

THE GUT–LIVER–PANCREAS INTERACTIONS IN GASTROINTESTINAL DISEASE: PROGNOSTIC AND THERAPEUTIC PERSPECTIVES

Ph.D. Thesis

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“I wish you a great many mistakes”

Peter Hegyi

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1. LIST OF ABBREVIATIONS

AEs	Adverse Event
AH	Alcoholic Hepatitis
ALD	Alcohol-associated Liver Disease
ANC	Acute Necrotic Collections
AP	Acute Pancreatitis
APFC	Acute Peripancreatic Fluid Collections
ARLD	Alcohol-related Liver Disease
CI	Confidence Interval
CLD	Chronic Liver Disease
FMT	Faecal Microbiota Transplantation
ICD	International Classification of Diseases
IPD	Individual Patient Data
MAFLD	Metabolic-associated Fatty Liver Disease
NAFLD	Non-alcoholic Fatty Liver Disease
NASH	Non-alcoholic Steatohepatitis
NSJ	Nasojejunal (tube feeding)
NSG	Nasogastric (tube feeding)
Nut	Nutritional Support
PC	Pancreatic Pseudocysts
PTX	Pentoxifylline
RCT	Randomized controlled trial
SAH	Severe Alcoholic Hepatitis
SIRS	Systemic Inflammatory Response Syndrome
SLD	Steatotic Liver Disease
SOC	Standard of Care

WON Walled-off Necrosis

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

Vision: A future where every gastrointestinal patient benefits from rigorous science, translated into practice without delay

Mission: To pursue new evidence in gastroenterology and continuously improve within the field.

Specific goals: Complete residency by 2027, facilitate Faecal Microbiota Transplantation (FMT) trials across the alcoholic liver disease spectrum by 2030, and sustain a long-term role in university teaching.



2.2. Scientometrics

Number of all publications:	10
Cumulative IF:	29.46
Av IF/publication:	2.79
Ranking (SCImago):	Q1:7, Q3:3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.2
Av IF/publication:	3,6
Ranking (Sci Mago):	D1:1, Q2:1
Number of citations on Google Scholar:	34
Number of citations on MTMT (independent):	17
H-index:	3

The student's detailed bibliography can be found on page 60.

2.3. Future plans

In the short term, I aim to complete my residency in gastroenterology while consolidating the methodological and critical-appraisal skills gained during my training in translational medicine. I plan to apply these skills directly to the clinical management of patients with focuses on hepatic and pancreatic diseases. Additionally, I intend to remain actively involved in educating medical students and junior colleagues. Over the medium term, my goal is to expand upon this research by contributing to high-quality studies on microbiota-based intervention in the fields of pancreatology and hepatology.

3. SUMMARY OF THE THESIS

This thesis presents results from two projects addressing clinically relevant questions in hepatopancreatology. The first study examined the prognostic impact of chronic liver disease on the outcomes of acute pancreatitis (AP). Including 36 studies, the analysis demonstrated that patients with concomitant chronic liver disease face approximately 2.5-fold higher in-hospital mortality compared to those without, alongside significantly increased rates of organ failure, systemic inflammatory response syndrome, and local pancreatic complications. These findings establish chronic liver disease as a clinically important risk factor warranting systematic incorporation into early risk stratification of acute pancreatitis.

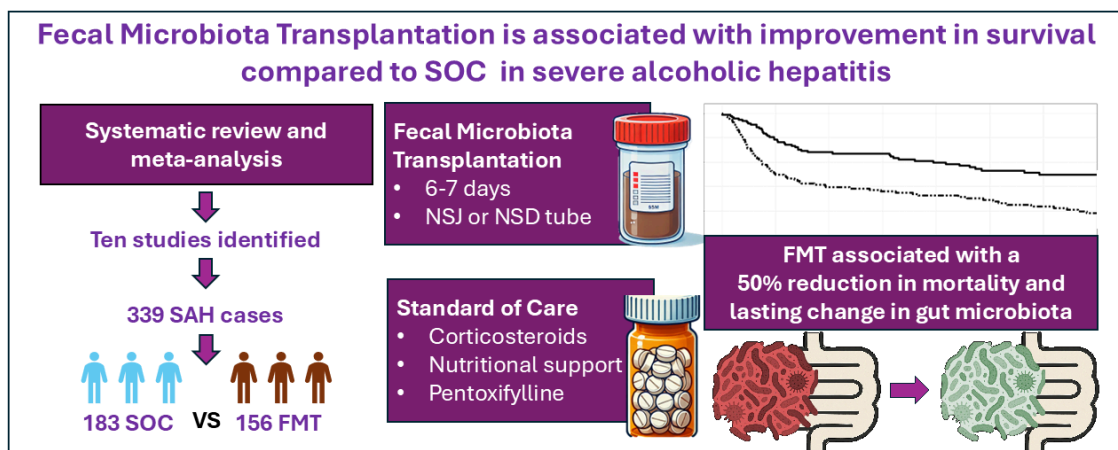
The second study evaluated faecal microbiota transplantation versus standard of care in severe alcoholic hepatitis, a life-threatening manifestation of alcohol-associated liver disease for which effective treatment options remain critically limited. Using both classical and individual patient data meta-analytic approaches, faecal microbiota transplantation was associated with a significant survival benefit at 28, 90, and 180 days, favourable restoration of gut microbiota composition, positioning it as a promising rescue therapy in patients ineligible for or unresponsive to corticosteroid treatment.

Together, these studies provide evidence-based contributions to the clinical management of two distinct yet interrelated conditions in hepato-pancreatology and define clear priorities for future research and clinical translation.

4. GRAPHICAL ABSTRACT

4.1. GRAPHICAL ABSTRACT STUDY I:

4.2. GRAPHICAL ABSTRACT STUDY II:



5. INTRODUCTION

5.1. Overview of the topic for Study I.

5.1.1. What is the topic?

AP ranks among the most common gastrointestinal causes of acute hospitalisation worldwide, following a highly variable clinical course that ranges from mild, self-limited illness to severe, life-threatening disease. The aetiological drivers of Chronic Liver Disease (CLD) and AP overlap substantially, most notably through alcohol use and obesity-related steatotic liver disease, resulting in the frequent co-occurrence of these two conditions in clinical practice. Patients with CLD carry a considerable comorbidity burden, encompassing cardiovascular disease, chronic kidney disease, malnutrition, and sarcopenia, each of which may independently contribute to a more adverse course of AP.

5.1.2. What is the problem to solve?

Despite this biological plausibility and clinical co-occurrence, the prognostic relationship of CLD on AP outcomes had not previously been systematically characterised.

5.1.3. What is the importance of the topic?

Standard imaging routinely performed during AP workup, like abdominal ultrasound, computed tomography, or magnetic resonance imaging, is capable of identifying CLD status, making it a potentially valuable, zero-additional-cost prognostic variable. Establishing whether CLD independently worsens AP outcomes is therefore of direct clinical relevance.

5.1.4. What would be the impact of our research results?

CLD status could be a candidate variable for incorporation into AP severity scoring systems and triage protocols. Such evidence would support earlier identification and closer monitoring of AP patients with concomitant CLD. Additionally, routine reporting of liver status could be incorporated into the reporting protocols for AP patients. Furthermore, this data could be a foundation for prospective studies evaluating CLD-tailored management pathways for AP treatment.

5.2. Overview of the topic for Study II.

5.2.1. What is the topic?

Alcohol-related liver disease (ALD) represents a major and growing global health burden. A significant subset of affected patients develops alcoholic hepatitis (AH), an acute inflammatory syndrome; its most severe form, severe alcoholic hepatitis (SAH), carries high short- and medium-term mortality.

5.2.2. What is the problem to solve?

SAH represents a clinical emergency for which therapeutic options remain critically limited. Corticosteroids, the only pharmacological treatment with an established, albeit mild survival benefit, are contraindicated in a substantial proportion of patients and are ineffective in a significant minority. No effective salvage therapy currently exists for patients who fail or cannot receive this treatment besides liver transplant.

5.2.3. What is the importance of the topic?

The gut-liver axis provides a mechanistically compelling and experimentally validated rationale for microbiota-based intervention. Preclinical and clinical models demonstrate promising results. Given the high unmet clinical need, a rigorous quantitative synthesis is needed to characterise any survival benefit and define patient selection criteria.

5.2.4. What would be the impact of our research results?

At the clinical level, this study would provide the most robust available estimate of the magnitude of any survival benefit associated with FMT. Identification of potential adverse events associated with FMT in the ALD population would help improve the risk-benefit calculation. At the mechanistic level, characterisation of post-FMT changes in gut microbiota composition could advance understanding of the mechanisms underlying therapeutic benefit and point toward targeted microbiome-based interventions. Furthermore, the findings of this study could support the design of future randomised controlled trials of FMT in ALD.

6. OBJECTIVES

6.1. Study I. – Chronic liver disease is an important risk factor for worse outcomes in acute pancreatitis: a systematic review and meta-analysis

The objective of the first study was to quantify the association between CLD and all-cause in-hospital mortality in patients with AP, as well as the associations with systemic and local complications and the possible pathophysiological drivers of this excess mortality.

6.2. Study II. – Faecal Microbiota Transplantation is Associated with Better Survival Compared to Standard of Care in Severe Alcoholic Hepatitis: A Systematic Review and Meta-analysis

The second study aimed to evaluate the effect of FMT on patients with ALD, with a primary focus on survival outcomes. Furthermore, we aimed to investigate the proposed causal chain following FMT application, specifically changes in microbiota composition, liver-related surrogate outcomes, as well as to identify potential safety signals associated with FMT in the ALD population.

7. METHODS

7.1. Study I.

7.1.1. Methodology and Protocol

The first project is a systematic review and meta-analysis. The study was conducted in accordance with the recommendations of the Cochrane Handbook (1) for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (2) guidelines. The study protocol was prospectively registered with PROSPERO, the international register of systematic reviews, under registration code CRD42022368905.

Studies were considered eligible for inclusion if they enrolled adult patients with a confirmed diagnosis of AP, in whom patients with concomitant CLD were explicitly compared against a control group without any documented history or clinical evidence of CLD. The primary outcome of interest was all-cause mortality, while secondary outcomes included AP severity, local and systemic complications, and length of hospital stay. For the purposes of this review, CLD was operationally defined as any liver disease of more than six months' duration, irrespective of the underlying etiology. Randomized controlled trials, prospective cohort studies, and retrospective cohort studies were all eligible for inclusion, whereas case reports and case series were excluded owing to the absence of a comparator group and their inherent susceptibility to selection and reporting bias.

7.1.2. Eligibility Criteria

Studies were considered eligible if they enrolled adult patients with a confirmed diagnosis of AP, with concomitant CLD, compared against controls without documented evidence of CLD. The primary outcome was all-cause mortality; secondary outcomes included AP severity, local and systemic complications, and length of hospital stay. CLD was defined as liver disease persisting for more than six months, regardless of etiology. Eligible study designs included randomized controlled trials, prospective cohort studies, and retrospective cohort studies, whereas case reports and case series were excluded due to the absence of a comparator group and their inherent susceptibility to selection and reporting bias.

7.1.3. Information Sources and Search Strategy

A systematic literature search was conducted on 10 October 2022 across three bibliographic databases, Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL), without language or date restrictions. To further enhance retrieval completeness, a supplementary backwards and forward citation search was performed on all included studies using the Citation Chaser tool (3). The following search string was applied: ("Acute pancreatitis" OR "biliary pancreatitis") AND (((("liver" OR "hepat*") AND (disease OR failure OR insufficiency OR fatty)) OR cirrhosis OR "sclerosing cholangitis" OR "biliary cholangitis" OR MAFLD OR NAFLD OR steatosis OR steatohepatitis OR NASH OR antitrypsin OR "Wilson disease" OR "hemochromatosis" OR "hepatitis")

7.1.4. Study Selection and Data Extraction

Screening and selection were conducted independently by two review authors following a structured, stepwise approach. Duplicate records were removed prior to screening using a combination of automated and manual deduplication in EndNote X20 (Clarivate Analytics, Philadelphia, PA, USA), followed by title and abstract screening in the Rayyan platform (4). Inter-rater agreement was formally quantified at each stage using Cohen's kappa coefficient; any disagreements were referred to a designated third independent reviewer for resolution. Data extraction from eligible studies was subsequently performed by the same two authors using a pre-specified, standardized Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA); both authors completed extraction independently, after which datasets were compared and discrepancies reconciled through consultation with a third independent reviewer. The following variables were extracted: first author, year of publication, study population size, geographical location, study period, diagnostic criteria for AP, type of CLD and its diagnostic criteria, mortality rate, AP severity, local complications including acute necrotic collections (ANC), acute peripancreatic fluid collections (APFC), pseudocysts (PC), and walled-off necrosis (WON) systemic complications including systemic inflammatory response syndrome (SIRS), infectious complications, sepsis, and respiratory, renal, and cardiac failure, as well as length of hospital stay.

