

## Review Article

# Impact of treatment on development of NAFLD in patients with inflammatory bowel disease: a meta-analysis

Gong Feng<sup>1</sup>, Xue-Ping Li<sup>1</sup>, Na He<sup>2</sup>, Chun-Yan Niu<sup>3</sup>, Man-Ling Liu<sup>1</sup>, Jie Gao<sup>1</sup>, Li-Ping Fan<sup>1</sup>, Ke-Lin Zhang<sup>2</sup>, Man Mi<sup>1</sup>

<sup>1</sup>*Xi'an Medical University, Xi'an, Shaanxi Province, China;* <sup>2</sup>*The First Affiliated Hospital of Xi'an Medical University, Xi'an, Shaanxi Province, China;* <sup>3</sup>*Department of Gastroenterology, Xiang'an Hospital Affiliated to Xiamen University, Xiamen, China*

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**Abstract:** Background: The prevalence of NAFLD has been estimated to reach as high as 40% in patients with inflammatory bowel disease (IBD), but the risk factors for the development of NAFLD in IBD remains unclear. Aim: This study aimed to assess whether IBD treatment with steroids, anti-TNF drugs, methotrexate, and the surgical treatment of IBD are associated with increased risk of NAFLD. Methods: A systematic literature review was carried out using various existing online databases from inception to August 2018, in order to identify risk factors for the development of NAFLD in IBD. The meta-analysis was conducted using the random effect model for heterogeneous data and the fixed effect model for homogeneous data. Results: The meta-analysis included seven studies, which involved 1,645 patients. Drug therapy for IBD had no significant impact on the development of NAFLD. The pooled odds ratios for NAFLD with the use of steroids, anti-TNF drugs and methotrexate were 1.31 (95% CI: 0.79-2.15,  $P = 0.29$ ), 0.86 (95% CI: 0.65-1.13,  $P > 0.05$ ) and 1.28 (95% CI: 0.83-1.95,  $P > 0.05$ ). The odds ratio for NAFLD with IBD-related surgical treatment was 1.50 (95% CI: 1.09-2.05,  $P < 0.05$ ), which was suggestive of a significant association. Conclusion: This meta-analysis revealed that steroid therapy, anti-TNF drugs and methotrexate were not associated with increased risk of NAFLD in IBD patients. In contrast, IBD-related surgical treatment was associated with elevated risk for NAFLD.

**Keywords:** Inflammatory bowel disease (IBD), nonalcoholic fatty liver disease (NAFLD), meta-analysis

## Background

Inflammatory bowel disease (IBD) is a chronic inflammatory disease associated with multi-organ involvement. It has a tendency for recurrence that requires long-term treatment, and involves high cost. The prevalence and incidence of IBD in North America is the highest in the world, causing huge medical burden [1]. Elevated transaminase levels are common in IBD patients, with nonalcoholic fatty liver disease (NAFLD) being the most common cause [2]. Recent studies have found that the prevalence of NAFLD in IBD patients is higher than in the general population [3, 4]. Cross-sectional studies have reported that the prevalence of NAFLD in IBD can reach between 8% and 40% [5, 6]. Liver fibrosis has been reported in 6.4% to 10% of IBD patients [7]. A recent study [8] also suggested that colitis- and IBD-like phenotypes are strongly associated with NAFLD.

