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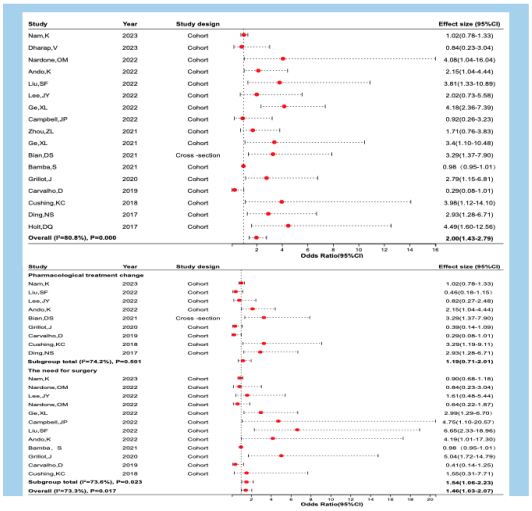
[Sarcopenia and Treatment Failure in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis]

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic disease characterized by a complex genetic disease that is instigated and amplified by the confluence of multiple genetic and environmental variables that perturb the immune-microbiome axis.

Sarcopenia is an age-related disease characterized by the loss of muscle mass, impaired motility, or decreased muscle strength. It is a novel predictor of unfavorable clinical outcomes in many diseases. The association between sarcopenia and treatment outcomes in IBD is currently a subject of controversy.

Seventeen studies were included in this meta-analysis with a sample size of 2,895 IBD patients. Sarcopenia increased the risk of treatment failure (OR 2.00), mainly by increasing the need for surgery (OR 1.54) but not by increasing the need of change of pharmacological treatment (OR 1.19) (for patients receiving either steroids or biologicals at baseline). Sarcopenia impacts treatment failure in both CD and UC, and in studies from different regions of the world.



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Sarcopenia and treatment failure in inflammatory bowel disease: a systematic review and meta-analysis

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Author contributions: this study was designed and conceived by FY and GHT. FY and GHT independently assessed studies for possible inclusion and collected the data. FWH and XM analyzed the data. FY wrote the manuscript. WCP, YHH and WY modified the picture. All authors read and approved the final manuscript.

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Lay summary

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic disease characterized by a complex genetic disease that is instigated and amplified by the confluence of multiple genetic and environmental variables that perturb the immune-microbiome axis.

Sarcopenia is an age-related disease characterized by the loss of muscle mass, impaired motility, or decreased muscle strength. It is a novel predictor of unfavorable clinical outcomes in many diseases. The association between sarcopenia and treatment outcomes in IBD is currently a subject of controversy.

Seventeen studies were included in this meta-analysis with a sample size of 2,895 IBD patients. Sarcopenia increased the risk of treatment failure (OR 2.00), mainly by increasing the need for surgery (OR 1.54) but not by increasing the need of change of pharmacological treatment (OR 1.19) (for patients receiving either steroids or biologicals at baseline). Sarcopenia impacts treatment failure in both CD and UC, and in studies from different regions of the world.

ABSTRACT

Background: the association between sarcopenia and treatment outcomes in inflammatory bowel disease (IBD) is currently a subject of controversy.

Methods: a systematic search was performed of PubMed, Embase, Web of Science, and the Cochrane Library for studies published until April 2023. The quality assessment of each included study was performed using the Newcastle-Ottawa Scale.

Results: seventeen studies were included with 2,895 IBD patients. Sarcopenia exhibited an increased risk of treatment failure (OR = 2.00, 95 % CI: 1.43-2.79) and notably increased the need for surgery (OR = 1.54, 95 % CI: 1.06-2.23) as opposed to a pharmacologic treatment plan change (OR = 1.19, 95 % CI: 0.71-2.01) among IBD patients. However, no significant association was found between sarcopenia and treatment failure in corticosteroid (OR = 1.21, 95 % CI: 0.55-2.64) or biologic agent (OR = 1.65, 95 % CI: 0.93-2.92) cohorts. Sarcopenia was also linked to elevated

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treatment failure risks in patients with Crohn's disease (OR = 1.82, 95 % CI: 1.15-2.90) and those diagnosed with ulcerative colitis (OR = 2.55, 95 % CI: 1.05-6.21), spanning both Asian (OR = 1.88, 95 % CI: 1.29-2.74) and non-Asian regions (OR = 2.17, 95 % CI: 1.48-3.18).