7.1.5. Risk of Bias and Quality of Evidence Assessment

The methodological quality of each included study was independently assessed by two review authors using the Quality In Prognosis Studies (QUIPS) tool (5) for risk of bias evaluation. Any disagreements arising during the assessment were resolved by a designated third independent party. The results of the risk of bias assessment were subsequently visualized using the robvis (Risk-Of-Bias Visualization) tool (6). The overall certainty of evidence was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach, implemented via the GRADEpro Guideline Development Tool.

7.1.6. Data Synthesis and Analysis

Given the anticipated between-study heterogeneity, a random-effects model was applied throughout all analyses to pool effect sizes within a frequentist framework. For studies providing individual patient counts and event data (referred to as "raw data"), study-specific and pooled odds ratios (ORs) were calculated using the Mantel-Haenszel method, with the exact Mantel-Haenszel approach (without continuity correction) applied to handle zero cell counts, as recommended. In cases where only a reported OR and its 95% confidence interval (CI) were available without accompanying raw data (referred to as "direct OR"), the inverse variance weighting method was used for pooling, with zero cell counts handled by applying a continuity correction of 0.5. A Hartung-Knapp adjustment for CIs was applied, which yielded more conservative estimates than the classical approach. Heterogeneity variance (τ^2) was estimated using the Paule-Mandel method for raw data analyses and the restricted maximum-likelihood estimator with the Q-profile method for direct OR analyses. Between-study heterogeneity was further quantified using Higgins and Thompson's I^2 statistic. Where the number of low-risk studies exceeded five, prediction intervals were reported to convey the expected range of effects in future studies, with calculations based on the t-distribution. Results were considered statistically significant when the pooled 95% CI did not include the null value ($p < 0.05$). For subgroup analyses, a fixed-effects plural (mixed-effects) model was applied, allowing different τ^2 values across subgroups, with between-subgroup differences assessed using the omnibus Cochran's Q test at a 5% significance level; subgroup analyses by CLD stage were pre-specified prior to data extraction. Publication bias was evaluated through visual inspection of funnel plots and

by Egger's test or Harbord's test (for raw data), with a p-value below 0.10 considered indicative of potential small-study effects, acknowledging the limited diagnostic accuracy of these tests when fewer than ten studies were available. Potential outlying studies were identified using leave-one-out influence analyses, and subset analyses were conducted restricted to studies rated as low risk of bias. Additional sensitivity analyses were performed, incorporating adjusted odds ratios to explore potential confounding, using the same methodology as for the direct OR values. All statistical analyses were conducted in R (v4.3.3) (7) using the meta (v7.0.0) and dmetar (v7.0.0) (8) packages for meta-analytic calculations, visualizations, and influential analysis.

7.2. Study II.

7.2.1. Methodology and Protocol

The present systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (1) and reported in accordance with the PRISMA 2020 guidelines (2). The study protocol was prospectively registered with PROSPERO prior to data search under the registration code CRD42023467455, and all procedures were carried out in full adherence to the pre-registered protocol.

1.1.1. Eligibility Criteria

The eligibility criteria were defined using the PICO framework. Included studies were required to enroll (P) adult patients with a confirmed diagnosis of ALD across its full clinical spectrum, encompassing alcoholic fatty liver disease, alcoholic hepatitis (AH), SAH, and alcoholic cirrhosis. The intervention of interest was (I) FMT, evaluated in comparison to (C) SOC. Primary outcomes comprised overall survival, alcohol use recidivism, and the incidence of Adverse Events (AEs). Case reports and case series were excluded on the basis of their inherent methodological limitations.

1.1.1. Information Sources and Search Strategy

On September 27, 2023, a systematic search was performed across three bibliographic databases: Embase, MEDLINE, and CENTRAL, with no language, publication date, or other eligibility restrictions, to ensure maximal retrieval sensitivity. The search was updated on February 4, 2026, to identify any additional publications indexed following

the original search date. Additional backward and forward citation tracking was carried out on all included studies via the Citation Chaser tool(3) to further minimize the risk of missing eligible evidence. The search string was built around two core conceptual domains: the first covering the full clinical spectrum of alcohol-associated liver disease (ALD), and the second addressing the FMT procedure. The following search string was applied uniformly across all three databases: (((fecal OR faecal OR faeces OR stool) AND (microbiota OR microbiome OR bacteria OR microflora) AND (transplantation OR transplant OR transfer)) OR fmt OR (faecal microbiota transplantation)) AND (liver OR hepa* OR sah OR ald OR arld OR stea* OR alco* OR cirr* OR cirrhosis)

1.1.1. Study Selection and Data Extraction

Two review authors independently carried out all stages of screening and selection following a pre-defined stepwise procedure. Prior to screening, duplicate records were eliminated through a combination of automated and manual deduplication in EndNote (Clarivate Analytics, Philadelphia, PA, USA); the remaining records then underwent title and abstract evaluation on the Rayyan platform (4). Cohen's kappa coefficient was calculated at each selection stage to quantify inter-rater agreement, with discordant decisions referred to a third independent reviewer for adjudication. Data extraction from eligible studies was conducted in parallel by the same two authors, each working independently from a pre-specified Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA); completed extractions were subsequently cross-checked, and any unresolved discrepancies were settled through consultation. Data extracted from each eligible study comprised the following variables: first author and year of publication, country and study period, total sample size, patient demographics including age, applicable disease severity scoring systems, and criteria used for ALD diagnosis. With respect to the intervention, details on the route of FMT administration, treatment dosage, and duration were recorded, along with the definition of SOC used in each study. Outcome-related data included overall survival, duration of follow-up, recurrence of alcohol use, gut microbiota composition, and a comprehensive range of AEs, including infection rates, sepsis, organ failure, new-onset or worsening ascites, hepatic encephalopathy, and longitudinal changes in disease severity scores.

1.1.1. Risk of Bias and Quality of Evidence Assessment

Risk of bias was assessed independently by two investigators using the ROBINS-I tool (9) for non-randomised studies and the ROB 2 tool (10) for randomised controlled trials. Disagreements were resolved by a third independent reviewer, and results were visualized using the robvis tool (6). The overall certainty of evidence was subsequently evaluated using GRADEpro.

1.1.1. Data Synthesis and Analysis

Given the anticipated considerable between-study heterogeneity inherent to the clinical question, random-effects models were applied across all analyses within a frequentist framework, with a minimum of three studies required for any pooled analysis. In cases of overlapping study populations, the study with the larger sample size or longer follow-up period was retained.

For time-to-event data, hazard ratios (HRs) with 95% confidence intervals (CIs) were used as the primary effect measure, calculated as FMT versus SOC. Pooled HRs were derived using two complementary approaches: a classical random-effects meta-analysis based on study-level HRs (hereafter "classical method"), and an individual patient data (IPD)-based random-effects Cox proportional hazards model with Gaussian random effects (hereafter "IPD-based method"). As a secondary measure, survival probabilities at pre-specified time points were estimated and pooled using a three-level multilevel model to enable indirect comparisons between groups. Distribution-free pooled survival curves were additionally estimated using the method described by Pandey et. al (10) (hereafter "curve estimate"). A supplementary IPD-based analysis was performed to compare HRs in the FMT group separately against each of the three distinct control conditions: nutritional support (Nut), pentoxifylline (PTX), and corticosteroids (CS).

When studies did not report HRs but provided Kaplan-Meier curves, IPD estimates were derived from these plots using the WebPlotDigitizer tool (12), and the extracted data were cross-validated against published results wherever possible. Results were considered statistically significant when the pooled 95% CI did not include the null value. Findings were summarized in tables, forest plots, Kaplan-Meier plots, and estimated survival curves.

For the classical method, effect sizes were pooled using the inverse variance method with a Hartung-Knapp adjustment for CIs, applied only when it yielded more

conservative estimates than the standard approach. Heterogeneity variance (τ^2) was estimated using the restricted maximum likelihood method with the Q-profile method for CI calculation. Between-study heterogeneity was further quantified using Higgins and Thompson's I^2 statistic. For the three-level model, I^2 statistics were reported for each level, with 95% CIs, and "total I^2 " was defined as the sum of the two levels relative to the total sampling variance. For IPD-based analyses, variance of random effects was reported.

Survival probabilities (proportions) within each group were pooled using a multilevel meta-analysis with an additional independent random effect, applying a logit transformation to the calculated proportions and inverse-variance weighting with restricted maximum likelihood estimation. When calculated proportions equaled 0 or 1, a continuity correction of 0.5 was applied prior to exact binomial 95% CI calculation. Confidence and prediction intervals were derived using the t-distribution. Survival curve estimation followed the method described by Combescure et al., as implemented in the MetaSurvival package, with Greenwood's formula for variance estimation. To avoid overfitting, given study sample sizes of 20–100 per group, only five time points were used for curve estimation.

Subgroup differences were assessed using Cochran's omnibus Q test at a 5% significance level. Potential outlying studies were identified through leave-one-out influence analyses, including dfbetas, Cook's distances, and hat values. Publication bias was evaluated by visual inspection of funnel plots and Egger's test at a 10% significance threshold, with formal testing applied only when at least ten studies were available.

All analyses were performed in R using (7) the meta (v7.0.0) and dmetar (v0.1.0) (8) packages for classical meta-analysis, metafor (v4.4.0) (11) for the multilevel model, survival (v3.7.0), survminer (v0.4.9) (12), and coxme (v2.2.20) (13) for IPD-based analyses, and MetaSurvival (v0.1.0) for curve estimation. (10)

2. RESULTS

2.1. Study I: Chronic liver disease is an important risk factor for worse outcomes in acute pancreatitis: a systematic review and meta-analysis

2.1.1. Study Search and Selection

A total of 14,963 records were identified through the initial database search. Following duplicate removal and title and abstract screening, 123 publications proceeded to full-text eligibility assessment. Inter-rater agreement was substantial at both screening stages, with Cohen's kappa of 0.80 for title and abstract selection and 0.92 for full-text selection. Of the 123 full-text articles assessed, 30 met the eligibility criteria and were included. An additional six publications were identified through citation and website searches, yielding a final total of 36 included studies (14-49); one of these was obtained from our institution in preprint form. Full details of the search and selection process are illustrated in the PRISMA flowchart (Fig. 1).

Figure 1. PRISMA 2020 flowchart representing the study selection process for I. Project(2) (50).

Potential population overlap was identified among database-derived studies. To address this, a maximum of one database study was permitted per synthesis, and where multiple studies reported on the same outcome using overlapping populations, all were excluded

from that particular synthesis to eliminate the risk of selection bias. Within the SLD subgroup, seven studies specifically reported on non-alcoholic fatty liver disease (20, 29, 37, 42-45), one on metabolic-associated fatty liver disease (40), and the remainder did not specify the fatty liver disease subtype. On cirrhosis there have been 12 reports(16, 19-22, 31, 33, 34, 44-46, 48). AP diagnosis was established via International Classification of Diseases (ICD) codes in five publications, while the remaining studies applied at least two of the three criteria defined by the revised Atlanta classification. Baseline characteristics of each included study are provided in Table 1.

Table 1. Basic characteristics of the included studies in the I. systematic review and meta-analysis (50).

Authors	Year	Design	Country (study period)	Population (n)	Age (years) Mean (SD) ^A	Female (%)	AP definition	CLD type	CLD diagnosis	Outcomes
Xu et al.	2015	Ret.	China (2000-2014)	2671	50.96 (17.35)	40.5	2/3	ALFD/NAFLD	CT Liver/spleen ratio + alcohol intake	Severity, systemic/local complications, ANC, Infection, SIRS, Renal, Cardiac, Respiratory failure, CRP, APACHE-II
Liu et al.	2022	Ret.	USA (2001-2021)	631	60.38 (47.08-72.54)	44.9	2/3	Cirrhosis	N/A	Mortality
Liu et al.	2022	Ret.	China (2016-2021)	186	53.06 (15.33)	35	2/3	Fatty liver	CT, US, MRI	Severity, ANC, SIRS, APACHE, LOS, CRP
Brivet et al.	1999	Pros.	France (1991-1993)	50	53.8 (12)	33	2/3	Cirrhosis	N/A	Mortality
Ding et al. ^B	2018	Ret.	China (2014-2016)	142	55.87 (15.47)	47.8	2/3	Fatty liver	N/A	IPN
Frey et al.	2007	Ret.	USA (1992-2001)	84,713	54.5 (N/A)	53.9	ICD	CLD	ICD	MODS

