Protocol

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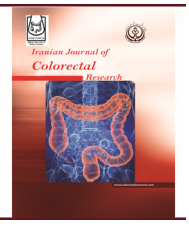

Does Inflammatory Bowel Disease Activity Alter Following Liver Transplantation? A Systematic Review And Meta-Analysis Protocol

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Abstract

Introduction: Inflammatory bowel disease (IBD) is associated with primary sclerosing cholangitis (PSC), an uncommon chronic and progressive cholestatic liver disease. Liver transplantation (LT) is the only therapeutic strategy for PSC that may also affect the IBD course. Considering the lack of systematic reviews and pursuing debates on this issue, we aim to systematically assess the frequencies of patients with an improved, unchanged, or exacerbated IBD course following LT and to conduct a meta-analysis.
Methods: In this systematic review, PubMed/MEDLINE, Scopus, WoS (Clarivate Analytics), and Embase will be searched. Our search strategy (i.e., the eligibility criteria) covers prospective and retrospective observational studies evaluating the clinical course of ulcerative colitis or Crohn's disease after LT, with no language limitation, published between 01/01/1970 and 30/12/2020. Two authors will independently implement the selection phase, data extraction, and quality assessment. In case of any disagreement between the authors, the issue will be resolved by consensus; if not resolved, the opinion of a third expert will be asked. If there are sufficient studies, the pooled frequencies (%) of patients with improved, unchanged, or exacerbated IBD activity following LT will be calculated using random or fixed effect models according to severity of methodological heterogeneity. Forest plots will show the separated and combined frequencies and the corresponding 95% CIs. The Q-statistic test and I^2 statistics will be used to evaluate statistical heterogeneity. We will use the funnel plot technique to assess reporting bias and Begg's and Egger's tests for publication bias. The trim and fill method will correct the effect of any potential publication bias.
Ethics and Dissemination: As this review will use published primary studies, an ethics committee review is not necessary. The results of our research will be published in peer-review journals and presented in relevant conference meetings.

Keywords: Liver transplantation, Inflammatory bowel disease, Primary sclerosing cholangitis, Crohn's disease, Ulcerative colitis

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Introduction

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD; ICD-10 diagnostic code K50.0-50.9) and ulcerative colitis (UC; ICD-10 diagnostic code K51.0-51.9), are characterized by idiopathic chronic inflammation and ulceration of the gastrointestinal tract. In 2017, there were 6.8 million IBD cases worldwide (1). There are marked differences in clinical and histological properties, anatomical distribution, risk factors, and response to treatment between UC and CD. However, abdominal pain and diarrhea are typical in both conditions (2). Evidence supports a robust association between IBD and primary sclerosing cholangitis (PSC) (3). It is estimated that 5% of patients with IBD have PSC, and 50% to 99% of patients with PSC have concomitant IBD (3, 4).

PSC (ICD-10 diagnostic code K83.01) is an uncommon chronic and progressive cholestatic liver disease. It is characterized by fibro-inflammatory reactions in medium to large bile ducts. Either intrahepatic or extrahepatic biliary systems may be affected. The incidence and prevalence of PSC in western countries are reported at about 0.07 to 1.3 per 10^5/person-years and 8.5 to 13.6 per 10^5 populations, respectively. PSC generally progresses to biliary cirrhosis and liver failure, often in an insidious manner. The median time from diagnosis to death or liver transplantation (LT) is approximately 9 to 18 years in centers with LT facilities. Liver transplantation is yet considered as the only curative treatment for patients with PSC and end-stage liver disease. Pancolitis, right-sided colitis, rectal sparing, and backwash ileitis are more frequently seen in patients with PSC-UC. However, UC usually runs a mild course in patients with concurrent PSC (5-7).

