (COX) enzymes[30]. Prostaglandin is a hormone-like substance that is essential in the maintenance of mucosal integrity in the bowel. Inhibition of COX enzyme, specifically COX-1, may lead to impaired microcirculatory blood flow in the mucosa. COX-2 enzyme has been linked to immunomodulatory effects in the gastrointestinal tract[20].

Current literature regarding the effect of NSAIDs on IBD has brought conflicting and inconsistent results[8]. This study aims to evaluate the association between NSAID and IBD with further exploration of disease relapse, progression, and risk of development of new-onset IBD using systematic review and meta-analysis.

We did not find a significant association between NSAID medication and disease relapse and worsening of patients with underlying IBD. Disease relapse in patients receiving NSAID medication is thought to be linked with a combination of impaired mucosal microcirculatory blood flow, and mucosal defense (mucus secretion and acid regulation) related to COX-1 inhibitor. The exact mechanism by which COX-2 inhibitors induce relapse remains unknown, although delayed wound healing, increased vascular permeability, and an increase in reactive oxygen metabolites have been hypothesized to induce relapse in IBD patients. Moreover, there was evidence that the colon with colitis has upregulated COX-2 expression and its inhibition may result in exacerbation of underlying injury by triggering a delay in healing[31], [32]. Upregulation of COX-2 expression in IBD is thought to result from exposure of the cells to proinflammatory cytokines, such as interleukin-1 and TNF-α, in inflammatory conditions [33]. Other studies also reported that biopsy of colonic mucosa in patients with IBD showed an increase in the production

of prostaglandin E2 (PGE2) and PG which both have protective effects on the owner. Inhibition of COX enzymes therefore potentially harmful to the patient[34]. It needs to be highlighted that included studies in our review used different types of NSAID (including both selective and nonselective NSAID) and dosing/frequency of use. Effects of NSAID on disease relapse may be more pronounced in a higher frequency of use, as reported by Meyer et al. who showed a higher risk of relapse (adjusted OR 6.31; 95% 1.16–34.38, p = 0.03) in patients receiving NSAID as daily dose or more before relapse[19].

The risk of relapse was also higher in nonselective NSAIDs, such as ibuprofen, naproxen, diclofenac, indomethacin, or mefenamic acid compared to selective COX-2 inhibitors (celecoxib), as the drug effect was targeting both COX-1 and COX-2 inhibitors involved in the maintenance of gastrointestinal integrity[15]. Previous studies have also reported the safety of selective COX-2 inhibitors in IBD, namely celecoxib and rofecoxib, which showed that administration of selective COX-2 inhibitors is beneficial to the alleviation of symptoms in the majority of patients, although there were reversible adverse events[35]. Another study conducted by El Miedany et al showed no significant difference in mean disease activity score in patients receiving selective COX-2 inhibitor (etoricoxib given daily) compared to placebo (1.19 ± 0.683 vs 1.20 ± 0.481; $p > 0.05$)[36]. Another study has suggested a time limit of 14 days for the use of selective COX-2 inhibitors without a greater relapse rate compared to a placebo[17]. Further study was needed to evaluate the safety of selective COX-2 inhibitors in a larger, multicenter trial.

Timing of NSAID is also important to note, as Evans et al.[12] reported higher risk of emergency admission in current (within 45 days before onset) and recent use (45 days to 180 days before onset) compared to past (more than 180 days) exposure to NSAID. The influence of NSAID dosage has also been reported by Bonner et al.[37], which showed that high-dose NSAID may result in a higher disease activity index IBD. However, an increase in disease activity index did not necessarily result in a significant increase in disease flare.

One of the included studies reported the association of NSAID and C. difficile infection[14]. Enteric infections are common in IBD patients with flare[38]. As such, the correlation between NSAID and C. difficile infection may be explained by the alteration of the intestinal barrier due to impaired microcirculation and vascular permeability, leading to patients more susceptible to infection[14], [39]. However, this study included a small number of patients. Further studies with larger samples are needed to evaluate the effect of NSAID on comorbidity associated with IBD.