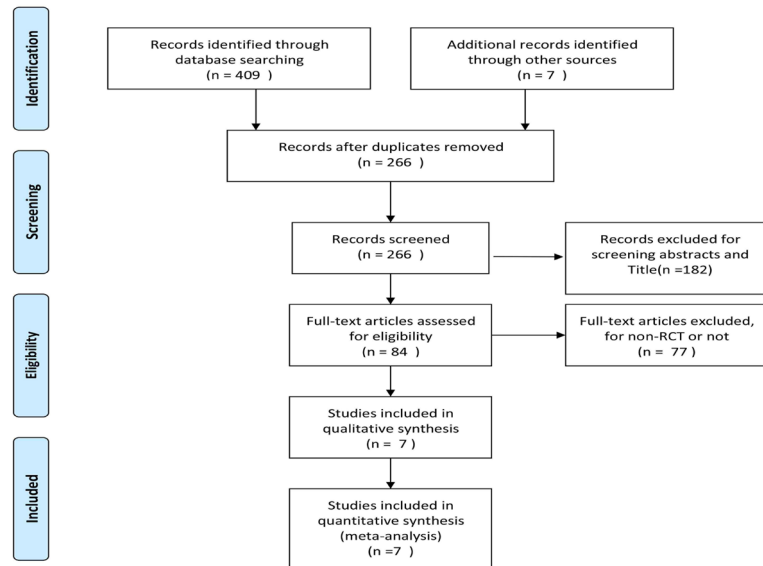
However, the pathophysiological mechanisms behind the development of NAFLD in IBD patients remain poorly understood. In addition, there are no guidelines for NAFLD detection, prevention and treatment in IBD patients. Hence, there is a need to conduct an in-depth study to understand the association between IBD and NAFLD.

NAFLD is a major public health problem that affects approximately one billion people worldwide [9]. In a society dominated by Western dietary patterns, NAFLD has been considered to be one of the most common liver diseases, resulting in a huge clinical and economic burden [10]. The occurrence of NAFLD in IBD patients appears to be multifactorial. However, the specific risk factors for the development of NAFLD in IBD patients remain unclear. In the present metaanalysis, studies that reported the impact of steroid therapy, anti-TNF drugs,



PRISMA 2009 Flow Diagram

Figure 1. PRISMA diagram of the literature search.



methotrexate and IBD-related surgery on the occurrence of NAFLD in IBD patients were collectively analyzed, in order to determine whether these are risk factors for the development of NAFLD in IBD patients.

## Materials and methods

### Data sources and retrieval

The literature review was carried out electronically through PubMed, Embase, the Cochrane Library English database, Wanfang, CNKI, and the Wipe Chinese database from the inception of the database to August 2018. All retrieved English and Chinese articles were included in the analysis. The following keywords were used: NASH (non-alcoholic steato-hepatitis), NAFLD, IBD, UC (ulcerative colitis), CD (Crohn's disease), steroids, methotrexate, tumor necrosis factor inhibitor, and histology. All human studies were included without language restrictions.

### Inclusion and exclusion criteria

The following criteria were used to include the studies in the meta-analysis: (1) randomized controlled clinical trials, cross-sectional, cohort, case-control, or observational studies that investigated the link between IBD treatment and NAFLD in adults; (2) studies that enrolled

patients with IBD, including both UC and CD; (3) studies that used the NAFLD diagnostic criteria to define non-alcoholic fatty liver disease; (4) studies that provided a detailed description of the medical and surgical therapy for IBD.

**Exclusion Criteria:** (1) studies that included patients with suspected or confirmed viral hepatitis, autoimmune liver disease, or drug-induced liver disease, including alcohol related liver disease; (2) studies on IBD that failed to differentiate NAFLD and non-NAFLD patients; (3) basic medical research, review articles, or case reports; (4)

studies with unclear data or different research contents.

### Data analysis

Revman software 5.2 was used for data processing and analysis. The binary data variables were described as odds ratio (OR) and 95% confidence interval (CI). The heterogeneity test was conducted using  $I^2$ , where  $I^2 > 50\%$  was considered heterogeneous. If the data was heterogeneous, the random effect model was used for the analysis, and when it was homogeneous, the fixed effect model was used for the analysis. The funnel plot was used to identify publication bias. Two independent reviewers (CE and CK) assessed the risk of bias, according to PRISMA recommendations. Subgroup and sensitivity analyses were used to analyze the sources of heterogeneity.

