International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Helicobacter pylori and Metabolic-Associated Fatty Liver Disease Severity: A Meta-Analysis

INPLASY202650080
doi: 10.37766/inplasy2026.5.0080
Received: 14 May 2026
Published: 14 May 2026

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ADMINISTRATIVE INFORMATION

Support - Beijing High-level Public Health Technical Talent Construction Project.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650080

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 May 2026 and was last updated on 14 May 2026.

INTRODUCTION

Review question / Objective P (Population)
Adults (≥18 years) diagnosed with metabolic-associated fatty liver disease (MAFLD) / non-alcoholic fatty liver disease (NAFLD), defined by hepatic steatosis plus metabolic dysfunction (overweight/obesity, type 2 diabetes, or metabolic dysregulation).
I (Exposure)
Helicobacter pylori (H. pylori) infection (confirmed via validated methods: $^{13}C/^{14}C$ urea breath test, gastric biopsy, stool antigen test, or serological anti-H. pylori antibodies).
C (Comparison)
H. pylori-negative status (no evidence of current or past infection via the same validated detection methods).
O (Outcome)
Severity of MAFLD/NAFLD, assessed via:
Histological grading (liver biopsy: MASH/NASH vs simple steatosis, fibrosis stage, steatosis/inflammation grade);
Non-invasive metrics (ultrasound severity grading, controlled attenuation parameter [CAP], liver stiffness measurement, fibrosis scores: NFS, FIB-4, APRI, BARD).
S (Study Design)
Observational studies (cross-sectional, cohort, case-control) published between January 2015 and December 2024, with English/Chinese full-text original research data.
Core Review Question
In adults with MAFLD/NAFLD, is H. pylori infection associated with increased disease severity compared to H. pylori-negative individuals?

Condition being studied Metabolic-associated fatty liver disease (MAFLD), formerly termed non-alcoholic fatty liver disease (NAFLD), is a chronic, metabolic-driven liver disorder characterised by excess fat accumulation (hepatic steatosis) in hepatocytes, unrelated to excessive alcohol consumption. It is defined by hepatic steatosis plus one or more metabolic risk factors: overweight/obesity, type 2 diabetes mellitus, or

evidence of metabolic dysregulation (e.g., insulin resistance, dyslipidaemia).
MAFLD encompasses a spectrum of progressive liver damage: from simple steatosis (fat accumulation alone, usually benign) to metabolic-associated steatohepatitis (MASH/NASH) (steatosis with inflammation and hepatocyte injury), and advanced stages including liver fibrosis, cirrhosis, and hepatocellular carcinoma. As the most common chronic liver disease globally (affecting ~25% of the population), MAFLD severity —particularly fibrosis stage—is the key predictor of liver-related morbidity and mortality.

METHODS

Participant or population Adults aged 18 years and older with a diagnosis of metabolic-associated fatty liver disease (MAFLD) or non-alcoholic fatty liver disease (NAFLD). MAFLD/NAFLD must be confirmed by liver biopsy, imaging (ultrasound, CT, MRI), transient elastography, or validated non-invasive algorithms.
The population includes both male and female participants, with or without common metabolic comorbidities (overweight/obesity, type 2 diabetes, dyslipidaemia, hypertension). No restrictions are applied on ethnicity or geographic region. Excluded are children/adolescents (<18 years), patients with significant alcohol intake, viral hepatitis, drug-induced liver injury, autoimmune liver disease, or other competing causes of chronic liver disease.

Intervention This review focuses on Helicobacter pylori (H. pylori) infection as the exposure (not a therapeutic intervention).
Exposed group: Participants with confirmed H. pylori infection diagnosed by validated methods: $^{13}C/^{14}C$ urea breath test, gastric mucosal biopsy (histology/rapid urease test), stool antigen test, or serum anti-H. pylori IgG antibodies.
Control group: Participants with no evidence of H. pylori infection (negative on the same validated tests).
No therapeutic interventions (e.g., H. pylori eradication therapy) are evaluated in this review; the analysis assesses the association between natural H. pylori infection status and MAFLD severity.