Our study showed a significant association between NSAID anthe d development of new-onset IBD, both Crohn's disease and ulcerative colitis. In patients without prior IBD, inhibition of COX enzymes is caused by leading to decreased prostaglandin levels. Aside from its inflammatory and pain modulation, prostaglandin has anti-inflammatory effects, in which reduction of prostaglandin would increase proinflammatory cytokines such as IL-1 and TNF-α seen in patients with Crohn's

disease[40], [41]. Moreover, nonspecific NSAIDs also inhibit COX-1 enzymes, resulting in a disturbance in microcirculatory blood flow. The inability to maintain adequate circulation leads to an ischemic environment, which aggravates the underlying chronic inflammatory condition[22], [42]. It needs to be highlighted that one of the included studies further explored the different effects associated with aspirin and other NSAIDs as a risk factor for the development of new-onset IBD onset, in which aspirin relatively exerts COX-1-selective inhibitory effects in low to moderate doses [23]. As such, aspirin alone was not significantly associated with the occurrence of new-onset IBD in patients without prior diagnosis of IBD. Moreover, previous animal models also showed that inhibition of either COX-1 or COX-2 enzyme alone did not result in colitis, while administration of nonselective NSAID may lead to the development of colitis[43]. However, as the number of studies was limited, the association needs to be used cautiously and other confounders (e.g. family history, smoking, other medication use, previous disease) need to be taken into account.

Interestingly, there was evidence that NSAID elicited protective effects to progression to colorectal cancer[18]. IBD is categorized as an autoimmune-related gastrointestinal disease, in which the bowel is more susceptible to injury due to the immune system. Aside from its relapse and remission cycle that significantly impairs patient quality of life, patients with IBD (Crohn's disease and ulcerative colitis) are also at a higher risk of progression to colorectal cancer. For instance, a study in North America reported that patients with Crohn's disease and ulcerative colitis were 2.64 times (95% CI 1.69–4.12) and 2.74 times [95% CI 1.91–3.97) more likely to develop colorectal cancer, respectively[44]. The mechanism related to the progression may be explained by the rapid progression of DNA damage caused by oxidative stress in the chronic inflammatory state of IBD[45]. Morphological damage in the bowel mucosa is also prone to dysplasia formation, which further develops into carcinoma[46]. Therefore, agents that may attenuate chronic inflammation in IBD, such as NSAID, have been of particular interest as a chemoprevention of colorectal cancer.

The mechanism by which NSAIDs may exert protective effects on colorectal cancer can be explained by the COX-2 pathway. COX-2 has been known to contribute to the development of tumors through the upregulation of cell proliferation-related to prostaglandin signaling. NSAID leads to a decrease in NF-κB-mediated DNA transcription, which results in suppression of cell growth[47]. The anti-inflammatory effect of NSAID is also important as antithe -tumor response was initiated in response to a decrease in proinflammatory cytokine, IL-1b[48], [49]. Also, COX-1 inhibition of NSAIDs, particularly aspirin leads to the o inhibition of angiogenic factors and release of cytokines by platelets which may be important in chemoprevention[50]. However, as there was a potential risk of flare associated with NSAID, if patients were to be given NSAID, it should be started with low-dose NSAID drugs and not during active flare-up. Using low-dose NSAID has also been reported with overall protective effects for colorectal cancer in patients

without prior IBD diagnosis[51]. It is also beneficial to use the effective dose as it may reduce the risk of potential adverse events related to NSAID[48].

There are some limitations to this study. The heterogeneity of the included studies, particularly in terms of NSAID types, dosages, and patient demographics. The small sample sizes in some studies give rise to the need for more extensive, multicenter trials to confirm these findings. Additionally, the potential for confounding factors, such as family history, smoking, and other medication use, must be considered when interpreting the results of this review.

5 Conclusion

This study investigated the relationship between NSAID use and inflammatory bowel disease (IBD). NSAID was not associated with a significant risk of disease relapse, although there was a significant association between NSAID and the development of new-onset IBD. Given low doses, NSAIDs may exert a protective effect on colorectal cancer. However, it is important to differentiate between non-selective NSAIDs and selective COX-2 inhibitors and their dosing and frequency, and careful NSAID management should be given in IBD patients.