Gupta et al.	2021	Ret.	India (2017-2019)	103	39.53 (12.73)	22.1	2/3	Fatty liver	CT	Mortality, Organ failure, MODS
Jang et al.	2021	Ret.	South Korea (2011-2020)	242	47 (12.6)	11.2	2/3 presumed AAP	Fatty liver Cirrhosis	CT Liver/spleen lab clinical finding	Severity, Renal, Cardiac, Respiratory failure
Mikolasevic et al.	2016	Ret.	Croatia (2011-2015)	822	63.9 (17)	51.1	2/3	NAFLD	CT	Mortality, Severity, AFC, ANC, PC, Organ failure, MODS, LOS, CRP, APACHE-II
Park et al.	2019	Ret.	South Korea (2008-2017)	672	N/A	N/A	2/3	Cirrhosis	N/A	Severity
Roussey et al.^B	2022	Ret.	France (2014-2020)	467	57 (19)	36	2/3	Fatty Liver	CT	LOS
Wu et al.	2019	Ret.	China (2014-2016)	656	43.93 (9.81)	37	2/3	NAFLD	CT	Severity, Organ failure, SIRS
Yoon et al.	2017	Ret.	South Korea (2009-2016)	200	54.3 (17.5)	40.5	2/3	Fatty Liver	CT Liver/spleen	Mortality, Severity, ANC, WON, AFC, PC, Organ failure, CRP
Zhang et al.	2021	Ret.	China (2013-2020)	234	52.35 (17.64)	44	2/3	Fatty liver	N/A	Mortality
Xiao et al.	2012	Ret.	China (2009-2011)	50	44 (12)	13.1	2/3	Fatty liver	MR	Severity
Jasdanwala et al.	2015	Ret.	USA (N/A)	574	N/A	65.5	2/3	NAFLD	CT, US	Mortality, Severity, LOS

Simons-Linares, Marrero et al.	2020	Ret.	USA (2003-2013)	2,860,464	52.83 (N/A)	N/A	ICD	Cirrhosis	ICD	Mortality, Sepsis, Renal failure, SIRS
Simons-Linares, Suha et al.	2020	Ret.	USA (2007-2017)	120	59.9 (N/A)	50	2/3	Cirrhosis	Biopsy, elastography, or imaging	Mortality, Severity, ANC, AFC, PC, Systemic complication, SIRS, Renal, Cardiac, Respiratory failure
Vogel et al.	2022	Ret.	Germany (2011-2020)	156	N/A	28.2	2/3	Cirrhosis	Fibroscan, Clinical lab, imaging	ANC, AFC, PC, Organ Failure
Jing et al.	2018	Ret.	China (2016-2017)	128	52.7 (14.9)	40.6	2/3	Fatty liver	CT Liver/spleen	Severity, ANC, AFC, Organ Failure
Morel-Cerda et al.	2019	Ret.	Spain (2017-2018)	186	41 (17.7)	63	2/3	Fatty liver	USG	Severity, Organ Failure, SIRS
Dou et al.	2017	Ret.	China (2013-2016)	251	45.37 (15.46)	N/A	2/3	NAFLD	USG	Severity, LOS
Yan et al.	2020	Ret.	China (2019-2019)	398	48 (N/A)	39.3	2/3	NAFLD	USG, CT	Severity, ANC, WON, AFC, PC, Organ Failure, MODS, SIRS, LOS, CRP
Váncsa et al.	Preprint	Pros.	Hungary (2013-2019)	2053	57 (17)	43.9	2/3	MAFLD	imaging+obesity/DM2/metabolic	Mortality, ANC, AFC, PC, Local, Systematic complication, Renal, Respiratory, Cardiac Failure
Ze-Hua et al.	2012	Ret.	China (2010-2011)	606	50 (16)	43.7	2/3	Fatty liver	CT Liver/spleen	Mortality
Simons-Linares CR et al. al^{B,C}	2019	Ret.	USA (2010-2015)	1,575,148	52.48 (17.22)	N/A	ICD	Cirrhosis	ICD9	Mortality, Infections, Sepsis, Renal Failure

Jimenez et al. ^c	2021	Pros.	Spain (2017-2017)	208	65.4 (N/A)	51	2/3	Cirrhosis	N/A	Severity, Local complication
Mahfouz et al. ^{B,C}	2022	Ret.	USA (2016-2019)	74,095	N/A	N/A	ICD	Cirrhosis	ICD10	Mortality, LOS
Lupulescu et al. ^c	2019	Ret.	Romania	150	55.9 (16.4)	42	N/A	Fatty liver	USG	Severity
Evans et al. ^c	2019	Ret.	USA (2016-2018)	844	49 (N/A)	N/A	2/3	Cirrhosis	N/A	Mortality, LOS
Simons-Linares, Chittajallu et al. ^{B,C}	2019	Ret.	USA (2009-2019)	409	N/A	N/A	N/A	Cirrhosis	N/A	IPN
Wang et al. ^c	2013	Ret.	China (2010-2011)	120	N/A	N/A	N/A	Fatty liver	N/A	Severity, Organ failure, Systematic complication, SIRS, Respiratory failure
Hao et al. ^c	2015	Ret.	China (2011-2013)	148	N/A	N/A	N/A	Fatty liver	N/A	Severity, Systemic complications, LOS
Shah et al. ^c	2020	Ret.	USA (2010-2014)	2,147,200	51.36 (N/A)	N/A	ICD	NAFLD	ICD	Mortality, PC, Infections, SIRS, Respiratory failure, LOS
Make et al. ^c	2022	N/A	India (Ongoing)	58	N/A	N/A	N/A	Fatty liver	CT Liver/spleen	Mortality, Severity, Local complication, Organ failure

Satapathy et al. c	2010	Ret.	USA (2002-2009)	108	53 (N/A)	48	N/A	Fatty liver	CT Liver/spleen	ANC, AFC, LOS
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AAP, alcohol-induced acute pancreatitis; AFC, acute peripancreatic fluid collections; AFLD, Alcoholic fatty liver disease; ANC, Acute necrotic collections; CLD, chronic liver disease; CRP, C-reactive protein; CT, computed tomography; CT Liver/spleen, ratio of density of liver to spleen; ICD, The International Classification of Diseases; IPN, Infectious pancreatic necrosis; LOS, Length of hospital stay; MAFLD, Metabolic associated fatty liver disease; MRI, Magnetic resonance imaging; NA, not available; NAFLD, Non-alcoholic fatty liver disease; MODS, Multiple Organ Dysfunction Syndrome; PC, Pancreatic pseudocysts; Pros.: Prospective; Ret.: Retrospective; SD, standard deviation; SIRS, Systemic Inflammatory Response Syndrome; US, Ultrasonography; WON, Walled-off necrosis.

A Parameters represented as mean with standard deviation, or median with range (minimum and maximum). B Study included only in systematic review. C Conference abstract.

2.1.2. In-Hospital Mortality and severity in AP with concomitant CLD

Mortality data were available from 13 publications (14, 15, 17, 20, 22, 26, 32, 35, 38, 41, 42, 44, 48). Concomitant CLD in patients with AP significantly increased the odds of in-hospital mortality (OR 2.53, 95% CI 1.30–4.93; $I^2 = 63\%$; $p = 0.01$), although this represented low-certainty evidence per GRADEpro assessment. In subgroup analysis, the pooled OR for in-hospital mortality was 2.01 (95% CI 0.87–4.64; $I^2 = 66\%$; $p = 0.09$) in patients with steatotic liver disease and 4.46 (95% CI 0.86–23.17; $I^2 = 43\%$; $p = 0.06$) in the cirrhotic subgroup (Fig. 2).

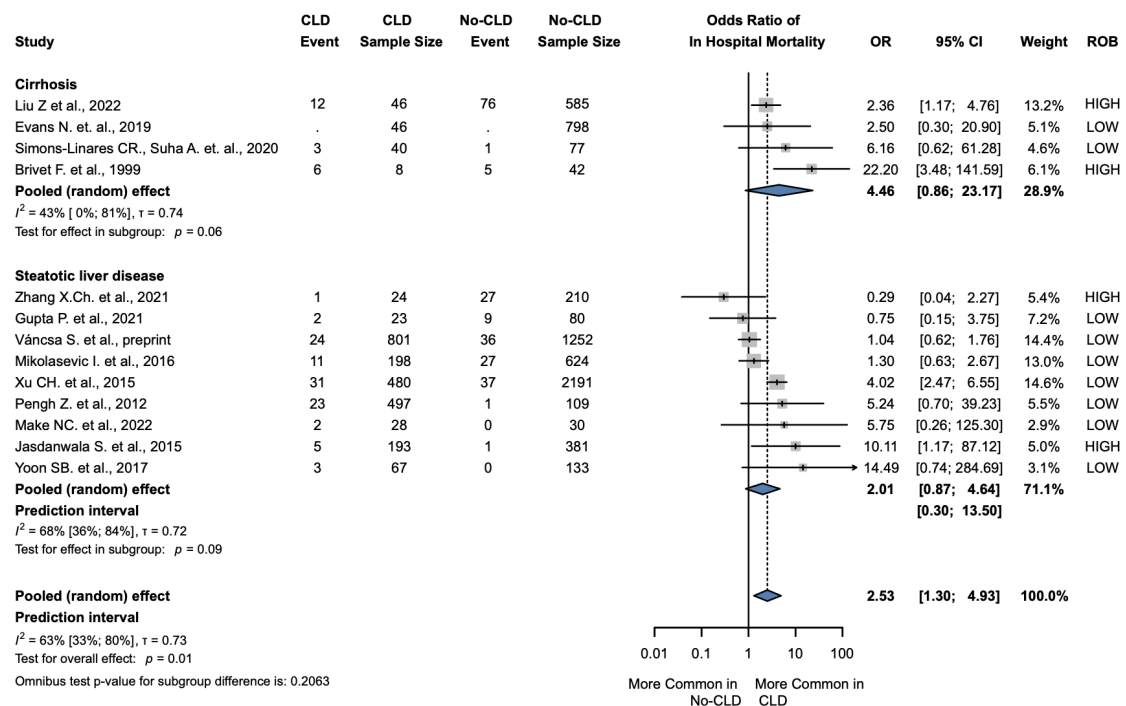


Figure 2. Forest plot of Odds for In-Hospital Mortality in patients with and without CLD

OR, odds ratio; ROB, risk of bias; CI, confidence interval; CIL, lower limit of confidence interval; CIU, upper limit of confidence interval; CLD, chronic liver disease (50).

Beyond mortality, the presence of CLD was associated with a significantly more severe clinical course. The odds of severe AP were notably elevated (OR 2.29, 95% CI 1.89–2.76, $I^2=0\%$, $p<0.01$), as were the odds of moderately severe AP (OR 2.07, 95% CI 1.44–2.96, $I^2=69\%$, $p=0.002$); see (Fig. 3) (50).

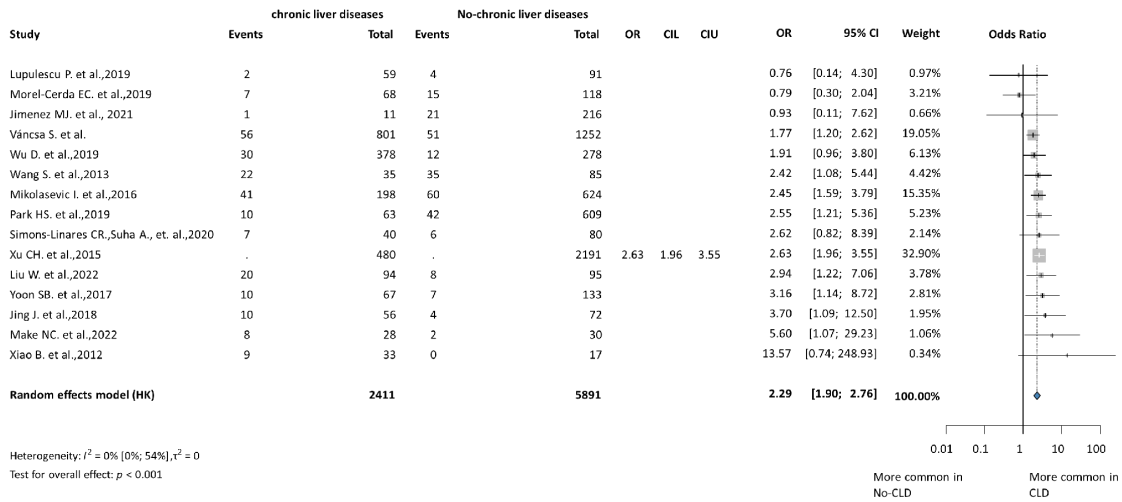


Figure 3. Forest plot of the pooled odds ratio of severe acute pancreatitis complications in patients with AP with and without CLD

OR: odds ratio; CI: confidence interval; CIL: lower limit of confidence interval; CIU: upper limit of confidence interval; CLD: chronic liver diseases (50).

2.1.3. Systemic and Local complications in AP with concomitant CLD

Regarding systemic complications, based on nine studies (15, 18, 26, 31, 32, 41, 43, 47, 49) encompassing 2,550 subjects, CLD was associated with a 2.59-fold increase in the odds of single organ failure (OR 2.59, 95% CI 1.69–3.97, $I^2=43\%$, $p<0.01$).