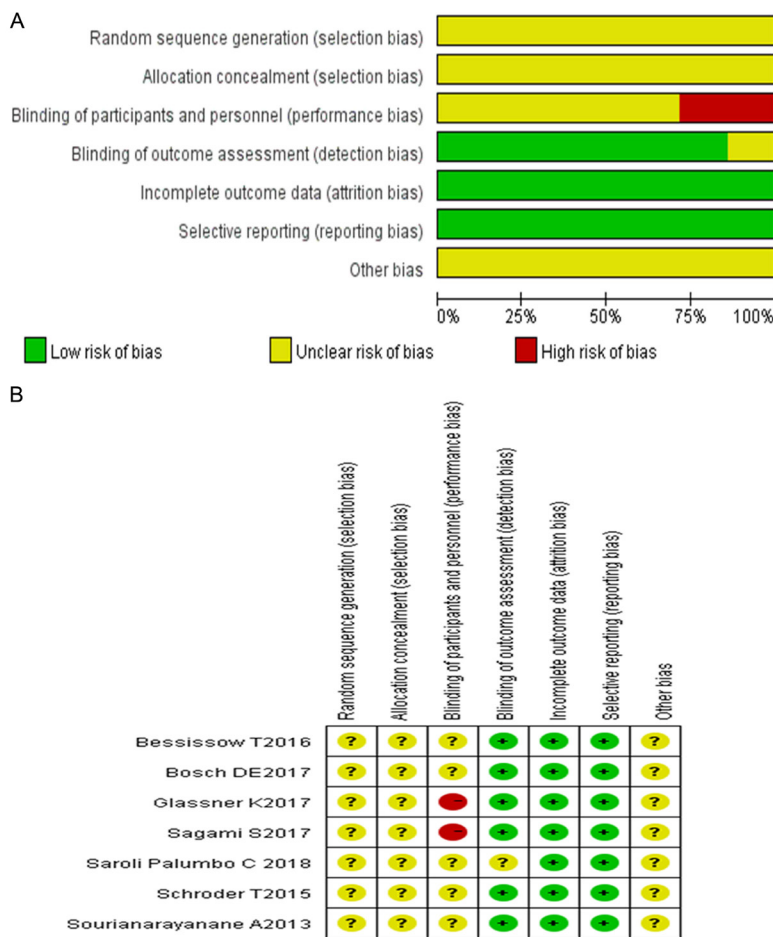
## Results

### Search results

A total of 416 articles were initially identified from the databases. Among these, 150 articles were excluded due to duplication of data, while 259 articles were excluded, because these did not satisfy the inclusion criteria. Finally, seven studies with a total of 1,645 patients were included in the meta-analysis (Figure 1). The

**Table 1.** Basic characteristics of the included studies

Author	Year	Country	Study sample (NAFLD in IBD patients)	Study sample (IBD patients)	NAFLD diagnostic means	Average age (year, NAFLD in IBD)	Proportion of men (NAFLD in IBD patient)	Type of study
Sourianarayanan A [11]	2013	USA	76	217	Abdominal imaging (CT, US, MRI)	37.2	31%	Retrospective
Schroder T [12]	2015	Germany	30	259	Abdominal US	44.1	33%	Retrospective
Bessissow T [13]	2016	Canada	108	321	Histology	37.7	47%	Retrospective
Bosch DE [14]	2017	USA	29	49	Liver biopsy	4.7	51%	Retrospective
Glassner K [15]	2017	USA	56	112	Liver imaging (CT, US, MRI)	45	34%	Retrospective
Sagami S [16]	2017	Japan	66	303	Abdominal US	28.2	53%	Retrospective
Saroli Palumbo C [17]	2018	Canada	126	384	Imaging (Transient Elastography)	50.2	65%	Prospective Cohort Study


**Figure 2.** Evaluation of the quality of included studies: (A) Sub-plots of the quality evaluation; (B) General plots of the quality evaluation.

basic features of these seven included studies are presented in **Table 1**.

#### Quality assessment of the included articles

All trials were screened according to the inclusion and exclusion criteria. The present meta-

analysis included six retrospective studies and one prospective study. The sub-plots of quality evaluation are presented in **Figure 2A**. The general plots of quality evaluation are presented in **Figure 2B**.