Conclusions: sarcopenia was considered as a novel marker for use in clinical practice to predict treatment failure, specifically, the need for surgery in IBD patients. This distinct cohort necessitates clinical attention and tailored care strategies.

Keywords: Inflammatory bowel disease. Sarcopenia. Treatment failure. Surgery.

INTRODUCTION

Sarcopenia is an age-related disease characterized by the loss of muscle mass, impaired motility, or decreased muscle strength (1). It may also be activity-related, nutrition-related, or disease-related. Numerous studies have underscored the pivotal role of sarcopenia as a predictor of unfavorable clinical outcomes in various diseases (2,3).

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic disease characterized by a complex genetic component that is instigated and amplified by the confluence of multiple genetic and environmental variables that perturb the immune-microbiome axis (4). Prevalent in Europe, IBD exhibits rates of 24.3 cases per 100,000 for UC and 12.7 cases per 100,000 person-years for CD (5). Given its lifelong and relapsing nature, the quality of life for IBD patients is intrinsically linked to treatment outcomes, posing a formidable challenge in clinical decision-making. Nowadays, treatment strategies for IBD remain complex and have high failure rates. Treatment failures in IBD mainly include primary non-response, rehospitalization due to complications, discontinuation of biologic agents, dose escalation of drugs, absence of endoscopic mucosal healing and the need for surgery. (6-8).

Sarcopenia is reported to be very common in IBD patients. A previous meta-analysis showed that the prevalence of sarcopenia was about 52 % in CD patients and 37 % in UC patients (9). Ando K et al. and Ding NS et al. reported that sarcopenic IBD patients

had a two-three times higher risk of experiencing loss of response to pharmacologic therapy than non-sarcopenic IBD patients (6,10). Conversely, the study by Campbell JP et al. indicated no correlation between sarcopenia and discontinuation of biological therapy (11). Meanwhile, the findings of Nam K et al. highlighted sarcopenia's negative influence on the need for surgery among IBD patients (12). The impact of sarcopenia on treatment efficiency in IBD patients remains controversial. Thus, this meta-analysis was performed to better understand the association between sarcopenia and IBD.

MATERIALS AND METHODS

This systematic review and meta-analysis were carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and were registered at PROSPERO (CRD42023409922).

Literature search

Primary articles were systematically retrieved from four electronic databases (PubMed, Embase, Web of Science, and the Cochrane Library) from their inception until April 2023. The search employed both Medical Subject Headings (MeSH) and free-text terms related to "sarcopenia", as well as encompassing synonyms such as "muscle loss", "muscle atrophy", "muscle wasting", "myopenia" and "dynapenia". These terms were combined using the Boolean operator "AND" with MeSH terms such as "Inflammatory Bowel Disease", "Crohn's disease", and "Ulcerative Colitis", as well as their associated free-text terms. Additionally, a manual search was undertaken to identify any potentially overlooked references.

Literature selection

Two authors separately selected the literature that examined the associations between sarcopenia and treatment outcomes in IBD patients. Discrepancies in selection were addressed via consultation with a third author.

Inclusion and exclusion criteria

Studies were included if they: a) were observational cohort studies, case-control studies, or randomized controlled trials; b) explicitly defined baseline conservative treatment and assessed sarcopenia's impact on treatment outcomes; and c) employed imaging modalities (such as computed tomography [CT], dual-energy X-ray absorptiometry [DXA], bioelectrical impedance analysis [BIA], and magnetic resonance imaging [MRI]) to diagnose low skeletal muscle mass. Conversely, studies were excluded if they: a) were animal or cell studies, conference abstracts, case reports or comments; b) included pediatric (< 18 years) IBD patients; c) did not report sarcopenia or IBD diagnostic criteria; d) focused on post-surgical outcomes or included IBD patients who had undergone prior abdominal surgery; e) included patients receiving drugs/supplements influencing skeletal muscle mass due to other acute or chronic conditions; f) solely involved surgical therapy, without prior medication therapy details; and g) failed to report incident rates or effect size of outcomes at their end-point.

Measurement of outcomes

IBD patients who did not have sarcopenia were defined as the control groups. The following items were used to define treatment failure: pharmacological plan change, the need for surgery, re-hospitalization, no remission or no response to treatment, active inflammation, or endoscopic recurrence. In fact, pharmacologic treatment plans changes mainly included: optimization, escalation, cessation or switch of prior regiments (including 5-amino salicylic acid, immunomodulators, corticosteroids, or biologic agents), along with the addition of concomitant therapy (immunomodulator, corticosteroids, and cytapheresis). The need for surgery referred to patients who had previously received baseline drug treatment and were resistant to medication or experienced treatment failure during follow-up.