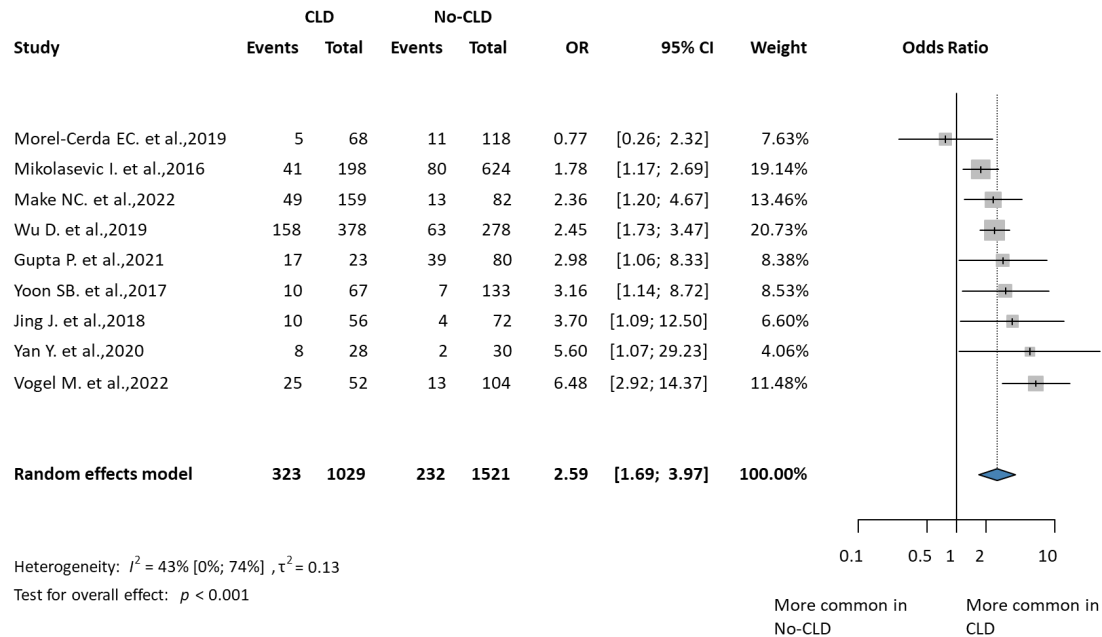


Figure 4. Forest plot of the pooled odds ratio for organ failure complication in patients with AP with and without CLD

OR: odds ratio; CI: confidence interval; CLD: chronic liver diseases (50)

The odds of multiple organ dysfunction syndrome, reported across four studies (18, 23, 26, 41), were likewise elevated, albeit more modestly (OR 1.37, 95% CI 1.07–1.75, $I^2=0\%$, $p=0.028$), rated as very low certainty of evidence. CLD was further associated with higher odds of renal failure (OR 1.92, 95% CI 1.30–2.83, $I^2=75\%$, $p=0.01$), cardiac failure (OR 2.11, 95% CI 0.93–4.77, $I^2=42\%$, $p=0.062$), and respiratory failure (OR 1.99, 95% CI 1.08–3.65, $I^2=97\%$, $p=0.033$) (Fig. 5).

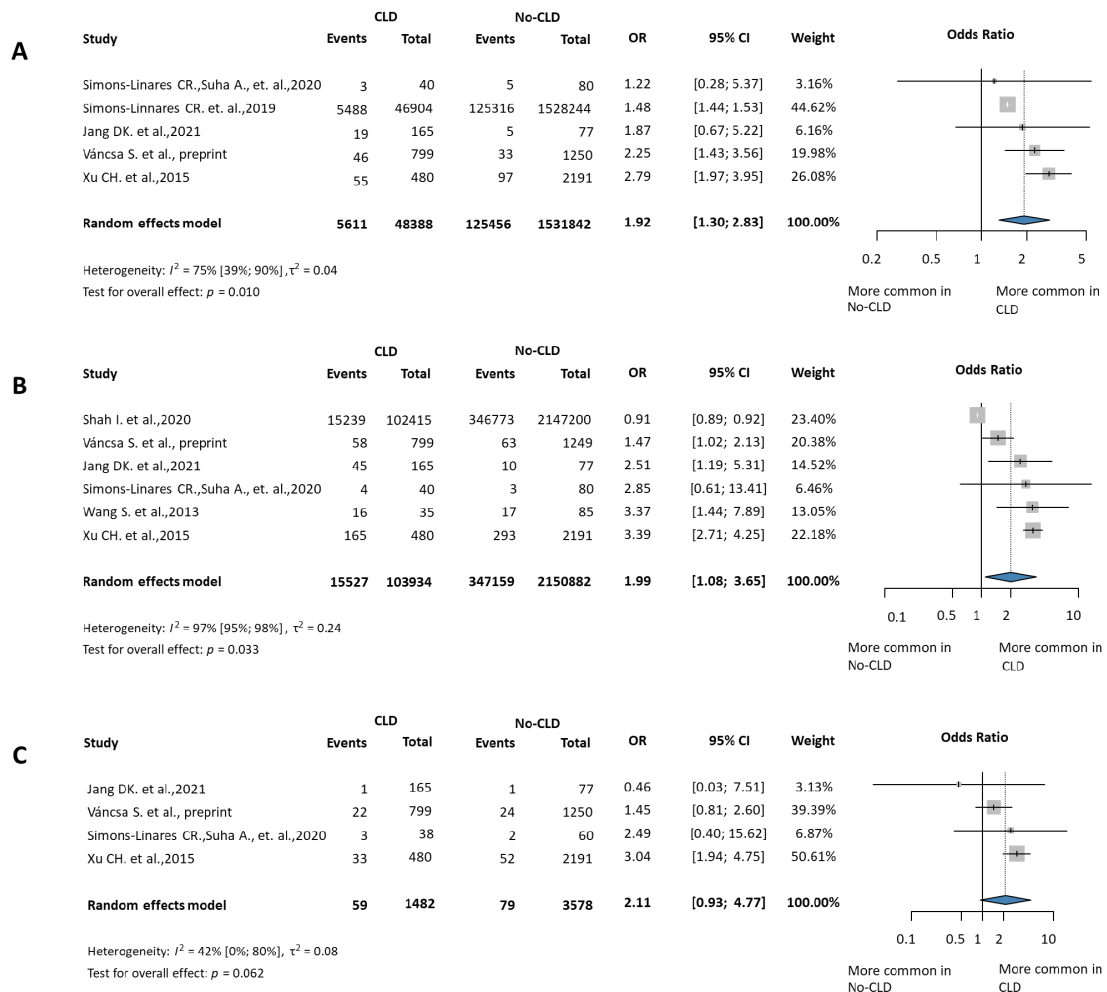


Figure 5. Forest plot of the odds ratio for organ failure by organ type complication in patients with AP with and without CLD

A: OR for renal failure; B: OR for respiratory failure; C: OR for cardiac failure. OR: odds ratio; CI: confidence interval; CLD: chronic liver disease (50).

The odds of systemic inflammatory response syndrome reported in seven studies (18, 20, 29, 35, 43, 44, 47), were similarly increased (OR 1.95, 95% CI 1.03–3.68, $I^2=66\%$, $p=0.042$) (Fig. 6). (51)

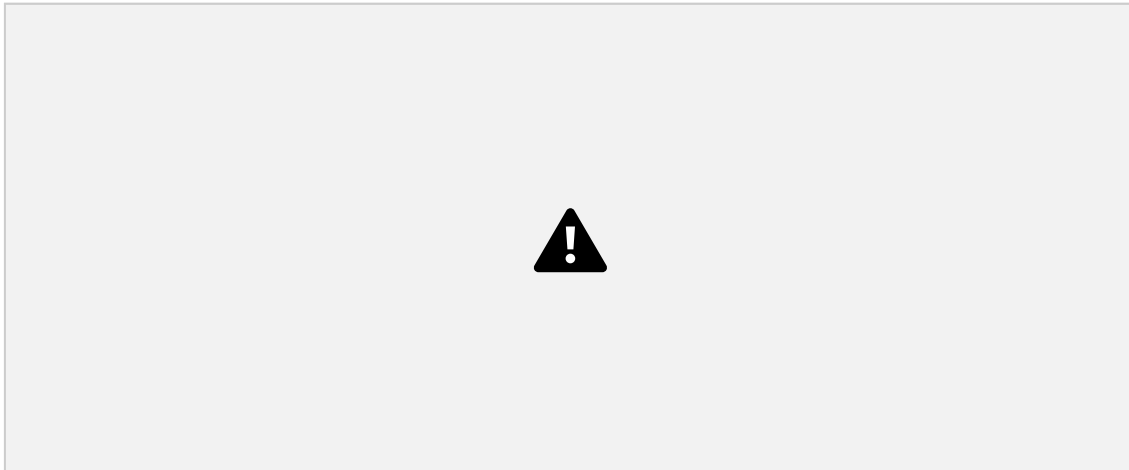


Figure 6: Forest plot of the pooled odds ratio of Systemic Inflammatory Response Syndrome in acute pancreatitis with and without concomitant chronic liver disease.

OR: odds ratio; CI: confidence interval; CLD: chronic liver diseases (50)

With respect to local complications, CLD was associated with significantly higher odds across all evaluated outcomes. Based on nine publications encompassing 4,788 subjects, the odds of acute necrotic collections (ANC) were 2.53-fold higher in patients with CLD (95% CI 1.86–3.45, $I^2=40\%$, $p=0.001$), rated as moderate certainty of evidence. Acute peripancreatic fluid collections (APFC), reported in seven publications ($n=3,815$), yielded a pooled OR of 2.39 (95% CI 1.62–3.52, $I^2=74\%$, $p=0.002$). The odds of pancreatic pseudocysts (PC), reported across eight publications, were also elevated (OR 1.53, 95% CI 1.03–2.27, $I^2=38\%$, $p=0.039$) (Fig. 7). Walled-off necrosis (WON) could not be pooled, as only two eligible studies were identified.

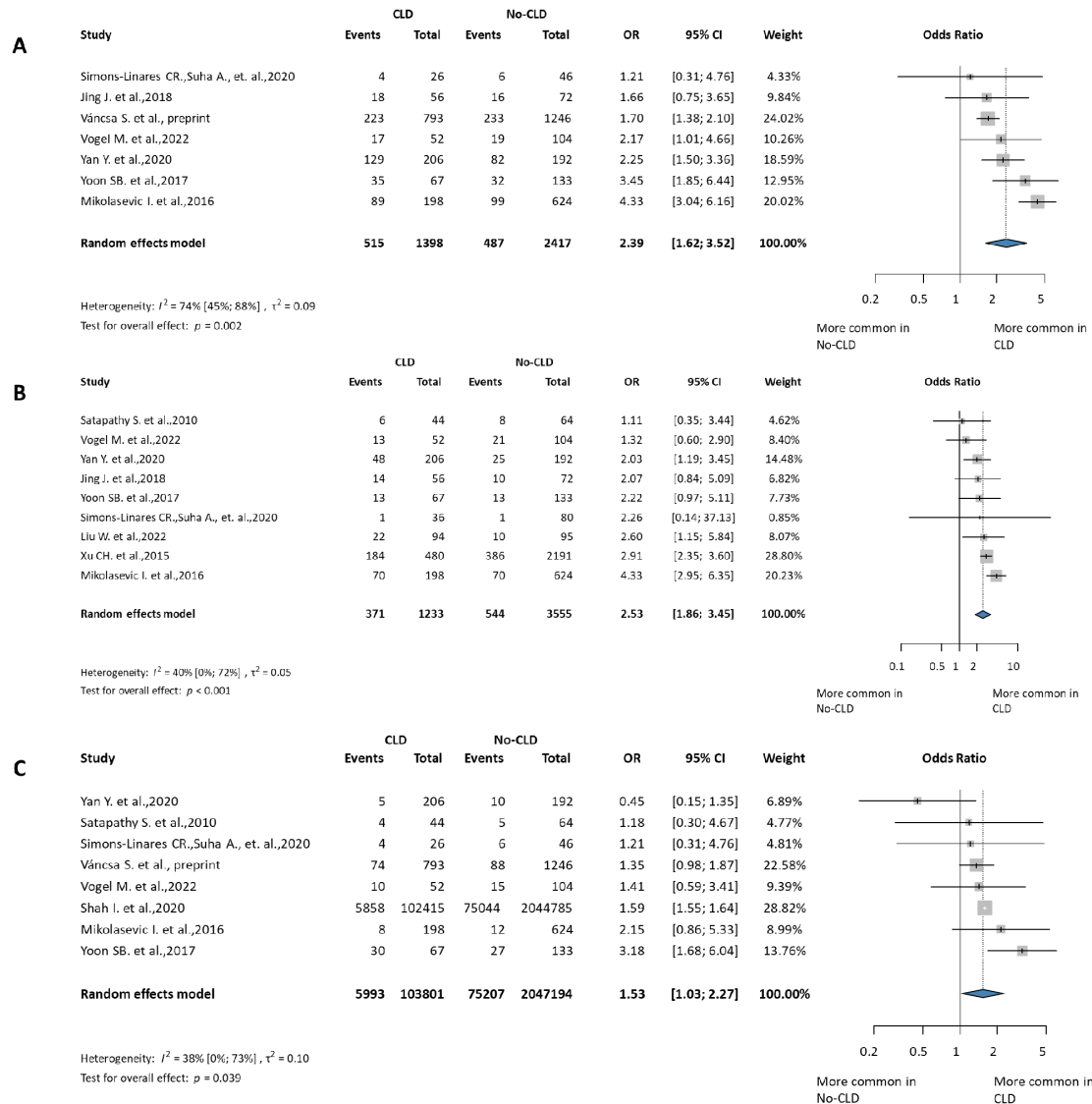


Figure 7. Forest plot of the pooled odds ratio of local complication in patients with AP with and without CLD

A: OR for acute peripancreatic fluid collections; B: OR for acute necrotic collection; C: OR for pancreatic pseudocysts. OR: odds ratio; CI: confidence interval; CLD: chronic liver diseases (50).