REFERENCES

[1] D. K. Podolsky, "Inflammatory Bowel Disease," *N. Engl. J. Med.*, vol. 347, no. 6, pp. 417–429, Aug. 2002, doi: 10.1056/NEJMra020831.

[2] H. J. Su *et al.*, "Inflammatory bowel disease and its treatment in 2018: Global and Taiwanese status updates," *J. Formos. Med. Assoc.*, vol. 118, no. 7, pp. 1083–1092, 2019, doi: 10.1016/j.jfma.2018.07.005.

[3] R. Wang, Z. Li, S. Liu, and D. Zhang, "Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: A systematic analysis based on the Global Burden of Disease Study 2019," *BMJ Open*, vol. 13, no. 3, 2023, doi: 10.1136/bmjopen-2022-065186.

[4] M. Fakhoury, R. Negrulj, A. Mooranian, and H. Al-Salami, "Inflammatory bowel disease: Clinical aspects and treatments," *J. Inflamm. Res.*, vol. 7, no. 1, pp. 113–120, 2014, doi: 10.2147/JIR.S65979.

[5] A. H. Sange, Natasha Srinivas, Mubashira K. Sarnaik, Srimy Modi, Yasaswi Pisipati, Sarayoo Vaidya, Naqvi Syed Gaggatur, *et al.*, "Extra-Intestinal Manifestations of Inflammatory Bowel Disease," *Cureus*, Aug. 2021, doi: 10.7759/cureus.17187.

[6] J. Wehkamp, M. Götz, K. Herrlinger, W. Steurer, and E. F. Stange, "Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis," *Dtsch. Arztebl. Int.*, Feb. 2016, doi: 10.3238/arztebl.2016.0072.

[7] M. Guslandi, "Exacerbation of inflammatory bowel disease by nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors: Fact or fiction?" *World J. Gastroenterol.*, vol. 12, no. 10, pp. 1509–1510, 2006, doi: 10.3748/wjg.v12.i10.1509.

[8] O. O. Moninuola, W. Milligan, P. Lochhead, and H. Khalili, "Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of Crohn's disease and ulcerative colitis exacerbation," *Aliment. Pharmacol. Ther.*, vol. 47, no. 11, pp. 1428–1439, 2018, doi: 10.1111/apt.14606.

[9]. M. J. Page, Joanne E McKenzie, Patrick M Bossuyt, Isabelle Boutron, Tammy C Hoffmann, Cynthia D. Mulrow, Larissa Shamseer, *et al.*, "The Prisma 2020 statement: An updated guideline for reporting systematic reviews," *PLoS Med.*, vol. 18, no. 3, 2021, doi: 10.1371/JOURNAL.PMED.1003583.

[10] National Heart Lung and Blood Institute, *Study Quality Assessment Tools*. 2014.

[11] D. S. Rampton, N. I. McNeil, and M. Sarner, "Analgesic ingestion and other factors preceding relapse in ulcerative colitis," *Gut*, vol. 24, no. 3, pp. 187–189, 1983, doi: 10.1136/gut.24.3.187.

[12] J. M. M. Evans, A. D. McMahon, F. E. Murray, D. G. McDevitt, and T. M. MacDonald, "Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease," *Gut*, vol. 40, no. 5, pp. 619–622, 1997, doi: 10.1136/gut.40.5.619.

[13] L. A. Feagins, R. Iqbal, and S. J. Spechler, "Case-control study of factors that trigger inflammatory bowel disease flares," *World J. Gastroenterol.*, vol. 20, no. 15, pp. 4329–4334, 2014, doi: 10.3748/wjg.v20.i15.4329.

[14] H. Regnault, Anne Bourrier, Valerie Lalande, Isabelle Nion-Larmurier, Harry Sokol, Philippe Seksik, Frederic Barbut, *et al.*, "Prevalence and risk factors of Clostridium difficile infection in patients hospitalized for a flare of inflammatory bowel disease: A retrospective assessment," *Dig. Liver Dis.*, vol. 46, no. 12, pp. 1086–1092, 2014, doi: 10.1016/j.dld.2014.09.003.