Comparator The comparator is absence of Helicobacter pylori (H. pylori) infection in adults with MAFLD/NAFLD.
Definition: Participants who test negative for H. pylori using the same validated diagnostic methods as the exposed group ($^{13}C/^{14}C$ urea breath test, gastric biopsy, stool antigen test, or serology).
Purpose: To compare MAFLD severity between H. pylori-positive (exposed) and H. pylori-negative (comparator) individuals.

Study designs to be included This review will include observational study designs that examine the association between Helicobacter pylori infection and MAFLD/NAFLD severity. Specifically:Cross-sectional studies: Assess H. pylori status and MAFLD severity at a single time point.Case-control studies: Compare H. pylori prevalence in participants with severe MAFLD (cases) versus those with mild MAFLD (controls).Cohort studies: Evaluate whether baseline H. pylori infection predicts subsequent MAFLD severity progression.Excluded study designs: Randomised controlled trials (RCTs), reviews, meta-analyses, case reports, c.

Eligibility criteria Additional Inclusion Criteria (beyond PICOS)
Studies published between January 2015 and December 2024.
Full-text original research articles written in English or Chinese.
Sufficient raw or analysed data to calculate odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs), or construct 2×2 contingency tables for MAFLD severity outcomes.
MAFLD/NAFLD severity defined by validated histological, imaging or non-invasive scoring systems (e.g., fibrosis stage, MASH/NASH diagnosis, ultrasound steatosis grade, CAP, liver stiffness, NFS, FIB-4).
Additional Exclusion Criteria (beyond PICOS)
Review articles, meta-analyses, editorials, commentaries, letters, case reports, conference abstracts and unpublished data.
Studies only reporting MAFLD/NAFLD prevalence without severity stratification.
Animal studies, in vitro experiments, genetic studies or mechanistic research without clinical participant data.
Studies with overlapping/duplicate participant populations (retain the largest sample size or most complete severity data).
Studies lacking key data for meta-analysis after full-text extraction.
Studies focusing exclusively on paediatric populations (<18 years), or participants with confounding liver diseases (viral hepatitis, autoimmune liver disease, drug-induced liver injury, alcoholic liver disease).

Information sources 1. Electronic databases (2015.01–2024.12)
International: PubMed, Embase, Web of Science
Chinese: CNKI, VIP, Wanfang Data
2. Grey literature & supplementary
Manual screening of reference lists from included studies and relevant systematic reviews
No direct author contact, trial registers or additional grey literature searches planned.

Main outcome(s) Primary outcome
Severity of metabolic-associated fatty liver disease (MAFLD/NAFLD) in adults with confirmed MAFLD/NAFLD, compared between Helicobacter pylori-positive and H. pylori-negative participants.
Outcome definitions & measurement
Histological severity (biopsy-based)
Severe: Metabolic-associated steatohepatitis (MASH/NASH), any fibrosis stage ≥F1, or moderate-to-severe steatosis/inflammation.
Mild: Simple steatosis without inflammation/fibrosis (F0).
Non-invasive severity
Imaging: Moderate/severe steatosis on ultrasound; elevated controlled attenuation parameter (CAP) or liver stiffness via transient elastography.
Scores: Elevated non-invasive fibrosis indices (NAFLD Fibrosis Score, FIB-4, APRI, BARD) above validated thresholds for significant fibrosis.
Timing
Outcomes assessed at the time of H. pylori testing (cross-sectional) or at study baseline (cohort); no long-term follow-up outcomes are included.
Effect measures
Primary: Pooled odds ratio (OR) with 95% confidence interval (CI) for severe vs mild MAFLD/NAFLD in H. pylori-positive vs H. pylori-negative groups.
Heterogeneity: Quantified via I^2 statistic, τ^2, and Cochran's Q test.