Data extraction and quality assessment

Two authors independently extracted data, including the first author's name, country, publication year, study design, patient number, gender, age, IBD type, sarcopenia measurement, prior drug treatment, treatment outcomes and follow-up

duration. Additionally, the Newcastle-Ottawa Scale (NOS) was applied to assess study quality, designating high-quality studies as those with a score ≥ 7. Quality evaluation and risk of bias assessment were performed independently by two authors.

Statistical analysis

A random-effects model was used to calculate pooled odds ratios (ORs) with 95 % confidence intervals (CIs) for treatment failure risk in sarcopenic IBD patients using Stata 14.1 (Stata Corp LLC, College Station, Texas, USA) and R version 4.1.2. The Q test ($p < 0.1$) and the I^2 statistic were used to measure statistical heterogeneity. Considerable heterogeneity was defined as $I^2 > 75$ % or $p < 0.1$. Sensitivity analysis was performed by removing only one study at a time to repeat the meta-analysis. Publication bias was evaluated through symmetry assessment of funnel plots, and Begg and Egger's tests for visual and quantitative analysis, respectively.

RESULTS

Characteristics of included studies

Initially, 922 studies were identified via four databases, including PubMed, Embase, Web of Science and the Cochrane Library. There were 17 observational studies finally included in this meta-analysis (Fig. 1), containing 16 retrospective studies (6-8,10-22) and one prospective (23) study. In total, 2,895 IBD patients were included in this meta-analysis. Among these patients, the prevalence of sarcopenia was 50.4 %. Table 1 summarizes the main characteristics of the included studies. Sarcopenia was assessed in the included studies through a range of methodologies, including calculating the skeletal muscle index (SMI) from CT scans (6-8,10-12,14-19,21,22), BIA (23) and body water analyzer (13).

Risk of bias in the included studies

According to the NOS for cohort studies and the NOS adapted for cross-sectional studies, all the included observational studies were of good quality with a median NOS quality score of 7 (range from 7 to 8) (Table 1).

Effects of sarcopenia on treatment failure

In the 17 studies estimating the effect of sarcopenia on IBD patients, the analysis showed that sarcopenia could significantly increase the risk of treatment failure by more than twice in IBD patients (OR = 2.00, 95 % CI: 1.43-2.79, I^2 = 80.8 %, p = 0.000) (Fig. 2). However, there was significant heterogeneity within these studies. Thus, subgroup analyses were performed based on different outcome indicators of treatment failure, including pharmacologic plan change and the need for surgery. The analysis showed that sarcopenia did not increase the risk of pharmacologic plan change (OR = 1.19, 95 % CI: 0.71-2.01, I^2 = 74.2 %, p = 0.501), but significantly increased the risk of the need for surgery in IBD patients (OR = 1.54, 95 % CI: 1.06-2.23, I^2 = 73.6 %, p = 0.023) (Fig. 3).

Classification of pharmaceuticals in treatment failure

There was significant heterogeneity among the studies on the relationship between sarcopenia and pharmacologic plan change. To further clarify whether sarcopenia impacted the drug treatment of IBD, the subgroup analysis was also stratified based on two classic medication regimens, including corticosteroid and biologic agent groups. However, sarcopenia was still not associated with treatment failure of corticosteroids (OR = 1.70, 95 % CI: 0.79-3.65, I^2 = 77.4 %, p = 0.171) or biologic agents (OR = 1.65, 95 % CI: 0.93-2.92, I^2 = 61.1 %, p = 0.084) (Fig. 4A). While the subgroup analysis did not prove that sarcopenia was related to the pharmacologic plan change of IBD, we considered that there might be less relevant research, thus, there should be more depth-research in the future.

Types of IBD in treatment failure

Considering that the treatment varies in the different types of diseases, subgroup analysis was implemented for CD and UC. The results found that sarcopenia was associated with more than twice the increased risk of treatment failure in UC patients (OR = 2.55, 95 % CI: 1.05-6.21, I^2 = 78.6 %, p = 0.039), and CD was associated with nearly twice the increased risk of treatment failure (OR = 1.82, 95 % CI:

1.15-2.90, I^2 = 66.7 %, *p* = 0.011) (Fig. 4B). Even so, there was no difference in the degree of sarcopenia impact on CD and UC patients.