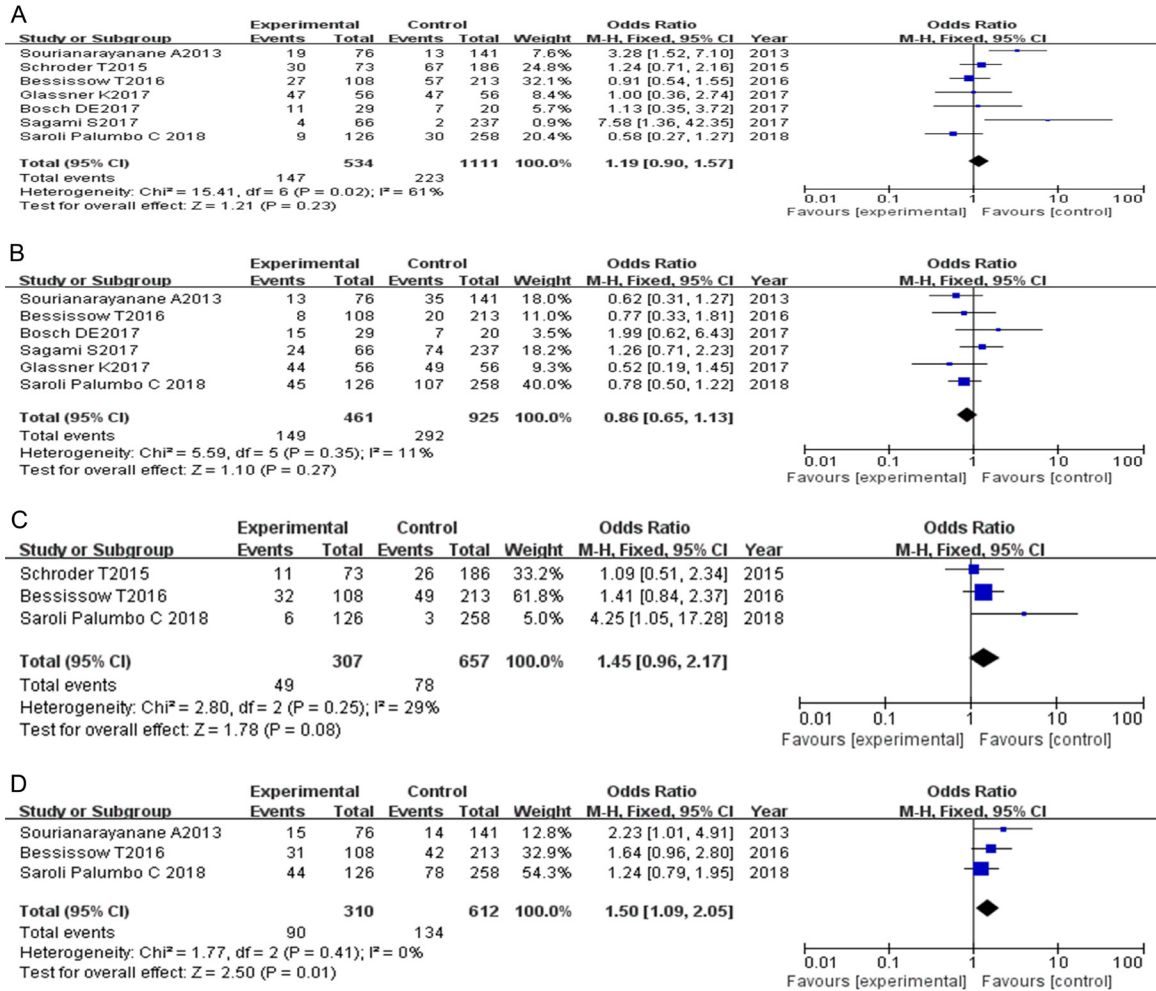
#### Results of the meta-analysis

**Effects of steroid treatment on NAFLD:** All seven studies described the impact of steroid treatment on NAFLD. The heterogeneity test revealed significant heterogeneity ( $I^2 = 61\%$ ). The random effect model was used. The combined OR value was 1.31 (95% CI 0.79-2.15), but the difference was not statistically significant ( $P = 0.29$ ) (**Figure 3A**). The funnel plot revealed no publication bias (**Figure 4A**).