2.1.4. Risk of Bias Assessment and Publication bias

Half of the publications had a low ROB, 31% had a moderate ROB, and 20% had a high ROB. This is the result of the high number of conference abstracts and poor diagnostic criteria for CLD in some studies. For an overview of ROB, see (Fig. 8). The lowest risk of bias was consistently observed in patient participation and attrition. Conversely, the highest risk was clustered in prognostic outcome measurement and in confounding,

which was primarily driven by a widespread lack of adjusted statistical models in the primary literature. A subsequent sensitivity analysis restricting the meta-analysis exclusively to studies with a low ROB reduced statistical heterogeneity for systemic complications but did not alter the global effect size, confirming the robustness of the overall clinical findings.

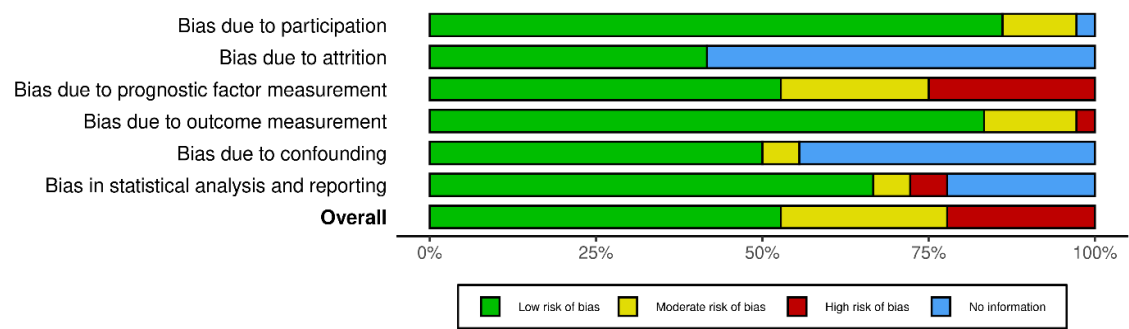


Figure 8. Robvis (6) summary plot of the risk of bias for I. study (50).

Funnel plot inspection and statistical testing did not reveal evidence of small-study publication bias across the analyzed outcomes (Fig. 9); however, the interpretation of these findings should be approached with caution, as several outcomes were informed by fewer than ten studies, which limits the diagnostic accuracy of available publication bias tests.

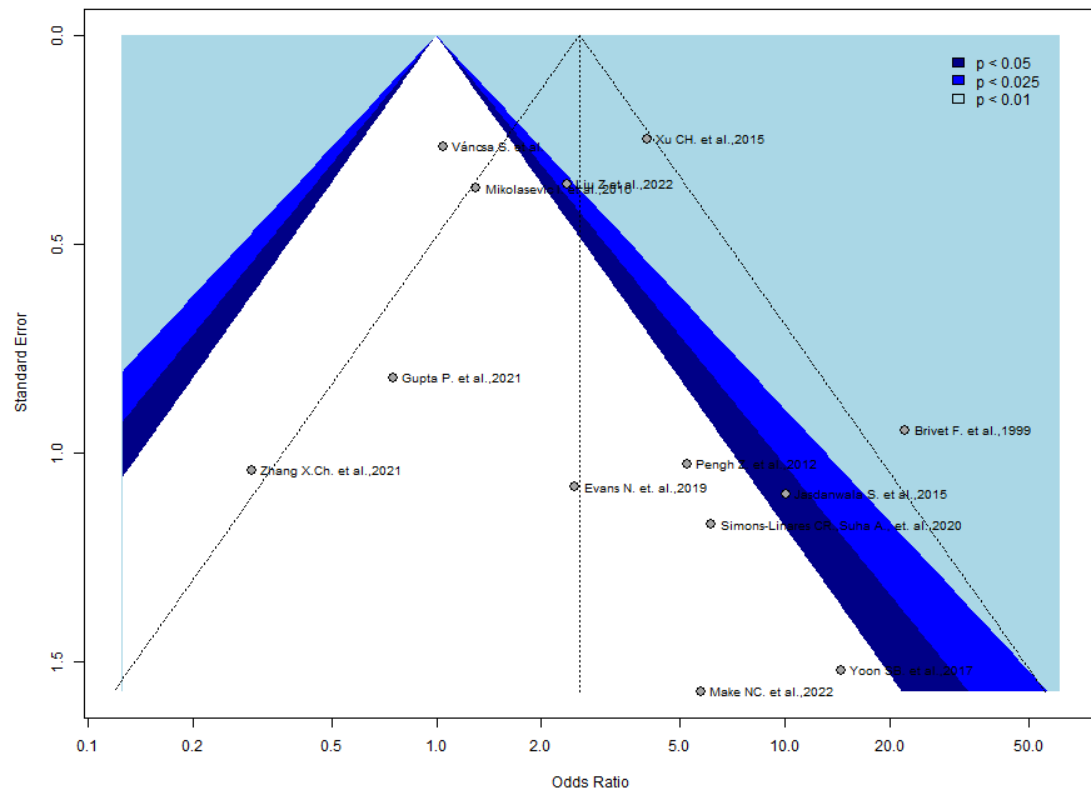


Figure 9. Funnel plot for primary outcome: in-hospital mortality in patients with and without chronic liver diseases (50).

2.1.5. Quality of Evidence

In-hospital mortality was significantly higher in patients with CLD, though this finding was rated as low certainty owing to serious inconsistency. Acute necrotic collections demonstrated a robust association with CLD, with rates of 30.1% versus 15.3% in patients without CLD, corresponding to an absolute effect of 161 additional cases per 1,000 patients, supported by moderate certainty of evidence. Severe acute pancreatitis showed a similarly elevated risk, supported by moderate certainty of evidence. Organ failure was significantly more frequent in patients with CLD, translating to an absolute risk increase of 17 additional cases per 100 patients, albeit rated as low certainty due to serious risk of bias. SIRS occurred more frequently in the presence of CLD, though this estimate carried very low certainty due to serious inconsistency and imprecision.

2.2. Study II: Faecal Microbiota transplantation is associated with better survival compared to standard of care in severe alcoholic hepatitis not responding to corticosteroids: A systematic review and meta-analysis

2.2.1. Study Search and Selection

The initial database search identified 6,512 records. Following duplicate removal, 4,852 records remained for title and abstract screening, of which 97 proceeded to full-text eligibility assessment (Cohen's kappa = 0.89). Ten studies (52-61) ultimately met the eligibility criteria and were included for data extraction (Cohen's kappa = 0.91). Citation searching of the reference lists of all included studies did not yield any additional eligible records. The updated search retrieved 3,535 new records, of which one additional study, previously published as a conference abstract, was identified and included (62). The updated PRISMA flowchart is presented in Fig. 10.

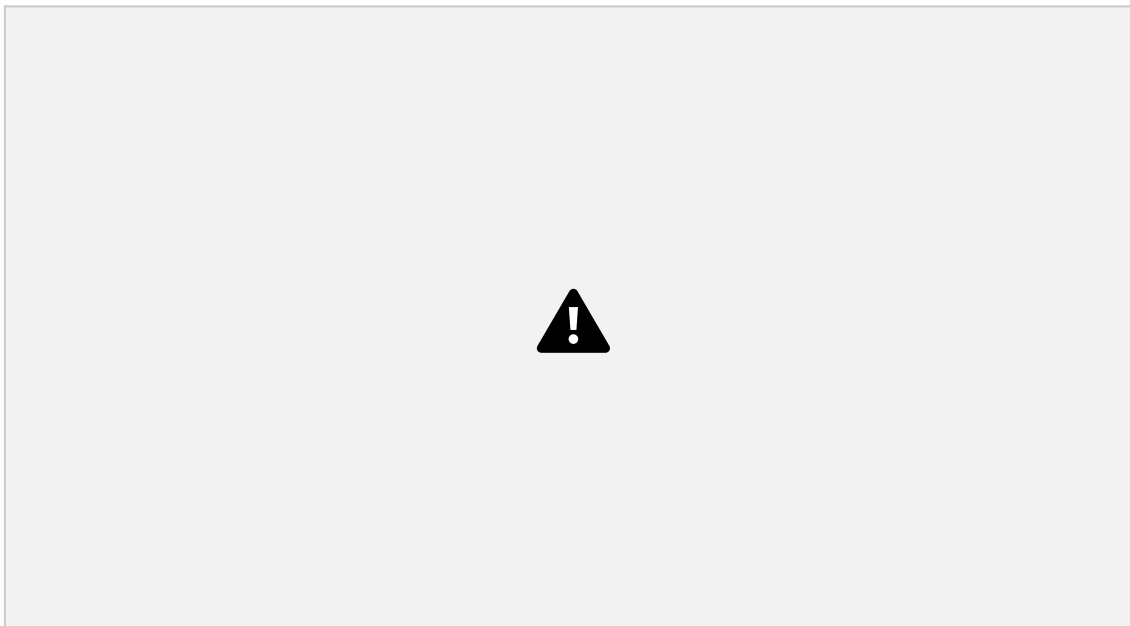


Figure 10. PRISMA 2020 flowchart representing the study selection process for II. study (2) (51).

Across the included studies, 494 patients were identified, of whom 339 met the criteria for quantitative synthesis. Nine of the eleven included studies enrolled patients with SAH(53-61), one focused on cirrhosis(52), and one examined SAH with concomitant acute-on-chronic liver failure(61); none addressed FMT in the setting of alcohol-related steatosis. Eight studies were conducted in India, one in the United States, and one in

Slovakia. Regarding the route of FMT administration, nasoduodenal delivery was employed in five studies, nasojunal tube in one, and enema in another. Reported doses ranged from 27–30 g or 100 ml administered once daily, with treatment durations of seven days in five studies and six days in one. Notably, a single-dose protocol described by Sharma et al.(61) yielded effect sizes comparable to the multi-dose regimens used in other studies. Considerable clinical heterogeneity was observed in the definition and composition of standard of care (SOC) across SAH studies. FMT donors were either unrelated healthy volunteers or healthy family members. Baseline characteristics of each included study are summarized in Table

Table 2. Basic characteristics of the included studies in the II study (51).

Author (year)	Study site	Design	No of patients (male %)	Age (year and SD) $\pm$		Liver Disease (Diagnostic Criteria)	MELD at baseline in FMT VS SOC (MD,95CI)	SOC (Donors)	FMT Administration Dosage	Length of FMT(days) ATB use	Reported outcomes
				FMT	SOC						
Sharma et al. (2022)	India	Pros	33 (100%)	39,6 (34,45-44,78) $\dagger$	40,7 (37,63-43,77) $\dagger$	SAH/ACLF (NIAAA)	-0.32 (-2.3; 1.7)	Nut (FM)	NSJ 30 g	Single dosage YES	Survival LFTs,AEs LFTs,
Pande et al. (2023)	India	RCT	121 (97,5%)	43,15 (8,73)	40,8 (7,91)	SAH (NIAAA)	0.28 (-0.6; 1.2)	Pred (HV*)	NSD 30 g	7 Per need	Survival, RAU, LFTs,AEs LFTs, Microbiota
Philips et al. (2018)	India	Retro	51 (100%)	47,6 (8,2)	47,9 (9,76)	SAH (NA)	NA	Pred, PTX, Nut (FM)	NSD 100 ml	7 Per need	Survival, LFTs, Microbiota
Philips et al. (2022a)	India	Retro	72 (100%)	45,2 (10,2)	47,7 (9,9)	SAH (histology)	-0.10 (2.7; 2.5)	PTX,ATB (FM)	NSD 100 ml	7 YES	Survival, RAU, AEs, Microbiota
Philips et al. (2022b)	India	Retro	61 (NA)	46,6 (10,1)	50,7 (11,5)	SAH (histology)	0.7 (-11.3; 12.7)	Pred (HV)	NSD 30 g	7 NA	Survival RAU AEs, Microbiota
Philips et al. (2023)	India	Retro	30 (100%)	53,3 (4,1)	51,8 (6,4)	SAH (NIAAA)	NA	Pred (HV)	NSD 100 ml	7 Per need	RAU
Philips et al (2017)	India	Retro	36 (NA)	NA	NA	SAH (NIAAA)	4.0 (-0.5; 8.5)	NA (FM)	NSD 30 g	7 NA	Survival, LFTs, Microbiota
Kumar et al. (2022) $\ddagger$	India	RCT	20 (NA)	NA	NA	SAH (NA)	NA	NA (NA)	NA NA	NA NA	Survival
Bystrianska et. al. (2022)	Slovakia	Pros	50 (NA)	NA	NA	SAH (NA)	NA	Nut (HV)	NA 100 ml	6 NA	Survival
Bajaj et al. (2020)	USA	RCT	20 (100%)	64,5 (5,1)	62,9 (9,8)	Cirrhosis (*)	-1.2 (-4.1; 1.7)	Placebo (HV)	Enema 27g/100ml	Single dosage NA	RAU

$\dagger$ parameters represented as mean with upper and lower confidence intervals, $\ddagger$ study included only in systematic review, * healthy volunteers living in the same household

ACLF: Acute-on-Chronic Liver Failure, AEs: Adverse Events, ATB: antibiotics, FMT: Faecal Microbiota Transplantation, FM: family members, HV: healthy volunteers, LFTs: Liver Function Tests, MD: Mean difference MELD: Model for End-Stage Liver Disease, SD:

standard deviation, NIAAA: National Institute on Alcohol Abuse and Alcoholism, NSD: Nasoduodenal tube, NSJ: nasojejunal tube Nut: Nutritional support, Pred: Prednisone Pro: Prospective study design, PTX: Pentoxifylline, RAU: Recurrence of alcohol use RCT: Randomized Controlled Trial Retro: Retrospective study design, SAH: Severe Alcoholic Hepatitis ,SOC: Standard of Care

1.1.1. Faecal microbiota transplantation was associated with a survival benefit in severe alcoholic hepatitis

A pooled analysis of six studies (53, 55, 57, 59-61) comprising 339 patients demonstrated significantly better overall survival with FMT compared with SOC. The classical random-effects model yielded an HR of 0.51 (95% CI 0.35–0.74), while the IPD-based random-effects Cox model produced a closely concordant estimate of HR 0.50 (95% CI 0.35–0.72, $p=0.0002$), both consistently favouring FMT (Fig. 11).