Races in treatment failure

As nearly half of the included studies were carried out in Asia, all the included studies were divided into only two groups (Asian *vs* non-Asian groups). The analysis found that sarcopenia was correlated with treatment failure, both in Asian IBD patients (OR = 1.88, 95 % CI: 1.29-2.74, I^2 = 82.4 %, *p* = 0.001) and non-Asian patients (OR = 2.15, 95 % CI: 1.09-4.21, I^2 = 62.0 %, *p* = 0.027) (Fig. 4C).

Publication bias and sensitivity analysis

The result showed a slight asymmetry on both sides of the funnel plot (Fig. 5), indicating a possible publication bias. In addition, the results of the Begg test (*p* = 0.54) and Egger linear regression (t = 4.25, *p* = 0.001) showed a lower likelihood of publication bias. Sensitivity analysis was carried out by excluding studies that may have significant effects on the result of the meta-analysis (that is, either outliers or having a high or unclear risk of bias in multiple domains). The analysis showed that the combined effect size did not change significantly. Therefore, all results were considered as a reliable discovery.

DISCUSSION

Numerous studies attempted to provide a potential explanation for the occurrence of sarcopenia in patients with IBD. Proinflammatory cytokines, such as TNF-α and IL-6, have been implicated in the suppression of insulin-like growth factor-1 (IGF-1), thereby disrupting protein synthesis through the IGF-1/AKT signaling pathway. Additionally, the activation of the NF-κB pathway by these proinflammatory cytokines might hinder protein degradation and regeneration of damaged myofibers, ultimately culminating in skeletal muscle loss (24,25).

Our systematic review and meta-analysis revealed that the influence of sarcopenia on pharmacologic plan changes in IBD patients was limited. Given the personalized nature of pharmacologic treatment strategies in IBD, skeletal muscle content might

not be a decisive factor to make treatment decisions. A multitude of factors, such as genetic variants, disease severity, inflammatory markers, disease location, and complications, can collectively influence treatment outcomes (26). Further research is imperative to identify novel biomarkers to predict pharmacologic treatment change and facilitate the early optimization of therapeutic approaches.

This study only categorized pharmaceuticals into two groups due to the scarcity of relevant studies. Previous studies showed that anti-tumor necrosis factor agents (anti-TNF-α), like infliximab, might increase muscle mass in IBD patients (27). Meanwhile, glucocorticoids, commonly used for inflammatory diseases, have been associated with sarcopenia development, particularly in cases of prolonged or high-dosage treatment (28). In addition, glucocorticoid-induced mice have been used as an *in vivo* animal model in a variety of studies regarding the loss of skeletal muscle mass (29,30). However, due to the lack of studies, whether short-term or low-dosage glucocorticoid treatment will cause muscle dysfunction remains elusive. In a randomized, double-blind cross-over trial by Short KR et al., glucocorticoid usage for six days in healthy adults had little effect on leg muscle or whole-body protein metabolism (31). The different drug mechanisms or dosages lead to dynamic changes in skeletal muscle, making pharmaceuticals a confounding factor. Therefore, this issue could be worthy of investigation in the future.

In our study, there was a significant association between sarcopenia and the need for surgery in IBD patients. Surgery intervention was considered as a significant component of the multimodality treatment of IBD. It is estimated that the incidence rates of surgery in patients with IBD are about 70 % with CD and 25 % with UC (32). The role of skeletal muscles as metabolic and endocrine organs that affect drug distribution throughout the body potentially impacts clinical pharmacokinetics, particularly drug clearance (10). In the included studies, most patients who needed surgery had previously experienced pharmacologic treatment failure, indicating an advanced disease stage.

The subgroup analysis based on IBD phenotype shows that UC and CD are two distinct chronic relapsing gastrointestinal disorders with an unclear pathogenesis (4). In CD patients, surgery was mainly indicated for complications such as intestinal

obstruction, fistula formation, abscesses, inflammatory masses or malnutrition, while in UC, surgical intervention was recommended for lower gastrointestinal hemorrhage, dysplasia, toxic megacolon, intestinal perforation or severe malnutrition (33,34). Sarcopenia was considered as an influential factor of malnutrition, thus determining the need for surgery in both UC and CD patients.