**Effect of anti-TNF drugs:** Six articles specifically described the effect of anti-TNF drugs on NAFLD. The heterogeneity test revealed no heterogeneity ( $I^2 = 11\%$ ). The fixed effect model was used.

The combined OR value was 0.86 (95% CI: 0.65-1.13), but the difference was not statistically significant ( $P > 0.05$ ) (**Figure 3B**). Funnel plot revealed no publication bias (**Figure 4B**).

**Effect of methotrexate:** Three studies specifically described the effect of methotrexate on



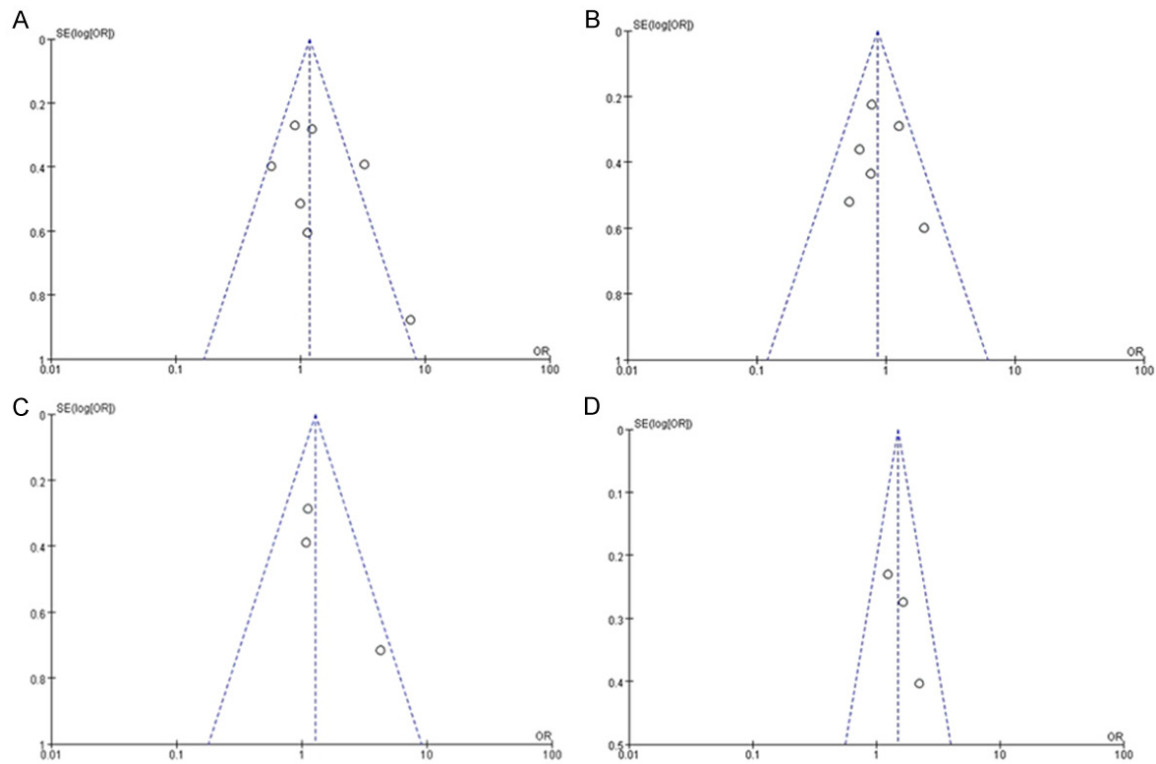
**Figure 3.** Forest plot for assessing the association between different IBD therapies and risk of NAFLD: (A) steroid treatment, (B) anti-TNF drugs, (C) methotrexate, and (D) previous IBD-related surgery.

NAFLD. The heterogeneity test revealed no heterogeneity ( $I^2 = 37\%$ ). The fixed effect model was used. The combined OR value was 1.28 (95% CI: 0.83-1.95), but the difference was not statistically significant ( $P > 0.05$ ) (**Figure 3C**). The funnel plot revealed no publication bias (**Figure 4C**).