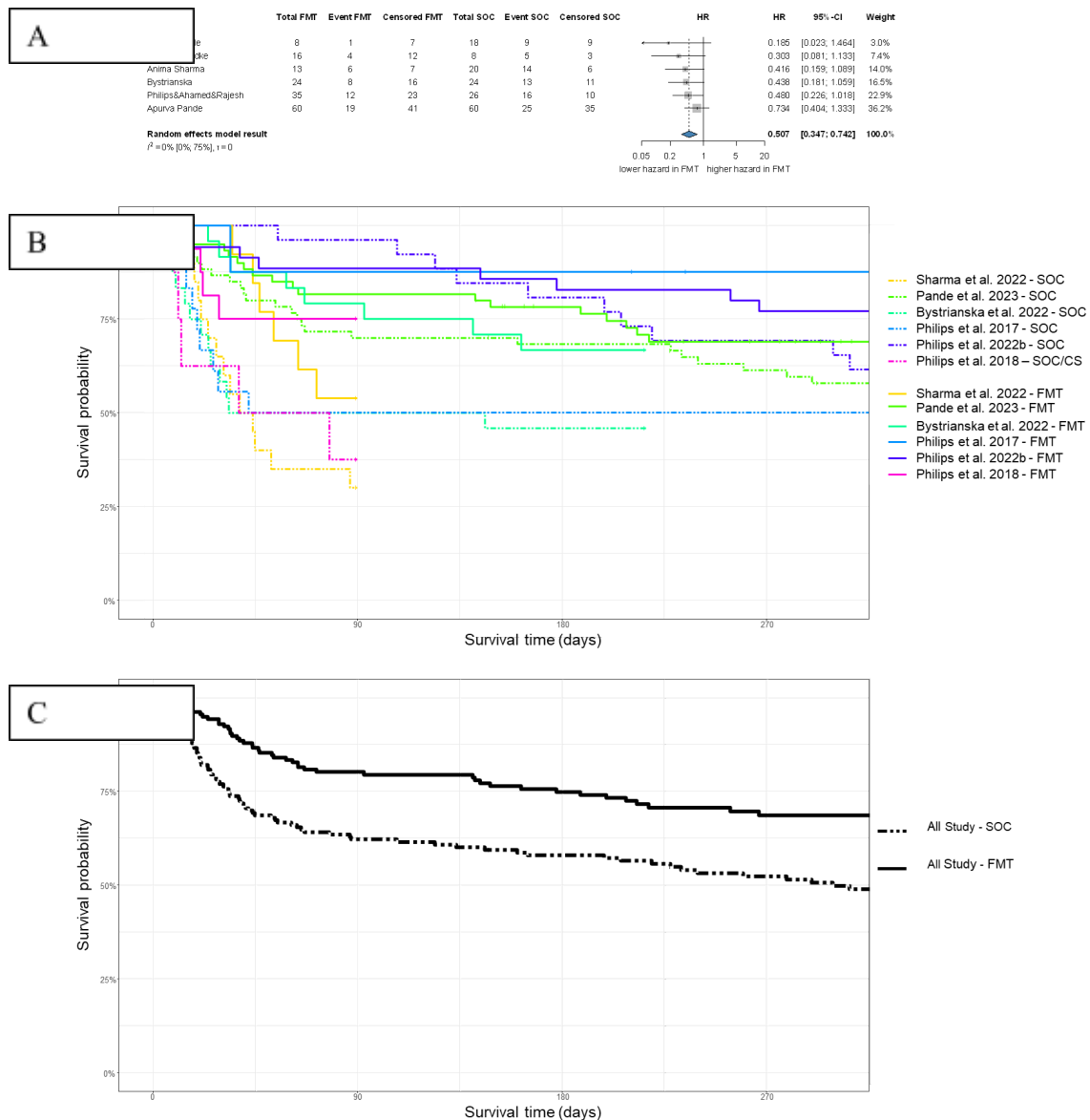


Figure 11. Survival analysis based on IPD. A. Forest plot representing pooled hazard ratio for survival comparing SOC vs FMT in SAH; B. Kaplan-Meier curve showing IPD survival data in SOC vs FMT; C. Pooled Kaplan-Meier curve for all studies.

IPD: Individual Patient Data; SAH: severe alcoholic hepatitis; SOC: Standard of Care; FMT: Faecal Microbiota Transplantation; HR: Hazard Ratio; CI: Confidence Interval (51).

In the study by Philips et al. (2018) (60), which employed multiple SOC comparator arms (pentoxifylline, nutritional support, and glucocorticoids), only the glucocorticoids arm was included in the primary pooled analysis to avoid population overlap with the

FMT arm. Additionally, as IPD estimates from Philips et al. (2022a) were nearly identical to those from Philips et al. (2022b) (57, 58), only the larger study was retained to prevent potential population overlap. IPD-based pairwise comparisons of FMT against each individual SOC arm demonstrated consistently favorable trends. HRs were 0.65 (95% CI 0.33–1.28, $p=0.364$) versus glucocorticoids, 0.45 (95% CI 0.21–0.96, $p=0.035$) versus pentoxifylline, and 0.36 (95% CI 0.19–0.66, $p=0.0001$) versus nutritional support, respectively (Table 3).

Table 3. Pairwise Comparisons of HRs for All Treatment Arms with Tukey Multiplicity Corrected p-values and CI (Calculated on Log-Scale)

	FMT	CS	PTX	NUT
FMT	-	1.54 (95CI 0.78 - 3.03) p 0.36	2.22 (95CI 1.04 – 4.76) p 0.03	2.78 (95CI 1.52 -5.26) $p<0.01$
CS	0.65 (95CI 0.33 - 1.28) p 0.36	-	1.43 (95CI 0.55 -3.70) p 0.77	1.82 (95CI 0.79 – 4.17) p 0.25
PTX	0.45 (95CI 0.21 - 0.96) p 0.03	0.70 (95CI 0.27 - 1.82) p 0.77	-	1.28 (95CI 0.54 - 3.03) p 0.89
NUT	0.36 (95CI 0.19 - 0.66) $p<0.01$	0.55 (95CI 0.24 - 1.27) p 0.25	0.78 (95CI 0.33 -1.85) p 0.89	-

95CI: 95% Confidence Interval, CS: Glucocorticoids, FMT: Fecal Microbiota Transplantation, HR: Hazard Ratio, NUT: Nutritional Support Only, PTX: Pentoxifylline (51).

Survival probabilities were consistently higher in the FMT group at all evaluated time points. In the SOC group, the survival probability was 79% (95% CI, 51–93%) at 28 days, 64% (95% CI, 33–86%) at 90 days, and 62% (95% CI, 24–89%) at 180 days. In contrast, the FMT group demonstrated survival probabilities of 95% (95% CI, 85–99%) at 28 days, 80% (95% CI, 47–95%) at 90 days, and 80% (95% CI, 42–95%) at 180 days. LOO sensitivity analysis identified the study by Pande et al. (55) as influential, with an effect size of 0.41 (95% CI 0.26–0.65); however, the overlapping confidence intervals across all LOO estimates confirm that the overall meta-analytic conclusion is robust and not driven by any single study.(Fig.12)

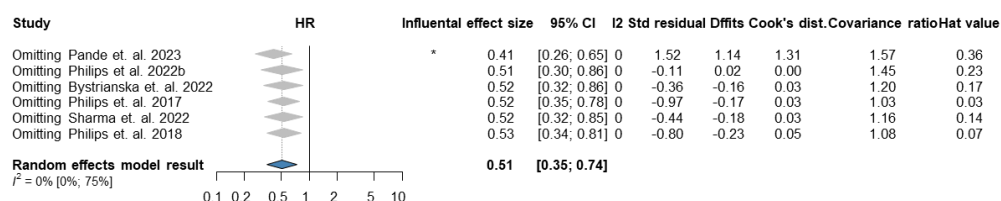


Figure 12. Leave-one-out sensitivity analysis of overall survival for FMT vs SOC in severe alcoholic hepatitis.

SOC: Standard of Care; FMT: Faecal Microbiota Transplantation, HR: Hazard ratio (51).

1.1.2. Post-FMT microbiota changes

Six studies (55-60) included microbiota analyses, all employing 16S rRNA sequencing targeting the V3–V4 hypervariable region. Three studies reported baseline differences in gut microbiome composition between SAH patients and FMT donors or healthy controls. Pande et al. observed a 23% variation in the first two principal components of bacterial taxa between donors and SAH recipients. Philips et al. (2018) (60) reported higher relative abundances of Proteobacteria and Lentisphaerae in controls, whereas Firmicutes and Actinobacteria were predominant in SAH patients. Philips et al. (2017) (59), however, found no significant baseline donor-recipient differences.

Changes in microbiota Post-FMT were reported in five studies, consistently demonstrating increased α -diversity and a compositional shift toward a donor-like microbial profile. At the family level, FMT was associated with increases in *Veillonellaceae*, *Lachnospiraceae*, *Bifidobacteriaceae*, *Bacteroidaceae*, *Porphyromonadaceae*, and *Tannerellaceae*, alongside consistent decreases in *Enterobacteriaceae*, *Streptococcaceae*, *Campylobacteraceae*, and *Desulfovibrionaceae*, with additional reductions in *Moraxellaceae*, *Weissellaceae*, *Leuconostocaceae*, and *Aerococcaceae* reported in some studies, changes collectively consistent with improved microbial stability and a healthier gut microbiota composition. Survival analyses identified favourable associations with higher abundances of *Succinivibrionaceae*, *Lachnospiraceae*, *Veillonellaceae*, and *Prevotellaceae*, whereas elevated *Enterobacteriaceae* and *Mycoplasmataceae* were more frequently observed among non-survivors.

1.1.1. Alcohol use recurrence and Disease severity scores

Alcohol use recurrence, reported across four studies (52, 55-57) encompassing 223 patients, was numerically lower in the FMT arm compared to SOC (OR 0.33, 95% CI 0.05–2.00, $p=0.144$, $I^2=40\%$, 95% CI 0–80%), though this difference did not reach statistical or clinical significance (Fig. 13).

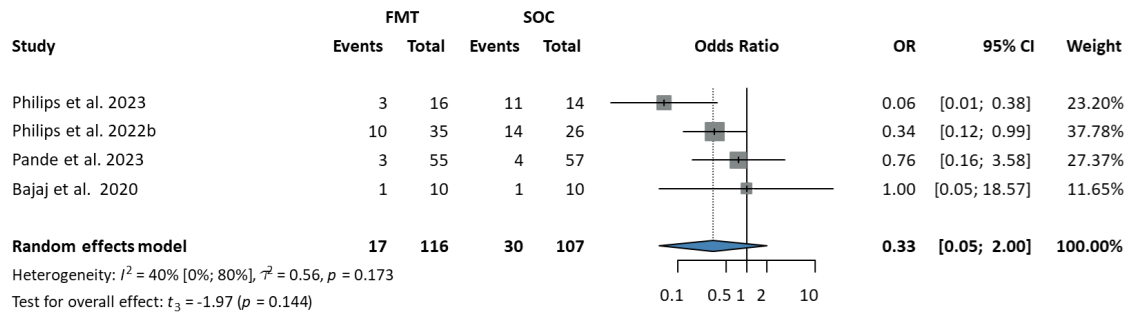


Figure 13. The odds ratio for the recurrence of alcohol use after treatment with FMT vs SOC (51).