Our subgroup analysis based on race observed a significant association between sarcopenia and treatment failure in Asia and non-Asia regions among IBD patients. Although the Asian Working Group on Sarcopenia (35) and the European Working Group on Sarcopenia in Older People (1) established different criteria to define sarcopenia, both groups recognized its clinical significance. There are regional differences in the characteristics of IBD, but our findings suggested that sarcopenia was an essential factor associated with treatment failure across different regions. More extensive cohort studies encompassing a more comprehensive range of geographic areas are needed to explore this relationship in the future.

There are numerous strengths to this meta-analysis. It is the first meta-analysis that investigates the relationship between sarcopenia and treatment failure in IBD patients. Furthermore, our subgroup analyses explored the impacts of IBD phenotypes, pharmaceutical classifications and races on this relationship. The quality of the included literature was assessed using a standardized scale, and the meta-results were frequently checked to ensure accuracy. However, there were still some limitations to our study. Most of the studies included had a retrospective design and small sample size, which may impact the validity of our findings. Additionally, the various methods used to measure sarcopenia raised concerns about heterogeneity.

In conclusion, our findings suggested that sarcopenia was a novel marker for use in clinical practice to predict treatment failure, specifically, the need for surgery in IBD patients. Early identification of sarcopenia to prevent treatment failure in IBD patients is advised for clinicians.

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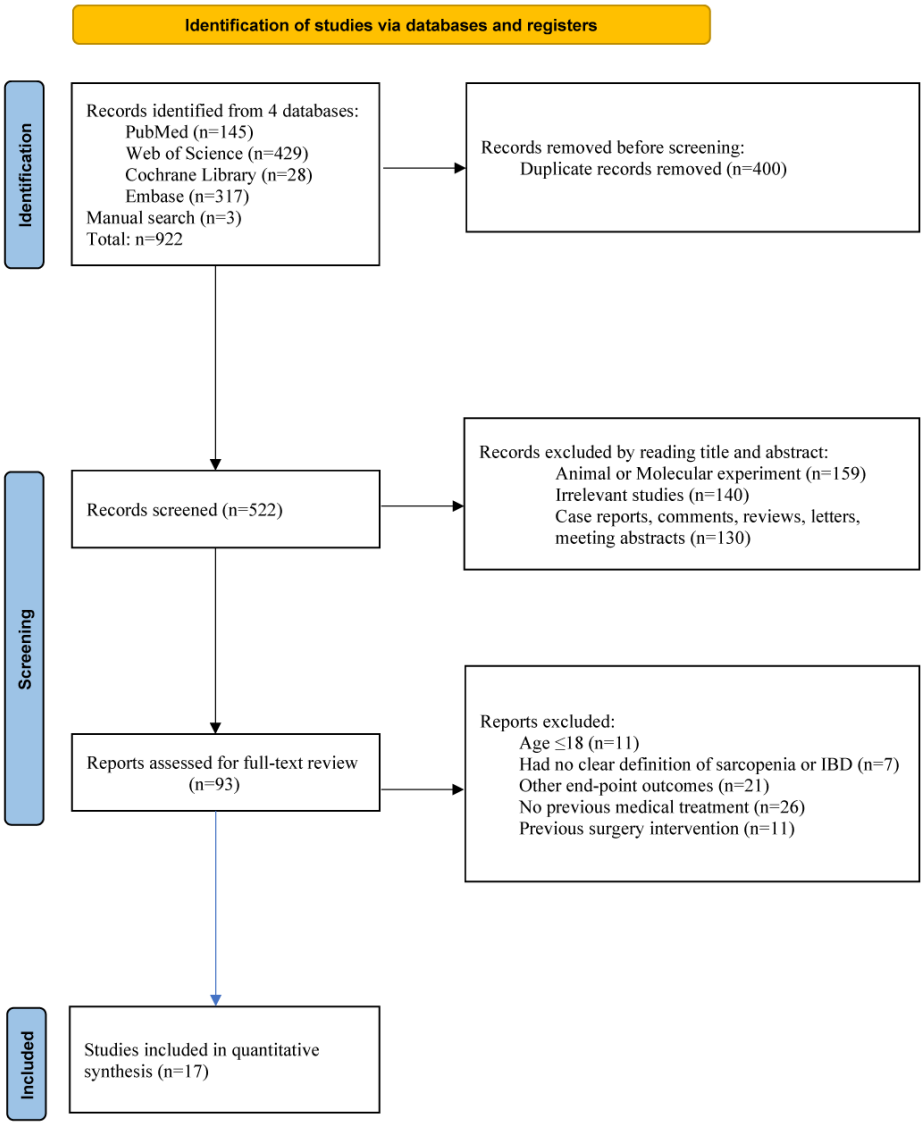

Fig. 1. Flow chart of the literature selection. IBD: inflammatory bowel disease.