Despite post-transplant immunosuppression therapy for organ rejection prevention and IBD remission expectation, exacerbation of IBD is reported in some studies. In one study, 16 patients with UC-PSC were followed before and after LT. The study showed that half of the cases had a worsening UC course after LT, but the rest remained in remission (8). In a similar study, Gelley *et al*. applied the Mayo score to assess the activity of UC before and after LT in 31 cases with PSC-UC. They found that despite an inactive or mild state in 95% of patients before LT, just 35% remained inactive/mild following LT (9). However, other studies concluded that the IBD activity would remain stable in most PSC-UC cases after LT. In a study performed in 2017, we evaluated 159 patients with PSC-UC before and after LT. Our research demonstrated no change or even alleviation in IBD symptoms in approximately 94% of LT cases, with worsening symptoms in just 6% (10). Similarly, Navaneethan *et al*. showed that most PSC-UC patients (83%) had a quiescent course after LT, while the remainder had exacerbations in symptoms (11). Considering the lack of systematic reviews and pursuing debates on IBD activity after LT, we decided to conduct a systematic review based on available prospective and retrospective observational studies assessing alterations in IBD activity following LT. This study will reveal the pooled frequencies of patients with an improved, unchanged, or exacerbated IBD course following LT, which are critical for informing efforts to control the condition and determine which operation of LT or colectomy should be prioritized.

Objectives

Primary Objective

This systematic review's primary objective is to estimate the frequency (%) of IBD patients with improved, unchanged, or exacerbated IBD activity following LT.

Secondary Objectives

This study's secondary objectives will be to estimate the frequency (%) of IBD patients with improved, unchanged, or exacerbated IBD activity after LT by (i) age group, (ii) sex, (iii) IBD type, (iv) region, (v) pre-LT disease severity, (vi) duration of post-LT follow-up, (vii) smoking status, and (viii) post-LT immunosuppressive regimen.

Methods

It is reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (12) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline.

Eligibility Criteria of Primary Studies

Study Type: This systematic review will include prospective and retrospective observational studies (prospective and retrospective cohorts, case-control studies, including traditional and nested or case-cohort studies, and cross-sectional studies) evaluating alterations in the clinical course of UC or CD following LT. No restriction on sample size and language will be applied for primary studies to be included. The exclusion criteria will be clinical trials, reviews, newspapers, book chapters, notes, surveys, letters to the editor, case reports, and case series.

Type of Participants: All patients of any sex and age with UC or CD who underwent LT will be included in this study. Patients who underwent pre-transplant colectomy or de novo IBD after LT will be excluded. Patients with post-transplant colectomy would be eligible only if the surgery were performed because of an IBD flare.

Outcome: The outcome of the present study is the frequencies (%) of patients with improved, unchanged, or exacerbated IBD following LT.

Search Strategy Components

We will search PubMed/MEDLINE, Scopus, WoS (Clarivate Analytics), and Embase for manuscripts published from 01/01/1970 to 30/12/2020. To obtain all relevant studies, we have developed search components related to the diseases (IBD, UC, CD, and PSC) and intervention (LT). The search syntax for the PubMed/MEDLINE database is presented in Table 1. To find the synonyms of search components, thesaurus systems (Emtree and MeSH), the free text method, the views of experts, and related articles and abstracts will be used. The other methods used to find relevant studies are manually searching grey literature (thesis, conference papers, and organizational reports) and contacting experts to find their relevant unpublished studies. The results of all search procedures will be collected in EndNote software.

Screening and Selection

After the searching process and in the screening stage, two authors (ARS and MM) will review the title and abstract of each study according to the inclusion and exclusion criteria. The studies with insufficient data in one or more aspects of the inclusion criteria will be excluded. In the next step, two independent authors (ARS and AAK) will review the full texts to determine the final studies. Any discordance in these steps will be resolved by consensus, and if the disagreement is not resolved, the opinion of a third expert (GS) will be used.