OR: Odds Ratio; CI: Confidence Interval; SOC: Standard of Care; FMT: Faecal Microbiota Transplantation

Disease severity scores, including Maddrey's Discriminant Function (MDF), Child-Pugh score (CPT), and Model for End-Stage Liver Disease (MELD), were evaluated in four, five, and seven studies, respectively. Baseline MDF and MELD scores were broadly comparable between the FMT and SOC arms, while CPT scores were marginally higher in the FMT group overall. Notable outliers were identified: for MELD, Philips et al. (2018) (60) reported a mean difference of -2.1 points favouring FMT in the pentoxifylline arm, whereas Philips et al. (59) reported a mean difference of $+4.0$ points favouring SOC. For CPT, Philips et al. (59) again represented a notable outlier with a mean difference of 2.3 points favouring SOC. For MDF, Philips et al. (60) reported mean differences exceeding 3 points across all three comparator arms, consistently favouring FMT. Despite these outliers, baseline disease severity was broadly similar across most included studies.

Post-treatment changes in disease severity scores were reported in four ALD studies, of which three focused on SAH (55, 59, 61) and one on cirrhosis (52). In the FMT group, score reductions ranged from -4.20 to -18.70 for MELD, -1.80 to -6.80 for CPT, and -64.80 to -7.43 for MDF. Corresponding changes in the SOC group ranged from -9.35

to -3.17 for MELD, -4.45 to +1.37 for CPT, and -58.05 to -8.33 for MDF (Table 4). No data on liver fibrosis were reported in any of the included studies.

Table 4. Severity Score Comparisons at Baseline during Follow-ups and the difference between baseline and end of follow-up.

Author (Year)	Severity score			Follow-up time							
				7 (Days)		28 (Days)		90 (Days)			
				FMT	SOC	FMT	SOC	FMT	SOC	FMT	SOC
Sharma et al. (2022)	MELD	25.2 ±0.73	25.55 ±0.69	22.7 ±1.32	25.5 ±0.64	22 ±1.80	24.5 ±1.84	12.71 ±1.89	16.2 ±2.82	- 12.49 ±2.03	- 9.35 ±2.9
Sharma et al. (2022)	CPT	11.46 ±0.35	12.05 ±0.23	10.38 ±0.27	11.85 ±0.28	9.92 ±0.51	10.58 ±0.56	6.57 ±0.64	7.6 ±0.68	- 4.89 ±0.73	- 4.45 ±0.72
Sharma et al. (2022)	MDF	87 ±8.03	83.59 ±6.96	76.8 ±10.23	87.53 ±8.03	66.93 ±12.78	80.9 ±15.68	22.2 ±7.71	25.54 ±11.36	- 64.8 ±11.13	- 58.05 ±13.33
Pande et al. (2023)	MELD	25.33 ±0.36	25.05 ±0.30	NA	NA	24.75 ±0.86	22.96 ±0.98	21.13 ±1.05	21.88 ±1.23	- 4.20 ±1.0	- 3.17 ±1.15
Pande et al. (2023)	CPT	11.09 ±0.12	11.18 ±0.12	NA	NA	10.96 ±0.14	10.67 ±0.26	10.07 ±0.19	9.80 ±0.32	- 1.02 ±0.17	- 1.37 ±0.27
Pande et al. (2023)	MDF	68.13 ±2.06	65.1 ±2.36	NA	NA	69.51 ±5.30	58.60 ±5.81	60.70 ±8.40	56.76 ±6.56	- 7.43 ±8.23	- 8.33 ±6.40
Philips et al. (2017)	MELD	31 ±1.98	27 ±1.23	NA	NA	NA	NA	12.3 ±1.31	NA	- 18.7 ±2.4	NA
Philips et al. (2017)	CPT	14.5 ±0.28	11.7 ±0.21	NA	NA	NA	NA	7.7 ±0.42	NA	- 6.8 ±0.5	NA
Bajaj et al. (2020)	MELD	12 ±2.9*	13.2 ±3.7*	NA	NA	NA	NA	NA	NA	- 0.1 ±2*	- 0.2 ±2*

CPT: Child–Pugh–Turcotte h, FMT: Faecal Microbiota Transplantation, MELD: Model for End-Stage Liver Disease, MDF: Maddrey Discriminant Function, SD: Standard Deviation, SE: Standard Error, SOC: Standard of Care, *mean and SD (51).

1.1.2. Adverse events

Adverse events were reported in six studies, with considerable heterogeneity in the type and completeness of reporting across publications. Among the most frequently documented AEs, ascites occurred in 50 SOC versus 24 FMT patients across five studies, and hepatic encephalopathy was recorded in 43 SOC versus 12 FMT patients across five studies. Infections were reported in three studies, with 41 cases in the SOC group and 23 in the FMT group. Spontaneous bacterial peritonitis was documented in three studies, with seven SOC and six FMT cases. Excessive flatulence, reported in three studies, was more frequent in the FMT arm, with 29 cases versus 3 in the SOC group.

1.1.3. Risk of Bias Assessment and Publication bias

The results of the risk of bias assessment are summarized in Fig. 14. Among the evaluated non-randomized studies, four exhibited moderate, and two demonstrated serious risk of bias, driven primarily by concerns related to participant selection and inadequate control for confounding factors, reflecting the predominantly retrospective nature of the included studies. Among RCTs, one study was rated as low risk of bias, while another raised some concerns. The studies by Kumar et al. (54) and Bystrianska et al. (53) could not be formally assessed, as both were available only as conference abstracts.

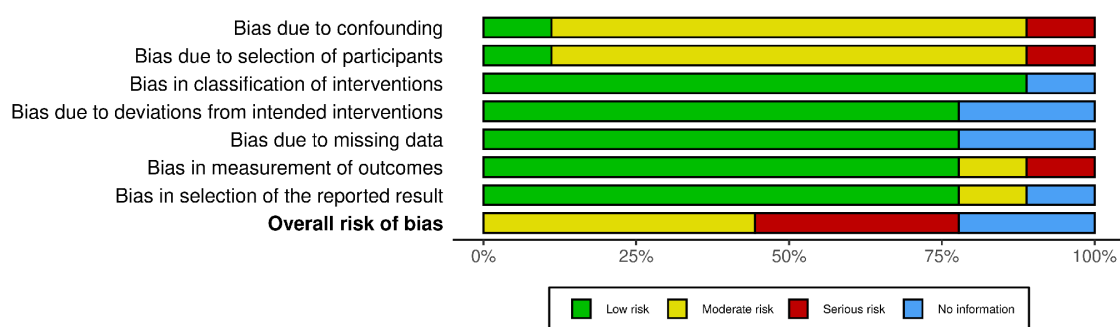


Figure 14. Robvis (6) summary plot depicting the risk of bias in non-randomized included studies for Study II (51).

As no pooled analysis included ten or more studies, a reliable assessment of small-study publication bias using Egger's test was not feasible for any of the evaluated outcomes. Overall heterogeneity was low, with a point estimate of $I^2=0\%$ (95% CI 0–75%) for the primary outcome. Higher heterogeneity was observed within the SOC group, consistent with the considerable clinical heterogeneity in the composition and definition of standard of care across included studies. (Fig. 15)

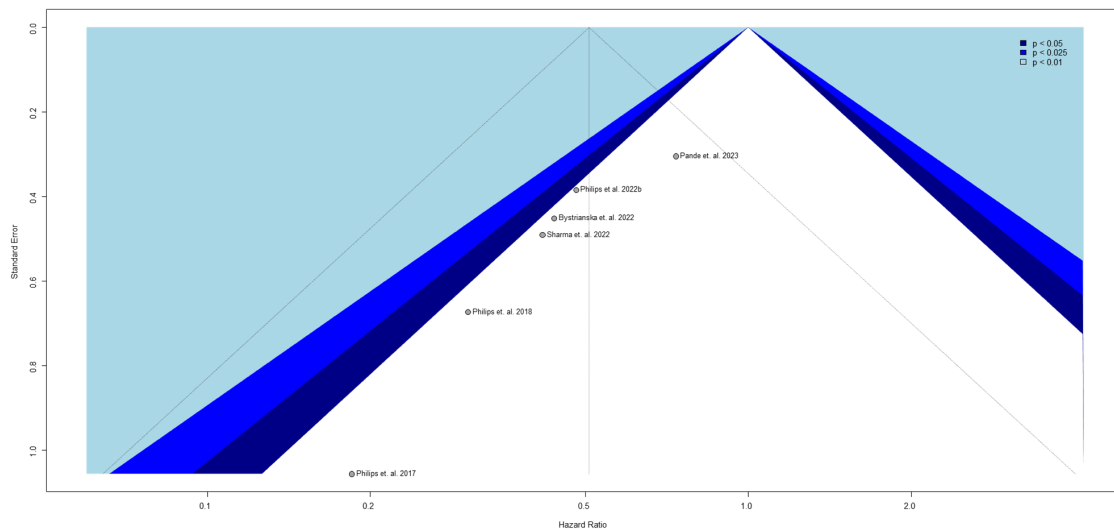


Figure 15. Funnel plot illustrating publication bias for overall survival in patients receiving FMT versus standard of care (51).

1.1.4. Quality of Evidence

Each evaluated outcome was rated as very low certainty according GRADEpro. Across all outcomes, serious risk of bias was the primary driver of the downgrading of the level of evidence.

2. DISCUSSION

2.1. Summary of Findings, International Comparisons (including all studies)

The first study findings provide robust evidence that CLD substantially worsens both mortality and disease severity in AP. Additionally, the analysis demonstrated that the rates of local and systemic complications were elevated in patients with CLD.

Both CLD and AP rank among the most prevalent conditions encountered in gastroenterology. The etiological landscape of AP is well characterized: biliary gallstones account for approximately 45% of cases, alcohol consumption for 20%, hypertriglyceridemia for around 5%, and the remaining 30% are attributable to less frequent causes (62). Notably, several etiological factors are shared between AP and CLD. Alcohol use underlies both alcohol-associated liver disease and alcohol-induced AP, while the relationship between obesity and Non-alcoholic Fatty Liver Disease (NAFLD)/Metabolic-associated Fatty Liver Disease (MAFLD) creates overlapping risk for biliary gallstone formation, hypertriglyceridemia, and the respective forms of AP in this population (63, 64).

This etiological convergence is reflected in studies documenting a higher prevalence of CLD among patients presenting with AP. A large US database study by Simons-Linares et al., encompassing 2.8 million AP patients, identified cirrhosis in 2.8% ($n = 80,093$), a prevalence that is 10-fold higher than the estimated 0.27% in the general US population (46, 65). In a separate prospective cohort, the Hungarian Pancreatic Study Group reported a MAFLD prevalence of 39% among AP patients, compared with 23% in the general population, with hypertriglyceridemia-induced AP occurring significantly more often in the MAFLD subgroup (14% vs. 3%) (38, 66).

Across all measured outcomes, our meta-analysis consistently demonstrated a trend toward worse results in CLD patients in AP. The pooled odds ratio for mortality was 2.5-fold higher in the CLD group, a statistically significant difference. Subgroup analysis suggested an even greater mortality risk in patients with cirrhosis, although definitive conclusions were precluded by the limited sample size and wide confidence intervals. Several large database studies reported mortality and other relevant outcomes but could not be incorporated into the meta-analysis due to overlapping patient populations (16, 19, 40, 46). Nevertheless, effect sizes across these studies were broadly

consistent with the pooled estimate, with individual mortality ORs ranging from 1.8 to 2.4, lending additional credibility to the meta-analytic findings. In the largest database study conducted by Simons-Linares et al. (21), decompensated cirrhosis emerged as the strongest independent predictor of in-hospital mortality, with an adjusted OR of 1.4 for decompensated versus compensated cirrhosis and 2.4 for decompensated versus no cirrhosis. Patients with decompensated cirrhosis represent a particularly vulnerable subgroup, given the cumulative burden of liver dysfunction-associated comorbidities and their heightened susceptibility to acute-on-chronic liver failure (ACLF), a syndrome defined by acute decompensation of cirrhosis, organ failure, and high short-term mortality. In keeping with this, Vogel et al (31) reported an ACLF incidence of 44% among AP patients with cirrhosis, with a considerable proportion presenting with more advanced grades II and III, likely reflecting the pronounced inflammatory burden in this population.

The mechanisms through which CLD adversely modifies AP outcomes are likely multifactorial. The most straightforward explanation involves the high comorbidity burden associated with CLD, including type 2 diabetes, arterial hypertension, obesity, cardiovascular disease, chronic kidney disease, and chronic obstructive pulmonary disease(67-69). An alternative hypothesis, proposed by several authors (32, 35), posits that CLD sustains a chronic pro-inflammatory state that potentiates the systemic inflammatory response triggered by AP(32). The latter is supported by our finding of a twofold increase in the odds of SIRS among CLD patients.