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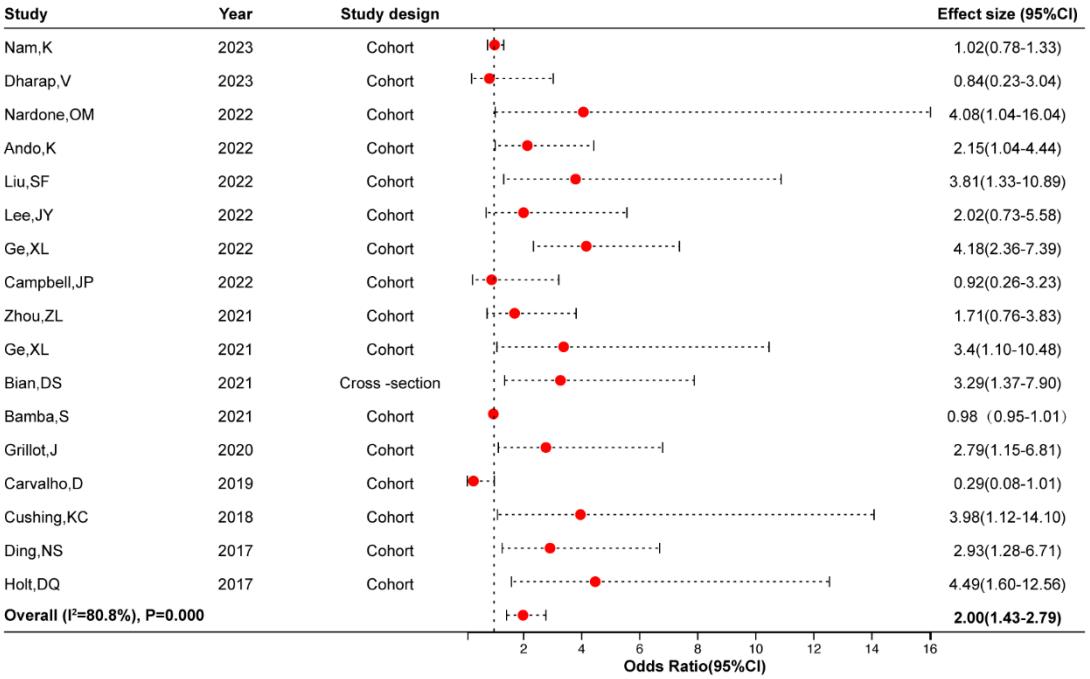

Fig. 2. Forest plot of the associations between sarcopenia and treatment failure in inflammatory bowel disease (IBD) patients.