Quality assessment / Risk of bias analysis
Quality Assessment Tool
The methodological quality and risk of bias of included observational studies (cross-sectional, case-control, cohort) will be evaluated using the Newcastle–Ottawa Scale (NOS).
NOS Domains & Scoring
The scale assesses three core domains, with a maximum total score of 9 points:
Selection of study groups (0–4 points)
Representativeness of the exposed cohort
Selection of the non-exposed cohort
Ascertainment of exposure (validated H. pylori testing)
Demonstration that outcome of interest (MAFLD) was not present at study start (for cohort studies)
Comparability of groups (0–2 points)
Control for the most important confounding factors (e.g., age, sex, BMI, diabetes)
Control for additional relevant confounders (e.g., dyslipidaemia, hypertension)
Ascertainment of outcome (0–3 points)
Independent/blind assessment of MAFLD severity
Sufficient follow-up duration for outcome assessment (for cohort studies)
Adequacy of follow-up (low loss to follow-up)
Quality Classification
High quality: 7–9 points
Moderate quality: 4–6 points
Low quality: 0–3 points (will be excluded from the meta-analysis)
Assessment Process
Two reviewers will independently score each included study.
Disagreements will be resolved by consensus or consultation with a third reviewer.

Strategy of data synthesis 1. Software
All analyses will be performed using R statistical software (v4.0+) with the meta and metafor packages.
2. Effect measure
For the binary outcome (severe vs mild MAFLD/NAFLD), we will calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs).
3. Meta-analysis model
A random-effects model will be used, fitted with restricted maximum likelihood (REML) for between-study variance (τ^2) and adjusted via the Hartung–Knapp method for CIs, to account for expected clinical and methodological heterogeneity across observational studies.
4. Heterogeneity assessment
Cochran's Q test
Between-study variance (τ^2)
I^2 statistic (interpreted as: low 50%)
5. Subgroup analyses (prespecified)
Severity assessment method: biopsy-based vs non-invasive (ultrasound/CAP/stiffness/scores)
Geographic region: Chinese vs non-Chinese populations
6. Sensitivity analysis
Leave-one-out analysis: iteratively remove one study at a time and recalculate the pooled OR, to test the stability of results and identify influential studies.
7. Publication bias
A funnel plot will be examined visually. Formal tests (Egger's test, trim-and-fill) will not be performed due to the expected small number of included studies (<10).
8. Significance level
A two-sided $p < 0.05$ will be considered statistically significant for pooled effect estimates.

Subgroup analysis Prespecified subgroup analyses will be performed to explore potential sources of between-study heterogeneity and to assess whether the association between Helicobacter pylori infection and MAFLD/NAFLD severity differs by key study and population characteristics.
Method of MAFLD severity assessment
Biopsy-based assessment (histological grading of steatohepatitis and fibrosis)
Non-invasive assessment (ultrasound grading, controlled attenuation parameter, liver stiffness measurement, validated fibrosis scores: NFS, FIB-4, APRI, BARD)
Geographic region
Chinese study populations
Non-Chinese study populations (Japan, Korea, Switzerland/Greece, etc.)
Helicobacter pylori detection method
Active infection tests ($^{13}C/^{14}C$ urea breath test, gastric biopsy/rapid urease test, stool antigen)
Serological testing (anti-H. pylori IgG antibodies, reflecting past exposure)
All subgroup analyses will use the random-effects model and report pooled ORs with 95% CIs. Between-subgroup differences will be evaluated using the χ^2 test for subgroup interaction. Given the expected small number of included studies, results will be interpreted as hypothesis-generating only, not confirmatory.

Sensitivity analysis To test the robustness of the primary meta-analysis results and assess the influence of individual studies, a leave-one-out sensitivity analysis will be conducted.
Approach: Repeatedly exclude one study at a time and recalculate the pooled OR and 95% CI.
Purpose: Evaluate whether any single study disproportionately drives the overall effect size or alters the statistical significance.
Interpretation: If pooled estimates remain stable in direction and significance after omitting each study, the main result is considered robust.
Additional checks:
Exclude low-quality studies (NOS <7) to assess the impact of study quality.
Exclude studies using serology-only H. pylori detection to focus on active infection.

Country(ies) involved China.

Keywords Helicobacter pylori; Severity of Illness Index; Meta-analysis; Metabolic-associated fatty liver disease;study.

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