Whether the adverse effect of CLD operates independently of confounding variables remains unresolved. A sensitivity analysis restricted to adjusted models was planned; however, the paucity of adjusted data in the existing literature rendered a comprehensive analysis unfeasible. Adjusted model data were identified only for mortality, organ failure, MODS, and SIRS, and were incorporated into a sensitivity analysis alongside unadjusted estimates. Comparison of individual and pooled effect sizes revealed no substantial difference between adjusted and unadjusted models, suggesting that the overall direction of findings is robust. Nonetheless, definitive conclusions remain limited by inconsistent and incomplete reporting of confounders across included studies. The results of the second study are less straightforward to interpret because the analysis is constrained by a series of limitations. First, only a single study has to date evaluated

FMT in the context of cirrhosis (70), and none in any severe case of AH. Hence, the present analysis focuses specifically on FMT for SAH. The pooled HR demonstrates that FMT was associated with approximately twofold improvement in survival relative to SOC. Subgroup analysis stratified by SOC type revealed that FMT was significantly superior to both nutritional support and pentoxifylline, whereas a statistically significant advantage over glucocorticoids was not demonstrated. Additionally, patients with SAH displayed a markedly distinct gut microbiota composition compared to controls.

Experimental evidence from animal models has established that intestinal microbiota dysbiosis critically contributes to the development and progression of AH (71). Complementing this, faecal transplantation from individuals with ALD, particularly those with AH, into murine recipients has been shown to amplify susceptibility to alcohol-induced hepatic injury (72). These observations have led several investigators to propose gut microbiota modulation as a potential therapeutic target in AH (70, 73). Consistent with this rationale, the present meta-analysis identified a uniform survival benefit associated with FMT across the included studies, corresponding to an approximately twofold reduction in the hazard of death. The sole exception was the report by Kumar et al. (54), in which adjunctive FMT was associated with higher rates of sepsis and mortality; however, this finding must be interpreted with caution given the markedly limited sample size of 10 patients per treatment arm. The most pronounced survival benefit was observed among patients who were either ineligible for glucocorticoid therapy or failed to respond to it, and were consequently managed with pentoxifylline or nutritional support alone. Direct comparison of FMT with glucocorticoid therapy yielded a trend in favour of FMT that did not attain statistical or clinical significance.

Leave-one-out sensitivity analysis identified the study by Pande et al. (55) as a particularly influential publication. As the only RCT included in the analysis, this likely accounts for the substantive difference in effect size observed relative to the remaining non-randomized studies. Given that Pande et al. (55) also reported the smallest effect size among all contributors, the possibility that the absence of randomization and blinding in other studies inflated the overall pooled estimate warrants consideration, and this constitutes a meaningful constraint on the current level of evidence.

While FMT is generally well tolerated across most clinical settings (74, 75), ALD and SAH represent a distinct condition characterized by dysregulated immune function, compromised intestinal barrier integrity, and heightened susceptibility to infection, all of which necessitate particular vigilance when applying this intervention (76). In other immunocompromised populations, including patients with inflammatory bowel disease, *Clostridioides difficile* infection, graft-versus-host disease, or HIV, FMT has demonstrated an acceptable safety profile with a low incidence of adverse events (77-80).

Formal synthesis of adverse event data was not feasible due to limited availability and considerable heterogeneity in reporting methodologies across the included studies. Among reports that did address this outcome, no significant between-group difference in serious adverse events was identified between FMT and SOC. Nevertheless, the quality of available AEs data precludes definitive conclusions, and future trials should adopt standardized, rigorous AEs reporting frameworks. This is especially pertinent given that events commonly attributed to an intervention may occur, resolve spontaneously, or even antedate treatment administration independently of FMT, and such outcomes are inherently susceptible to survival bias.

Baseline disease severity scores including MDF, MELD, and Child-Pugh-Turcotte were broadly comparable across studies, indicating a reasonable degree of population homogeneity between treatment arms. Serial MELD assessment has established prognostic value: both upward and downward trajectories in patients listed for liver transplantation provide meaningful additional information regarding mortality risk(81). Both Sharma et al. (61) and Pande et al. (55) reported reductions in MELD at 90-day follow-up in both the FMT and SOC arms. The substantially smaller effect size reported by Pande et al. (55) most likely reflects differences in the enrolled population, as Sharma et al.(61) recruited exclusively patients with acute-on-chronic liver failure, a clinically more severe subgroup with correspondingly greater scope for measurable improvement.

2.2. Strengths (including all studies)

Both studies demonstrate several notable methodological strengths. The first meta-analysis draws on a large and geographically diverse patient population spanning

European, American, and Asian cohorts, thereby broadening the external validity of the findings and enhancing their applicability across clinical settings and ethnic populations. Methodological rigour was further ensured through the use of a pre-registered protocol minimising the risk of outcome reporting bias and formal certainty-of-evidence grading using GRADEpro.

The second study represents the first meta-analysis of IPD estimates specifically examining FMT in SAH. Unlike conventional aggregate data meta-analyses, the IPD approach based on reconstruction of survival data from Kaplan–Meier curves enables patient-level analysis, yielding a more precise and methodologically nuanced assessment of treatment effect. This methodology allowed the achievement of a comparatively large effective sample size, especially for SOC subgroups, despite the limited number of available studies and relatively small sample sizes.

2.3. Limitations (including all studies)

Several limitations must be acknowledged across both analyses. In the first study, the limitations are primarily due to the lack of prospective study designs and the absence of more granular patient-level data, which precluded more robust, detailed subgroup analyses.

In the second study, more severe limitations were observed, primarily driven by low quality and high ROB assessment of underlying studies. Additionally, the geographic and demographic homogeneity limited the interpretability of the findings. The included studies originated from only three countries, with the substantial majority of patients recruited in India. Furthermore, the study population consisted almost exclusively of male patients, which is partly reflective of the epidemiology of SAH but nonetheless restricts applicability to female patients. At the disease level, SAH is a clinically heterogeneous condition spanning a broad spectrum from patients with relatively preserved hepatic function to those presenting with acute-on-chronic liver failure and is further stratified by glucocorticoid eligibility and treatment response status, each subgroup carrying a distinct prognosis. Although the present analysis encompasses a comparatively large and clinically representative SAH population, the sample size and data granularity remain insufficient for definitive conclusions for specific

subpopulations. Furthermore, the inconsistent reporting of adverse events across included studies precluded meaningful pooled analysis.

3. CONCLUSIONS

Chronic liver disease is an important risk factor in patients with AP, leading to higher mortality and increased odds of both local and systemic complications. Systemic inflammatory response syndrome could be a possible driver of worsened outcomes.

FMT was associated with a statistically significant survival benefit in patients with SAH compared to standard of care, with survival probabilities consistently higher in the FMT group at 28, 90, and 180 days. The benefit was most pronounced in patients treated with pentoxifylline or nutritional support, while direct comparison with glucocorticoids yielded a favourable trend that did not reach statistical significance. Clinical applicability remains questionable due to the numerous limitations and low level of evidence.

4. IMPLICATIONS FOR PRACTICE

Awareness of CLD association with adverse outcomes is particularly important in the early phase of the AP, where it should inform appropriate zero-additional-cost prognosis stratification. Additionally, patients presenting with concomitant AP and CLD warrant heightened clinical vigilance and more rigorous monitoring.

With respect to SAH, notwithstanding the promising data presented in this thesis, no clear recommendation for routine clinical practice can be issued given the substantial limitations of the current evidence base. Its clinical application should therefore remain restricted to trial settings or carefully monitored clinical contexts.

5. IMPLICATIONS FOR RESEARCH

5.1. Methodology and Study Design

In the case of CLD co-occurring with AP, more prospective studies are needed. These should report more granular data in order to generate stronger evidence for specific subpopulations of CLD. Regarding FMT in SAH, given the limitations of current literature, there is an urgent need for adequately powered, multicenter RCTs with well-reported AEs.

5.2. New Areas

For future studies focused on CLD AP co-occurrence, incorporation of liver elastography measurements and stratification according to the Baveno VII classification would provide greater clarity and should be considered a priority.

Future research should address the full spectrum of ALD, including cirrhosis, hepatic steatosis, and milder forms of AH beyond SAH. The potential role of FMT as an adjunct to glucocorticoid therapy also warrants rigorous evaluation. At the translational level, research should focus on elucidating the mechanistic effects of FMT on the liver by identifying specific microbiome-derived metabolites and mediators of therapeutic response, with the ultimate goal of developing more targeted microbiota-based therapies and broadening their clinical applicability.

6. IMPLICATIONS FOR POLICY MAKERS

The limited therapeutic options and high disease burden associated with both CLD-complicated AP and SAH highlight the need for sustained investment in clinical trial infrastructure. International collaborative networks should be established to generate geographically diverse and generalizable evidence. Regulatory frameworks for FMT in liver disease should facilitate trial participation while ensuring patient safety. Moreover, rapid translation of scientific findings into practice should be supported as a key healthcare priority.

7. FUTURE PERSPECTIVES

Having studied and worked at a Centre for Translational Medicine, the experience gained during the preparation of this thesis opens several avenues for future clinical and scientific development.

As I plan to continue as a gastroenterology resident, I am committed to providing the highest possible standard of care to patients with hepatic and pancreatic diseases, integrating current evidence-based recommendations into every aspect of clinical decision-making, an approach that can now be more critically evaluated and interpreted having consolidated the skills acquired through translational medicine training.

Alongside direct patient care, I intend to actively participate in the education of medical students and junior colleagues, fostering a culture of scientifically informed clinical reasoning. Teaching grounded in methodology, critical appraisal of evidence, and translational thinking represents the standard I aspire to uphold and to transmit to the next generation of physicians.

I aspire to continue research work focused on the applications of faecal microbiota transplantation in hepatology and pancreatology, and within the expanding field of microbiome-targeted therapies more broadly. Building on the systematic review work presented in this thesis, I plan to contribute to prospective collaborative research projects investigating the clinical applications of faecal microbiota transplantation across a broader spectrum of indications. These efforts will aim to generate high-quality, multicenter data to inform future guideline development and improve patient outcomes at national and international levels.

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9. BIBLIOGRAPHY

9.1. Publications Related to the Thesis

1. **Hoferica, Jakub**; Borbély, Ruben Zsolt; Aghdam, Ali Nedjati; Szalai, Eszter Ágnes; Zolcsák, Ádám; Veres, Dániel Sándor; Hagymási, Krisztina; Erőss, Bálint; Hegyi, Péter; Bánovčin, Peter, Péter Jenő Hegyi

Chronic liver disease is an important risk factor for worse outcomes in acute pancreatitis: a systematic review and meta-analysis

SCIENTIFIC REPORTS (2024)

Q1, IF:3.9

2. **Hoferica, Jakub**; Budai, Bettina Csilla; Szalai, Eszter Ágnes; Zolcsák, Ádám; Engh, Marie Anne; Lenti, Katalin; Hegyi, Péter; Yu, Jun; Hegyi, Péter Jenő; Bánovčin, Peter
Fecal Microbiota Transplantation Is Associated with Better Survival Compared to Standard of Care in Severe Alcoholic Hepatitis Not Responding to Corticosteroids: A Systematic Review and Meta-Analysis

JOURNAL OF CLINICAL MEDICINE (2026)

Q1, IF:3.3

9.2. Publications not Related to the Thesis

1. Nyirády, Loretta Enikő; Czébely-Lénárt, András; **Hoferica, Jakub**; Hegyi, Péter; Fehérvári, Péter; Nyirády, Péter; Riesz, Péter; Ács, Nándor; Szijártó, Attila; Klárik, Zoltán

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SCIENTIFIC REPORTS (2026)

Q1, IF:4,9

2. Altenni, Mohammed; Fehérvári, Péter; **Hoferica, Jakub**; Hegyi, Péter; Ács, Nándor; Fazekas, Tamás; Vargha, Judit; Grünwald, Viktor; Darr, Christopher; Riesz, Péter; Nyirády, Péter; Szarvas, Tibor

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GASTROINTESTINAL DISORDERS (2025)

Q3, IF:1,9

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Q1, IF:3.4

5. Bánovčin, Peter; Lipták, Peter; Vážanová, Diana; **Hoferica, Jakub**; Tatár, Miloš; Ďuriček, Martin
Esophageal Infusion of Menthol Does Not Affect Esophageal Motility in Patients with Gastroesophageal Reflux Disease

DYSPHAGIA (2024)

Q1, IF:3.0

6. Liptak, Peter; **Hoferica, Jakub**; Vojtko, Marek; Banovcin, Peter
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CLINICAL JOURNAL OF GASTROENTEROLOGY (2026)

Q3,IF:0.8

7. Nosakova, Lenka; Uhrik, Peter; Pindura, Miroslav; Vojtko, Martin; **Hoferica, Jakub**; Cmarkova, Kristina; Miklusica, Juraj; Banovcin, Peter
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BRATISLAVA MEDICAL JOURNAL (2024)

Q3,IF:1.4

8. Frivaldszky, Lőrinc; Lőrincz, Kincső; **Hoferica, Jakub**; Hegyi, Péter; Ács, Nándor;
Melczer, Zsolt; Fehérvári, Péter; Keszthelyi, Márton

Esketamine reduces the risk of postpartum depression in women undergoing cesarean
section: A systematic review and meta-analysis

JOURNAL OF PSYCHIATRIC RESEARCH (2025)

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During the preparation of this manuscript, the authors used AI-assisted tools for the following purposes: proofreading, grammar correction of the manuscript text, language editing for clarity and style, and generation of illustrations for the graphical abstract. All AI-generated or AI-assisted content was reviewed, verified, and approved by the authors. The authors take full responsibility for the integrity and accuracy of the published work.