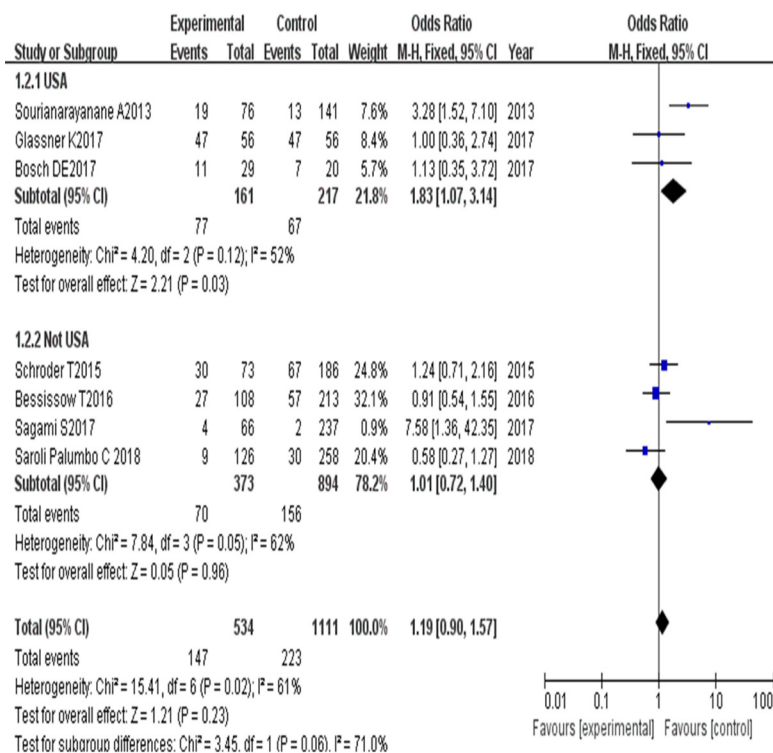
**Association between the surgical treatment for IBD and NAFLD:** Three articles described the effect of IBD-related surgical treatment on NAFLD. The heterogeneity test revealed no heterogeneity ( $I^2 = 0\%$ ). The fixed effect model was used. The combined OR value was 1.50 (95% CI: 1.09-2.05), and the difference was statistically significant ( $P < 0.05$ ) (**Figure 3D**). The funnel plot revealed no publication bias (**Figure 4D**).

#### Subgroup and sensitivity analysis

Heterogeneity ( $I^2 = 61\%$ ) was found in the analysis of the association between steroid and NAFLD in IBD patients. Six articles were eliminated one by one for the sensitivity analysis. It was found that when the study conducted by Sourianarayanan A et al. [11] was excluded, the heterogeneity decreased from  $I^2 = 61\%$  to  $I^2 = 36\%$ , indicating that this study was the main cause of heterogeneity. Further analysis revealed that this study was a case-control study, in which there was uniformity in the diagnostic method for NAFLD, and this study included abdominal B-ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). However, the duration and frequency of steroid therapy and anti-TNF drugs were not detailed in this study.



**Figure 4.** Funnel plot to assess for publication bias in studies that reported the association between different IBD therapies and NAFLD: (A) steroid treatment, (B) anti-TNF drugs, (C) methotrexate, and (D) previous IBD-related surgery.