[15] A. Hensley and I. L. P. Beales, "Use of cyclo-oxygenase inhibitors is not associated with clinical relapse in inflammatory bowel disease: A case-control study," *Pharmaceuticals*, vol. 8, no. 3, pp. 512–524, 2015, doi: 10.3390/ph8030512.

[16] M. D. Long, M. D. Kappelman, C. F. Martin, W. Chen, K. Anton, and R. S. Sandler, "Role of Non-Steroidal Anti-Inflammatory Drugs in Exacerbations of Inflammatory Bowel Disease," vol. 50, no. 2, pp. 152–156, 2017, doi: 10.1097/MCG.0000000000000421.Role.

[17] W. J. Sandborn, William F Stenson, Jørn Brynskov, Robin G Lorenz, Gina M Steidle, Jeffery L Robbins, Jeffery D Kent, *et al.*, "Safety of celecoxib in patients with ulcerative colitis in remission: A randomized, placebo-controlled, pilot study," *Clin. Gastroenterol. Hepatol.*, vol. 4, no. 2, pp. 203–211, 2006, doi: 10.1016/j.cgh.2005.12.002.

[18] F. S. Velayos, Edward V Loftus Jr, Tine Jess, W Scott Harmsen, John Bida, Alan R Zinsmeister, *et al.*, "Predictive and Protective Factors Associated With Colorectal Cancer in Ulcerative Colitis: A Case-Control Study," *Gastroenterology*, vol. 130, no. 7, pp. 1941–1949, 2006, doi: 10.1053/j.gastro.2006.03.028.

[19] A. M. Meyer, N. N. Ramzan, R. I. Heigh, and J. A. Leighton, "Relapse of inflammatory bowel disease associated with the use of nonsteroidal anti-inflammatory drugs," *Dig. Dis. Sci.*, vol. 51, no. 1, pp. 168–172, 2006, doi: 10.1007/s10620-006-3103-5.

[20] K. Takeuchi, Simon Smale, Purushothaman Premchand, Laurence Maiden, Roy Sherwood, Bjarni Thjodleifsson, Einar Bjornsson, *et al.*, "Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease," *Clin. Gastroenterol. Hepatol.*, vol. 4, no. 2, pp. 196–202, 2006, doi: 10.1016/S1542-3565(05)00980-8.

[21] C. N. Bernstein, S. Singh, L. A. Graff, J. R. Walker, N. Miller, and M. Cheang, "A prospective population-based study of triggers of symptomatic flares in IBD," *Am. J. Gastroenterol.*, vol. 105, no. 9, pp. 1994–2002, 2010, doi: 10.1038/ajg.2010.140.

[22] S. S. M. Chan, R Luben, M M Bergmann, H Boeing, A Olsen, A Tjonneland, *et al.*, "Aspirin in the etiology of Crohn's disease and ulcerative colitis: A European prospective cohort study," *Aliment. Pharmacol. Ther.*, vol. 34, no. 6, pp. 649–655, 2011, doi: 10.1111/j.1365-2036.2011.04784.x.

[23] A. N. Ananthakrishnan, Leslie M Higuchi, Edward S Huang, Hamed Khalili, James M Richter, Charles S Fuchs, Andrew T Chan ., "Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn's disease and ulcerative colitis," *Ann. Intern. Med.*, vol. 156, no. 5, pp. 350–359, 2012, doi: 10.7326/0003-4819-156-5-201203060-00007.

[24] Y. F. Wang, Qin Ou-yang, Bing Xia, Li-Na Liu, Fang Gu, Kai-Fang Zhou, *et al.*, "Multicenter case-control study of the risk factors for ulcerative colitis in China," *World J. Gastroenterol.*, vol. 19, no. 11, pp. 1827–1833, 2013, doi: 10.3748/wjg.v19.i11.1827.

[25] W. Y. Mak, M. Zhao, S. C. Ng, and J. Burisch, "The epidemiology of inflammatory bowel disease: East meets west," *J. Gastroenterol. Hepatol.*, vol. 35, no. 3, pp. 380–389, 2020, doi: 10.1111/jgh.14872.