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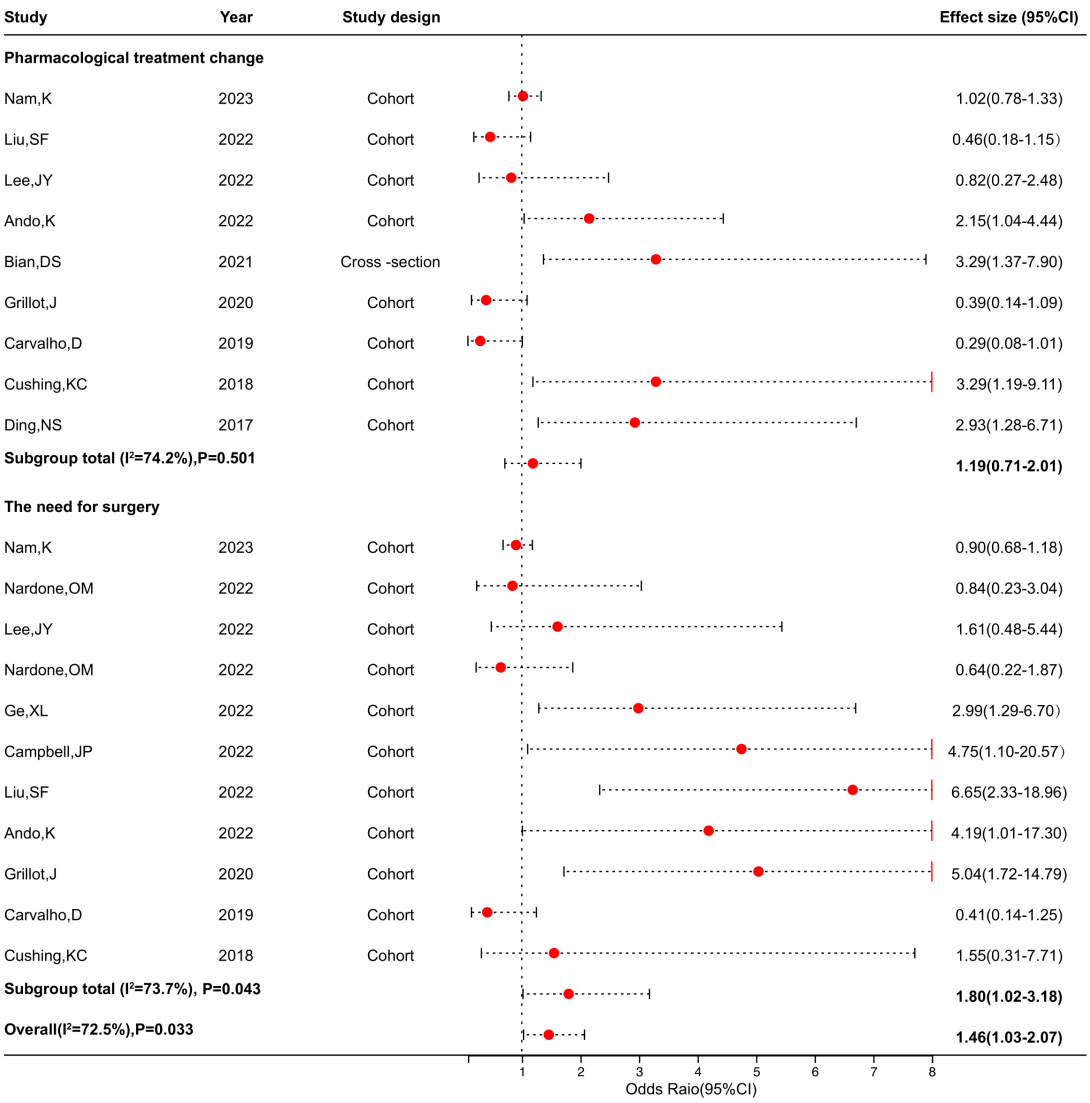

Fig. 3. Subgroup analysis based on two indicators of treatment failure including pharmacologic plan change and the need for surgery.

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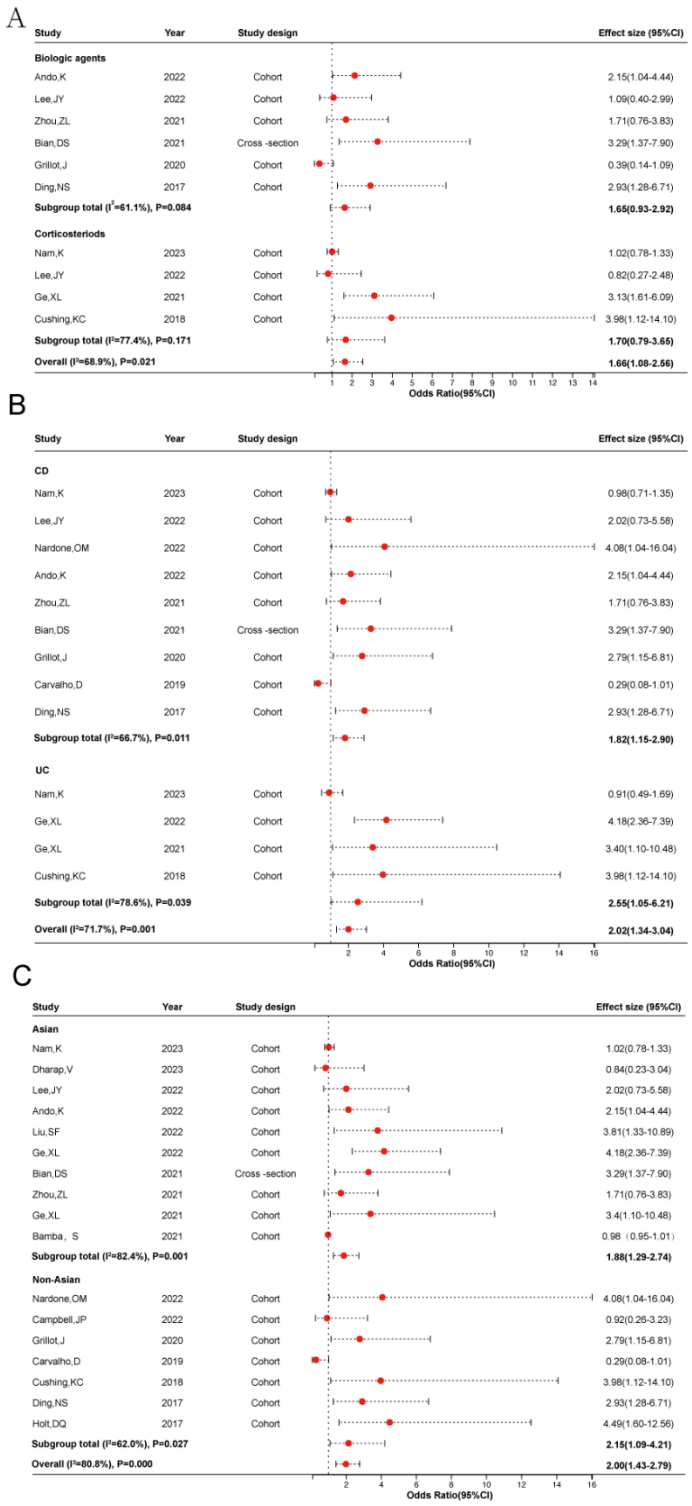