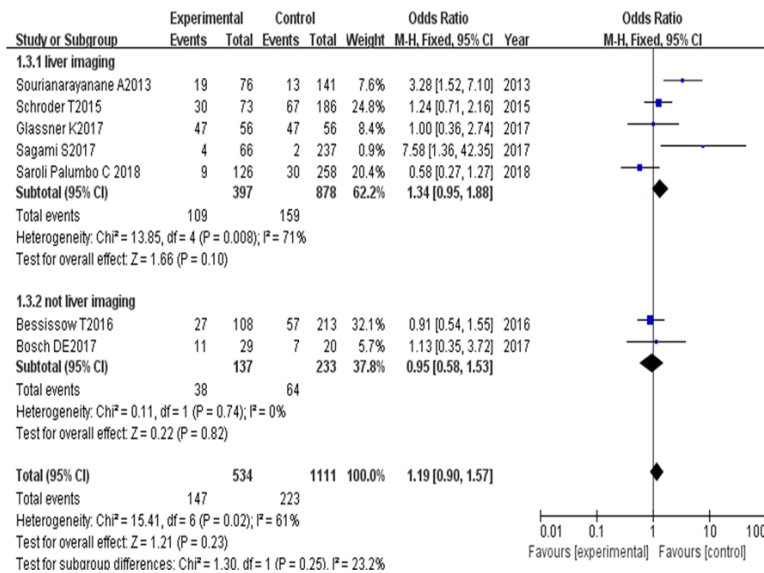
**Figure 5.** Subgroup analysis of the association between steroid therapy and NAFLD based on the country of origin of patients (USA and non-USA).

Subgroup analysis of the association between steroid therapy and NAFLD in IBD patients was performed according to the country of origin of patients in these studies (U.S. and non-U.S.) and the diagnostic tools (imaging and non-imaging) used for diagnosing NAFLD (Figures 5 and 6, respectively). No significant heterogeneity was found in the subgroup analysis.

## Discussion

Although a variety of etiologies have been proposed to explain the increased prevalence of NAFLD in IBD patients, including the presence of metabolic syndrome (MS), intestinal inflammation and drugs used to treat IBD, the underlying causes and mechanisms remain largely





**Figure 6.** Subgroup analysis based on the diagnostic methods used to detect NAFLD (imaging and non-imaging methods).

unknown, and require further investigation. In the present meta-analysis, steroid therapy for IBD was not found to be a risk factor for NAFLD development in IBD patients (OR = 1.31,  $P = 0.29$ ). However, on subgroup analysis, it was found that when grouped according to country of origin (USA and non-USA), steroid treatment may be a risk factor for NAFLD in the US population (Figure 5). Glucocorticoid analogues (GC) are commonly used as induction therapy for IBD. Furthermore, some patients with poorly controlled IBD may need a repeated or prolonged use of steroids. In addition, the effects on carbohydrate and lipid metabolism may lead to metabolic syndrome (MS) and predispose to the development of NAFLD. *In vitro* studies [18] have shown that GC may induce hepatocyte adipogenesis and steatosis by upregulating fatty acid synthase and acetyl coenzyme A carboxylase 1 and 2. GC and high-fat diet in rodent models can also exacerbate the development of NAFLD and liver fibrosis [19]. However, there has been a lack of clinical evidence linking GC and NAFLD in human studies. Furthermore, no prospective clinical-study has found GC to be an independent risk factor for NAFLD. In a study conducted by Hubel et al., compared with the control group, there was no significant difference in plasma cortisol concentration in NAFLD or obese patients [20]. Although no clear guidelines have been established, corticosteroids should be used with

caution in IBD patients with metabolic diseases, such as type-2 diabetes mellitus and hypothyroidism.

In the present meta-analysis, anti-TNF drugs were not found to be associated with NAFLD in IBD patients (OR = 0.86,  $P > 0.05$ ). Serum TNF- $\alpha$  levels and the corresponding mRNA expression in hepatocytes of NASH patients were significantly higher than those of healthy controls [21]. Anti-TNF- $\alpha$  agents have been widely used in various inflammatory diseases, and are by far the most effective drugs for the induction and maintenance of IBD. It has been speculated that anti TNF- $\alpha$  agents may

be protective against NASH. Infliximab has been shown to reduce steatosis and increase insulin signaling in rodents on a high-fat diet [22]. In addition, infliximab attenuates methionine and choline deficiency-induced liver inflammation, necrosis and fibrosis in rodents [23]. Adalimumab has also been shown to have a similar effect [24]. Pentoxifylline is a nonselective phosphodiesterase inhibitor that reduces TNF production, and has been reported to induce improvements in biochemical liver enzymes in NASH patients [25]. Based on the present evidence and the present meta-analysis, anti-TNF- $\alpha$  agents are not likely to be risk factors for NAFLD in IBD.