[26] B. Cryer, "NSAID-associated deaths: The rise and fall of NSAID-associated GI mortality," *Am. J. Gastroenterol.*, vol. 100, no. 8, pp. 1694–1695, 2005, doi: 10.1111/j.1572-0241.2005.50565.x.

[27] G. Onder, F. Pellicciotti, G. Gambassi, and R. Bernabei, "NSAID-related psychiatric

adverse events: Who is at risk?" *Drugs*, vol. 64, no. 23, pp. 2619–2627, 2004, doi: 10.2165/00003495-200464230-00001.

[28] S. Wongrakpanich, A. Wongrakpanich, K. Melhado, and J. Rangaswami, "A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly," *Aging Dis.*, vol. 9, no. 1, pp. 143–150, 2018, doi: 10.14336/AD.2017.0306.

[29] R. Sohail, Midhun Mathew, Khushbu K Patel, Srija A Reddy, Zaroon Haider, Mansi Naria, *et al.*, "Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: A Narrative Review," *Cureus*, 2023, doi: 10.7759/cureus.37080.

[30] A. Klein and R. Eliakim, "Non-Steroidal Anti-Inflammatory Drugs and Inflammatory Bowel Disease," *Pharmaceuticals*, vol. 3, no. 4, pp. 1084–1092, Apr. 2010, doi: 10.3390/ph3041084.

[31] J. W. Paulley, "Why do patients with ulcerative colitis relapse?" *Gut*, vol. 31, no. 12, p. 1419, 1990, doi: 10.1136/gut.31.12.1419-b.

[32] J. O'Brien, "Nonsteroidal anti-inflammatory drugs in patients with inflammatory bowel disease," *Am. J. Gastroenterol.*, vol. 95, no. 8, pp. 1859–1861, 2000, doi: 10.1016/S0002-9270(00)01033-9.

[33] J. Hendel and O. H. Nielsen, "Expression of cyclooxygenase-2 mRNA in active inflammatory bowel disease," *Am. J. Gastroenterol.*, vol. 92, no. 7, pp. 1170–1173, 1997.

[34] S. A. McCartney, J. A. Mitchell, P. D. Fairclough, M. J. G. Farthing, and T. D. Warner, "Selective COX-2 inhibitors and human inflammatory bowel disease," *Aliment. Pharmacol. Ther.*, vol. 13, no. 8, pp. 1115–1117, 1999, doi: 10.1046/j.1365-2036.1999.00585.x.

[35] U. Mahadevan, E. V. Loftus, W. J. Tremaine, and W. J. Sandborn, "Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease," *Am. J. Gastroenterol.*, vol. 97, no. 4, pp. 910–914, 2002, doi: 10.1016/S0002-9270(02)03964-3.

[36] Y. El Miedany, S. Youssef, I. Ahmed, and M. El Gaafary, "The gastrointestinal safety and effect on disease activity of etoricoxib, a selective Cox-2 inhibitor in inflammatory bowel diseases," *Am. J. Gastroenterol.*, vol. 101, no. 2, pp. 311–317, 2006, doi: 10.1111/j.1572-0241.2006.00384.x.

[37] G. F. Bonner, A. Fakhri, and S. R. Vennamanemi, "A long-term cohort study of nonsteroidal anti-inflammatory drug use and disease activity in outpatients with inflammatory bowel disease," *Inflamm. Bowel Dis.*, vol. 10, no. 6, pp. 751–757, 2004, doi: 10.1097/00054725-200411000-00009.

[38] J. E. Axelrad, Andrew Joelson, Peter H R Green, Garrett Lawlor, Simon Lichtiger, Ken Cadwell, Benjamin Lebwohl. "Enteric Infections Are Common in Patients with Flares of Inflammatory Bowel Disease," *Am. J. Gastroenterol.*, vol. 113, no. 10, pp. 1530–1539, 2018, doi: 10.1038/s41395-018-0211-8.