Risk of Bias Assessment of the Included Studies

The risk of bias of the final included studies will be independently assessed by two authors (ARS and AK) using the revised Hoy tool. This scale has ten items regarding the representativeness of the target population and the sampling frame, random selection, the response rate, data collection, case definition, reliability and validity of the measurement tools, the length of the shortest prevalence period, and appropriateness of the numerator(s) and denominator(s) (13, 14). Questions will be scored either as "0" or "1" corresponding to high or low risk of bias, respectively. Then, studies will be tiered according to the total scores to the following groups: high risk of bias (0-3), moderate risk of bias (4-6), or low risk of bias (>6). Any inconsistencies between the two authors will be resolved by consensus, and if no agreement is reached yet again, the case will be resolved by seeking the views of a third expert (GS).

Data Extraction

For the final included studies, two independent authors (ARS and GS) will extract the following summary data: first author's name, study design, country, sample size, demographic variables of the participants, type of IBD, duration of disease before LT, follow-up duration after the operation, cytomegalovirus infection, steroid consumption, smoking status, the number of patients with improved/unchanged/exacerbated IBD following LT, and use of tacrolimus or cyclosporine medication.

We will provide a summary of the data in a table. In the absence of the required statistical data in the original studies, the authors will contact their authors to obtain the appropriate data. However, the study will be eliminated if the author fails to respond to

Table 1: The search syntax for the PubMed/MEDLINE database

Number	Search terms
1	(("idiopathic proctocolitis"[tiab] OR "ulcerative colitis"[tiab] OR "colitis gravis"[tiab] OR ("inflammatory bowel disease"[tiab] AND "ulcerative colitis type"[tiab]) OR "chronic ulcerative colitis"[tiab] OR "colitis ulcerative"[tiab] OR "colitis ulcerosa"[tiab] OR "colitis ulcerosa chronic"[tiab] OR (colitis[tiab] AND ulcerative[tiab]) OR (colitis[tiab] AND mucosal[tiab]) OR (colitis[tiab] AND ulcerous[tiab]) OR (colon[tiab] AND "chronic ulceration"[tiab]) OR "histiocytic ulcerative colitis"[tiab] OR "mucosal colitis"[tiab] OR "ulcerative colorectitis"[tiab] OR "ulcerative procto colitis"[tiab] OR "ulcerative proctocolitis"[tiab] OR "ulcerous colitis"[tiab])
2	("Crohn's enteritis"[tiab] OR "regional enteritis"[tiab] OR "Crohn's disease"[tiab] OR "Crohns disease"[tiab] OR "inflammatory bowel disease"[tiab] OR "granulomatous enteritis"[tiab] OR ileocolitis[tiab] OR "granulomatous colitis"[tiab] OR "terminal ileitis"[tiab] OR "regional ileitides"[tiab] OR "regional ileitis"[tiab] OR "cleron disease"[tiab] OR "Crohn's disease"[tiab] OR "Crohns disease"[tiab] OR "enteritis regionalis"[tiab] OR ("intestinal tract"[tiab] AND "regional enteritis"[tiab]) OR "morbuscrohn"[tiab] OR "regional enterocolitis"[tiab])
3	("inflammatory bowel disease"[tiab] OR ("bowel diseases"[tiab] AND inflammatory[tiab]) OR "indeterminate colitis"[tiab] OR "undetermined colitis"[tiab])
4	(cholangitides[tiab] AND sclerosing[tiab]) OR "sclerosingcholangitides"[tiab] OR "sclerosing cholangitis"[tiab] OR (cholangiitis[tiab] AND sclerosing[tiab]) OR (cholangiitides[tiab] AND sclerosing[tiab])OR"sclerosingcholangiitides"[tiab] OR "sclerosingcholangiitis"[tiab] OR "primary sclerosing cholangitis"[tiab] OR (cholangitides[tiab] AND "primary sclerosing"[tiab]) OR "primary sclerosingcholangitides"[tiab] OR "primary sclerosingcholangitides"[tiab] OR ("sclerosing cholangitis"[tiab] AND primary[tiab]) OR (cholangitis[tiab] AND "primary sclerosing"[tiab])
5	1 OR 2 OR 3 OR 4
6	(liver[tiab] AND transplantation[tiab])OR "liver transplantations"[tiab])
7	1970/01/01:2020/12/31[dp]
8	5 AND 6 AND 7

us three times.

