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ORIGINAL RESEARCH

Impact of Glucagon-Like Peptide-1 Receptor Agonists on Liver-Related Outcomes, Laboratory and Physiologic Parameters in Metabolic Dysfunction-Associated Steatohepatitis: A Systematic Review and Meta-Analysis

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Background: Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of chronic liver disease globally, with limited treatment options. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) show potential for MASH due to their metabolic benefits, but evidence on histological outcomes remains inconclusive.

Methods: We conducted a PRISMA 2020-compliant systematic review and meta-analysis, including 25 randomized controlled trials (RCTs, n=2481). Primary outcomes were resolution of MASH without fibrosis worsening and fibrosis improvement without steatohepatitis worsening. Secondary outcomes included anthropometric and biochemical parameters. Risk of bias was assessed via ROB 2, and evidence certainty via GRADE. Trial sequential analysis (TSA) addressed random errors.

Results: GLP-1 RAs significantly increased MASH resolution without fibrosis worsening (OR=4.04; 95% CI [2.69–6.05]; P<0.00001; 7 RCTs, n=1456). No significant improvement in fibrosis was observed (OR=1.54; 95% CI [0.95–2.48]; P=0.08; 5 RCTs, n=1277). Secondary outcomes showed reduced BMI (MD=−0.52 kg/m^2; P=0.05) but no significant changes in weight, waist circumference, liver enzymes, or lipids. TSA confirmed sufficient evidence for MASH resolution (RIS=197) but not fibrosis improvement (RIS=1693). GRADE indicated high certainty for primary outcomes.

Conclusion: GLP-1 RAs promote MASH resolution but do not significantly improve fibrosis. Their benefits appear to be driven by metabolic mechanisms rather than direct antifibrotic effects. Larger RCTs targeting fibrosis endpoints are warranted.

Trial Registration: The protocol for our meta-analysis and systematic review was registered and recorded in PROSPERO (registration no. CRD420251090801).

Keywords: glucagon-like peptide-1 receptor agonists, GLP-1 RAs, metabolic dysfunction-associated steatohepatitis, meta-analysis

Background

Metabolic dysfunction-associated steatohepatitis (MASH), as an advanced form of metabolic-associated fatty liver disease (MAFLD), has become the leading cause of chronic liver disease worldwide.[1,2] Studies indicate that approximately 25% of adults worldwide have MAFLD, with 20–30% progressing to MASH. These patients not only face long-term risks of liver fibrosis, cirrhosis, and hepatocellular carcinoma but also have significantly increased mortality rates from cardiovascular disease and type 2 diabetes mellitus (T2DM).[3–6] Traditional treatment is based on lifestyle interventions, but patient compliance is poor and efficacy is limited. The development of targeted drugs that combine liver protection and metabolic regulation is urgently needed in current clinical research.

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Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as revolutionary drugs for the treatment of T2DM, demonstrating multifaceted benefits beyond glycaemic control in recent years.[7,8] They achieve significant weight loss by activating the hypothalamic appetite centre, while also improving insulin resistance, regulating lipid profiles, and inhibiting inflammatory pathways—actions that precisely target the core pathophysiological mechanisms of MASH.[9–11] Notably, multiple studies have confirmed that obesity and insulin resistance are independent risk factors for the progression of MASH to fibrosis, and GLP-1RAs exert liver protection via both direct and indirect mechanisms. Directly, GLP-1 receptors on hepatocytes and hepatic stellate cells enable GLP-1 RAs to suppress de novo lipogenesis and promote fatty acid oxidation, reducing intrahepatic triglyceride accumulation; they also alleviate oxidative stress.[7–10] Indirectly, beyond improving insulin resistance and weight, GLP-1 RAs modulate the gut-liver axis: they restore gut microbiota balance, strengthen intestinal barrier function, and reduce LPS translocation—thus inhibiting pro-inflammatory cytokines that drive steatohepatitis.[7–10] Clinical studies have further revealed that T2DM patients treated with GLP-1RAs exhibit significant improvements in liver enzyme levels and the degree of fatty liver on imaging, providing theoretical support for exploring their direct anti-MASH effects.[12–14]