[39] G. Thiéfin and L. Beaugerie, "Toxic effects of non-steroidal anti-inflammatory drugs on the small bowel, colon, and rectum," *Rev. du Rhum. (Edition Fr.*, vol. 72, no. 7, pp. 601–611, 2005, doi: 10.1016/j.rhum.2004.04.017.

[40] H. Jing, E. Vassiliou, and D. Ganea, "Prostaglandin E2 inhibits the production of the inflammatory chemokines CCL3 and CCL4 in dendritic cells," *J. Leukoc. Biol.*, vol. 74, no. 5, pp. 868–879, 2003, doi: 10.1189/jlb.0303116.

[41] X. J. Xu, J. S. Reichner, B. Mastrofrancesco, W. L. Henry, and J. E. Albina, "Prostaglandin E2 Suppresses Lipopolysaccharide-Stimulated IFN-β Production," *J. Immunol.*, vol. 180, no. 4, pp. 2125–2131, 2008, doi: 10.4049/jimmunol.180.4.2125.

[42] J. L. Wallace, W. McKnight, B. K. Reuter, and N. Vergnolle, "NSAID-Induced gastric damage in rats: Requirement for inhibition of both cyclooxygenase 1 and 2," *Gastroenterology*, vol. 119, no. 3, pp. 706–714, 2000, doi: 10.1053/gast.2000.16510.

[43] D. J. Berg, Juan Zhang, Joel V Weinstock, Hanan F Ismail, Keith A Earle, Hector Alila, Rifat Pamukcu, *et al.*, "Rapid development of colitis in NSAID-treated IL-10-deficient mice," *Gastroenterology*, vol. 123, no. 5, pp. 1527–1542, 2002, doi: 10.1053/gast.2002.1231527.

[44] J. K. Dyson and M. D. Rutter, "Colorectal cancer in inflammatory bowel disease: What is the real magnitude of the risk?" *World J. Gastroenterol.*, vol. 18, no. 29, pp. 3839–3848, 2012, doi: 10.3748/wjg.v18.i29.3839.

[45] S. C. Shah and S. H. Itzkowitz, "Colorectal Cancer in Inflammatory Bowel Disease:

Mechanisms and Management," *Gastroenterology*, vol. 162, no. 3, pp. 715-730.e3, 2022, doi: 10.1053/j.gastro.2021.10.035.

[46] P. Tavakoli, U. Vollmer-Conna, D. Hadzi-Pavlovic, and M. C. Grimm, "A Review of Inflammatory Bowel Disease: A Model of Microbial, Immune and Neuropsychological Integration," *Public Health Rev.*, vol. 42, 2021, doi: 10.3389/phrs.2021.1603990.

[47] E. Gurpinar, W. E. Grizzle, and G. A. Piazza, "NSAIDs inhibit tumorigenesis, but how?," *Clin. Cancer Res.*, vol. 20, no. 5, pp. 1104–1113, 2014, doi: 10.1158/1078-0432.CCR-13-1573.

[48] P. Newman and J. Muscat, "Potential Role of Non-Steroidal Anti-Inflammatory Drugs in Colorectal Cancer Chemoprevention for Inflammatory Bowel Disease: An Umbrella Review," *Cancers (Basel).*, vol. 15, no. 4, 2023, doi: 10.3390/cancers15041102.

[49] N. Kaneko, M. Kurata, T. Yamamoto, S. Morikawa, and J. Masumoto, "The role of interleukin-1 in general pathology," *Inflamm. Regen.*, vol. 39, no. 1, 2019, doi: 10.1186/s41232-019-0101-5.

[50] A. Ornelas, Niki Zacharias-Millward, David G Menter, Jennifer S Davis, Lenard Lichtenberger, David Hawke *et al.*, "Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention," *Cancer Metastasis Rev.*, vol. 36, no. 2, pp. 289–303, Jun. 2017, doi: 10.1007/s10555-017-9675-z.

[51] X. Wang, Y. Luo, T. Chen, and K. Zhang, "Low-dose aspirin use and cancer-specific mortality: a meta-analysis of cohort studies," *J. Public Heal. (United Kingdom)*, vol. 43, no. 2, pp. 308–315, 2021, doi: 10.1093/PubMed/fdz114.