Strategy for Data Synthesis

A set of scoring systems, including the Mayo score (disease activity index), simple clinical colitis activity index, need for hospitalization, need for escalation in medical therapy, and need for colectomy, have been applied in studies to assess the clinical course of IBD (8, 10, 11). Considering the lack of mean value and standard deviation of the scores in the relevant studies and diversity of the scoring instruments used, we will extract the number of patients (n) with improved, unchanged, or exacerbated IBD activity following LT to calculate the relevant frequencies (%).

The results of the eligible original studies will be presented concisely in a table encompassing the first author's name, year of publication, study design, sample size, and demographic data of the participants.

Statistical Analysis

If there are sufficient studies (more than three), the pooled frequencies (%) of patients with improved, unchanged, or exacerbated IBD following LT, as key measures, will be calculated using random or fixed effect models according to severity of methodological heterogeneity. The data regarding these three categories of patients will be analyzed separately. Forest plots will be plotted for all the studies to show the separated and pooled frequencies and their corresponding 95% CIs. The software used in the present study will be Stata V.14.1 (Stata Corp, college station, TX, USA). If meta-analysis is not possible, a systematic narrative synthesis will be provided with the information presented in the text and tables to summarize and explain the characteristics and findings of the included studies.

Assessment of Heterogeneity

The Q-statistic test and I^2 statistics and their corresponding 95% CIs will be used to assess the statistical heterogeneity in the included studies. The references provided in the Cochrane Handbook will be used as the basis for determining the degree of heterogeneity. Accordingly, heterogeneity values of 0–40% will be taken as perhaps not important, 30–60% as moderate heterogeneity, 50–90% as substantial heterogeneity, and 75–100% as considerable heterogeneity (15). The level of statistical significance will be set at $P<0.05$ for the Q-test.

Subgroup Analysis

If sufficient data are available, subgroup analysis or meta-regression will be used appropriately to investigate the effect of statistical heterogeneity. In this study, variables such as age, sex, IBD type, region, smoking, type of medication, duration of follow-up after LT, and severity of IBD before LT are the variables that will be used in subgroup analysis.

Sensitivity Analysis

The one-out remove method will be used for sensitivity analysis. If one of the combinations (K-1) of the studies shows a different result to the others, we will carefully consider the features of that study.

Quality Analysis

Quality analysis will be performed if there is a statistically significant difference between the results of high-quality and low-quality studies.

Assessment of Publication Bias

If there are sufficient studies (more than ten), both the funnel plot method and Begg's and Egger's statistical tests will be used to evaluate publication bias. If these methods show evidence of bias, the fill and trim method will be used to correct the publication bias effect.

Patient and Public Involvement

No patients will be involved in this study.

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Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Contributions

ARS is the guarantor of this study. All authors contributed to the conception and design of the protocol as follows. ARS worked on the topic refinement, formulation of the research question, review design, study selection forms, data extraction sheets, analysis plan, and wrote the protocol. ARS also designed the search strategy under the supervision of AK, GRS, and MM. GRS, MM, and AK contributed to the topic refinement, formulation of the research question, review design, and analysis plan, and gave critical feedback on the intellectual content of the draft protocol. GRS, AK, MM, HA, and SSZ reviewed the manuscript. As the senior author, GRS supervised the preparation of the study protocol and addressed the reviewers' comments. All the authors read and approved the final manuscript.

Abbreviations

CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; LT, liver transplantation; PSC, primary sclerosing cholangitis; UC, ulcerative colitis

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Conflicts of interest: None declared.

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