

Citation: Mirandola IB, Pires Alves ATP, Silva DFP, Brandão Rangel MAR. Impact of Metabolic Syndrome, Type 2 Diabetes Mellitus, and Metabolic Pharmacotherapies on the Progression of MASLD/MASH to Advanced Fibrosis and Cirrhosis: A Systematic Review. *Arch Gastroenterol Res.* 2026;7(1):47–59.

SUPPLEMENTARY MATERIAL

1. Study Design and Search Strategy

This is a systematic literature review conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA 2020) guidelines. The review protocol was registered in advance with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261322056.

This work was structured around two core axes of interest:

- Metabolic dysfunction as a driver of disease progression: to evaluate how metabolic syndrome and type 2 diabetes mellitus influence the progression of MASLD/MASH toward advanced fibrosis and cirrhosis;
- Metabolic pharmacotherapies as potential modifiers of liver outcomes: to assess the effects of pharmacological interventions used for metabolic control on liver-related clinical and histological outcomes.

Literature searches were performed across the PubMed/MEDLINE, Embase, and Cochrane Library databases, covering studies published from January 2016 through September 2025, which represents the date of the final search. The search strategy was adapted to the specific syntax and indexing requirements of each database to ensure optimal sensitivity and specificity. The complete, detailed search strategy for each platform is provided as Supplementary Material. In addition, manual searches were conducted in the reference lists of all included studies and relevant systematic reviews to identify potentially relevant articles not retrieved by the initial electronic search.

The search strategy was as follows:

(“Liver Cirrhosis” OR “Chronic Liver Disease” OR “Liver Fibrosis” OR “MASLD” OR “MASH” OR “Nonalcoholic Fatty Liver Disease”)

AND

(“Metabolic Syndrome” OR “Type 2 Diabetes Mellitus” OR “Obesity” OR “Insulin Resistance”)

AND

Citation: Mirandola IB, Pires Alves ATP, Silva DFP, Brandão Rangel MAR. Impact of Metabolic Syndrome, Type 2 Diabetes Mellitus, and Metabolic Pharmacotherapies on the Progression of MASLD/MASH to Advanced Fibrosis and Cirrhosis: A Systematic Review. Arch Gastroenterol Res. 2026;7(1):47–59.

(Metformin OR Pioglitazone OR “GLP-1 Receptor Agonists” OR Liraglutide OR Semaglutide OR Tirzepatide OR “SGLT2 Inhibitors” OR Empagliflozin OR Dapagliflozin OR Statins)

AND

(“Fibrosis” OR “Cirrhosis” OR “Disease Progression” OR “Mortality” OR “Hepatocellular Carcinoma”)

2. Eligibility Criteria

Studies were included if they met all of the following criteria:

- Randomized controlled trials;
- Prospective controlled studies;
- Studies conducted in human adults (aged ≥ 18 years);
- Patients diagnosed with MASLD/MASH, chronic liver disease, liver fibrosis, or cirrhosis;
- Presence of metabolic syndrome and/or type 2 diabetes mellitus;
- Evaluation of metabolic pharmacological therapies, including metformin, pioglitazone, GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, statins, and related agents;
- Reporting of at least one relevant liver-related or metabolic outcome, including fibrosis progression, MASH resolution, progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma, mortality, histological changes, liver enzyme levels, or hepatic fat content.

Studies were excluded based on the following criteria:

- Retrospective observational studies;
- Cross-sectional studies;
- Case reports or case series;
- Narrative reviews, systematic reviews, and meta-analyses;
- Experimental studies in animals;
- Articles without full text available;
- Studies lacking relevant clinical or liver-related outcomes;
- Duplicate publications.

Citation: Mirandola IB, Pires Alves ATP, Silva DFP, Brandão Rangel MAR. Impact of Metabolic Syndrome, Type 2 Diabetes Mellitus, and Metabolic Pharmacotherapies on the Progression of MASLD/MASH to Advanced Fibrosis and Cirrhosis: A Systematic Review. Arch Gastroenterol Res. 2026;7(1):47–59.

No restrictions were applied regarding the country of origin of the studies. Only articles published in English were included.

3. Study Selection

Study selection was performed independently by two reviewers in two stages. First, titles and abstracts retrieved from the databases were screened. Subsequently, potentially eligible studies underwent full-text review to assess inclusion and exclusion criteria. Disagreements between reviewers were resolved by consensus, and when necessary, a third reviewer was consulted. The study selection process was described using a flow diagram following PRISMA 2020 guidelines.

4. Data Extraction

Data extraction was performed independently by two reviewers using a standardized form developed in advance. The following information was collected:

- Author names;
- Year of publication;
- Country of origin;
- Study design;
- Population characteristics;
- Sample size;
- Age and sex of participants;
- Metabolic comorbidities assessed;
- Pharmacological intervention used;
- Duration of follow-up;
- Liver-related and metabolic outcomes analyzed;
- Key clinical and laboratory findings.

Following extraction, data were reviewed and compared between evaluators to minimize inconsistencies and reduce the risk of extraction bias.

Citation: Mirandola IB, Pires Alves ATP, Silva DFP, Brandão Rangel MAR. Impact of Metabolic Syndrome, Type 2 Diabetes Mellitus, and Metabolic Pharmacotherapies on the Progression of MASLD/MASH to Advanced Fibrosis and Cirrhosis: A Systematic Review. *Arch Gastroenterol Res.* 2026;7(1):47–59.

5. Risk of Bias Assessment

Risk of bias in included randomized controlled trials was evaluated using the *Revised Cochrane Risk-of-Bias Tool for Randomized Trials* (RoB 2.0).

The RoB 2.0 tool assesses five domains:

- Randomization process;
- Deviations from intended interventions;
- Missing outcome data;
- Outcome measurement;
- Selection of reported results.

Each domain was classified as:

- Low risk of bias;
- Some concerns;
- High risk of bias.

An overall risk-of-bias judgment was determined according to the tool's guidelines. Assessment was performed independently by two reviewers, with any disagreements resolved by consensus.

6. Data Synthesis and Analysis

A qualitative synthesis of included studies was performed, considering methodological characteristics, pharmacological interventions, and key liver-related and metabolic outcomes.

Studies were grouped according to the therapeutic class evaluated:

- GLP-1 receptor agonists;
- Dual incretin agonists;
- SGLT2 inhibitors;
- DPP-4 inhibitors;
- Insulin sensitizers;

Citation: Mirandola IB, Pires Alves ATP, Silva DFP, Brandão Rangel MAR. Impact of Metabolic Syndrome, Type 2 Diabetes Mellitus, and Metabolic Pharmacotherapies on the Progression of MASLD/MASH to Advanced Fibrosis and Cirrhosis: A Systematic Review. *Arch Gastroenterol Res.* 2026;7(1):47–59.

- Statins and lipid-modifying agents.

Due to the methodological heterogeneity of the included studies — particularly regarding outcomes assessed, diagnostic methods, follow-up duration, and pharmacological interventions — a structured narrative synthesis was chosen, and no quantitative meta-analysis was performed.

7. Quality of Evidence Assessment

The overall quality of evidence was rated using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) system, considering the following criteria:

- Risk of bias;
- Inconsistency;
- Indirectness of evidence;
- Imprecision;
- Publication bias.

Evidence quality was classified as:

- High;
- Moderate;
- Low;
- Very low.

This approach enabled a critical interpretation of methodological robustness and clinical reliability of the outcomes analyzed.