The present meta-analysis found no association between methotrexate therapy and the occurrence of NAFLD in IBD patients (OR: 1.28,  $P > 0.05$ ). Methotrexate is a folate antagonist, which competitively inhibits dihydrofolate reductase, interferes with the synthesis of purine and pyrimidine, and produces anti-inflammatory effects. It can be used as an induction and maintenance monotherapy for IBD treatment, or combined with anti-TNF $\alpha$  agents [26]. The serum levels of liver enzymes may be elevated in 15-50% of patients with methotrexate, although most of them are self-limiting, and the underlying mechanism has been speculated to be correlated to oxidative stress [27]. A retrospective analysis revealed that approximately

24% of IBD patients had elevated serum liver enzymes after using methotrexate. However, obvious liver fibrosis or cirrhosis is not common, and occur in merely 5% of patients receiving long-term low-dose methotrexate therapy. The correlation between methotrexate and NAFLD is relatively low. In a multivariate analysis, an average weekly dose of 13.1 mg of methotrexate was shown to be an independent predictor of NAFLD [28] in patients with rheumatoid arthritis, but methotrexate use has not been shown to cause NAFLD in IBD patients. Methotrexate is prone to increase liver enzymes, but does not necessarily lead to the occurrence of NAFLD.

The present meta-analysis revealed that IBD-related surgical treatment is a risk factor for NAFLD development in IBD patients (OR: 1.50,  $P < 0.05$ ). One possible explanation for this finding is that IBD patients undergoing surgery often need parenteral nutrition (PN) after surgical resection, postoperatively. Hepatic steatosis is a common complication of PN [29], which can occur in less than five days after the initiation of PN. Hepatic steatosis may progress to NAFLD with prolonged total parenteral nutrition (TPN), coexisting MS, and the use of hepatotoxic drugs in IBD patients.

The focus of treatments for NAFLD is generally dietary and lifestyle changes aimed for achieving weight loss, but these treatments have not been specifically evaluated in the IBD population. Prevention or reversal of liver fibrosis should ultimately lead to a reduction in NAFLD related complications. No drug preparation has been formally approved for NASH treatment. Pioglitazone (a peroxisome proliferator-activated receptor agonist), Vitamin E and obeticholic acid (a farnesol X-receptor agonist) can improve the histological markers of NASH [30]. Several anti-inflammatory and anti-fibrosis agents are also being actively studied. Bariatric surgery may also lead to the improvement of NASH in morbidly obese patients. However, it remains unclear whether there is a need to change the drug therapy for IBD in patients who develop NAFLD. In addition, NAFLD treatment has not been specifically studied in the IBD population. Hence, at present, the treatment of these patients should be individualized and guided through existing protocols for non-IBD NAFLD patients.

There are some shortcomings in the present meta-analysis. First, the dosage and duration of drugs used in each study was inconsistent. Second, the sample size of the included articles was small. Third, other risk factors for NAFLD were not consistently studied and controlled in the included studies. Fourth, there were inconsistencies in the tools used for diagnosing NAFLD. Future multicenter and larger sample size prospective studies are required to verify the results of the present meta-analysis.

In conclusion, the existence of NAFLD in IBD is increasingly being recognized. This is partly correlated to the increased incidence of MS and complex IBD-related factors. The real impact of IBD therapy on the development of NAFLD needs further evaluation through prospective studies. Furthermore, the long-term prognosis of IBD patients with NAFLD requires further qualitative evaluation. In addition, there is a lack of guidance for appropriate screening tools and strategies for NAFLD in IBD patients. Addressing these problems may facilitate early intervention and improve prognosis.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Man Mi, Xi'an Medical University, No. 74, Hanguang North Road, Xi'an 710021, Shaanxi Province, China. E-mail: a1774-2321665@163.com; Na He, The First Affiliated Hospital of Xi'an Medical University, Xi'an 710021, Shaanxi Province, China. E-mail: ylhen@163.com

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