Fig. 4. Subgroup analysis of the association between sarcopenia and treatment failure in: A. Classification of pharmaceuticals in treatment failure. B. Types of inflammatory bowel disease (IBD) in treatment failure. C. Races.

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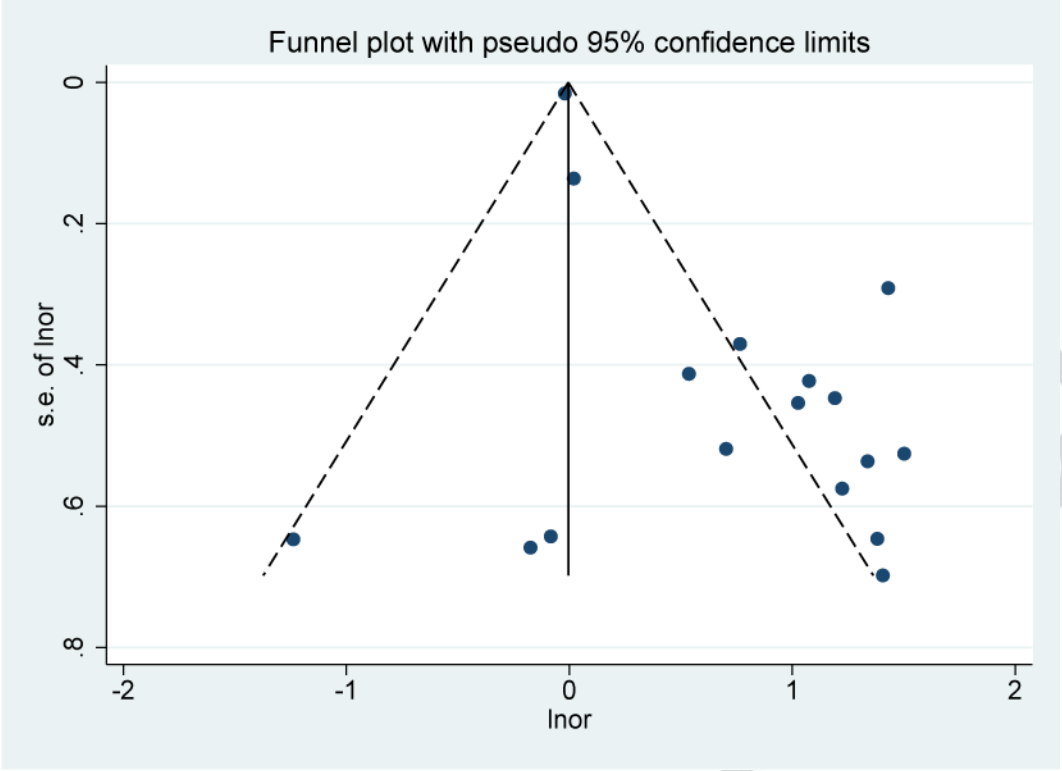

Fig. 5. Funnel plot with pseudo 95 % confidence limits.