Although the mechanism of liver benefits of GLP-1 receptor agonists is highly plausible, there is still no consensus on their direct impact on MASH histological endpoints. Existing clinical trials have insufficient sample sizes and do not focus on fibrosis endpoints; meta-analyses include inconsistent patient populations and lack methodological rigour. Additionally, existing studies vary significantly in inclusion criteria and follow-up periods, making it difficult to establish a unified basis for clinical decision-making.[15,16] Therefore, there is an urgent need to conduct a systematic review to integrate high-quality RCT evidence and clarify the efficacy of GLP-1RAs on MASH.

Methods

Protocol and Registration

We designed and conducted this systematic review and meta-analysis following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) 2020 guidelines.[17] PRISMA Checklist is shown in Supplementary File 1. Table S1. The study protocol was registered with PROSPERO (registration no. CRD420251090801).

Inclusion Criteria

Following the PICOS method, the inclusion criteria were as follows:

- P (Participants): Adult patients (age ≥18 years) diagnosed with metabolic dysfunction-associated steatohepatitis.
- I (Intervention): Patients in the experimental group received glucagon-like peptide-1 receptor agonists as intervention.
- C (Comparison): Patients in the control group only received placebo.
- O (Outcomes): Primary outcomes: Resolution of MASH without worsening of fibrosis: Defined as meeting the pathological criteria of no MASH (per SAF scoring system: Steatosis = 0–1, Activity = 0, Fibrosis unchanged or improved) based on liver biopsy, consistent with the NASH Clinical Research Network (NASH CRN) guidelines. Improvement in fibrosis without worsening of steatohepatitis: Defined as a ≥1-stage reduction in fibrosis (per NASH CRN fibrosis staging system: F0–F4) with no deterioration in steatohepatitis (SAF Activity score unchanged or reduced) via pathological assessment. Secondary outcomes: physiologic parameters (including change in body weight (kg), change in body mass index (BMI) (kg/m^2), change in waist circumference (WC) (cm)); biochemical parameters (including ALT (U/L), AST (U/L), triglyceride (mmol/L), total cholesterol (mmol/L), low-density lipoprotein cholesterol (LDL-C) (mmol/L), high-density lipoprotein cholesterol (HDL-C) (mmol/L)).
- S (Study design): Randomized controlled trials (RCTs).

Exclusion Criteria

The exclusion criteria included: non-human studies (animal experiments), crossover studies, non-randomized methodologies, conference materials without peer-reviewed full texts, and published in languages other than English will be excluded from this systematic review and meta-analysis.

Literature Sources and Retrieval Strategy

To ensure accuracy and completeness, two reviewers (Mei-jun Wang and Yu-nuo Jiang) will independently perform a comprehensive literature search across four databases: PubMed, Web of Science, Embase, and the Cochrane Library. Studies meeting the inclusion criteria were included for analysis. The complete search strategy is detailed in Supplementary File 1. Table S2.

Literature Screening and Data Extraction

To ensure data integrity, two reviewers (Mei-jun Wang and Yu-nuo Jiang) independently conducted literature screening and data extraction in accordance with PRISMA guidelines. Discrepancies were resolved through consensus discussions within the investigative team. Data extraction was performed using a standardized Microsoft Excel form capturing, which included study design, baseline patient information, statistics on resolution of MASH without worsening of fibrosis, improvement in fibrosis without worsening of steatohepatitis; change in body weight, change in body mass index (BMI), change in waist circumference (WC), change in ALT, AST, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol. Studies with incomplete or missing outcome data were excluded to maintain the reliability and accuracy of pooled analyses.

Assessment of Risk of Bias

To ensure methodological rigor, two reviewers (Mei-jun Wang and Yu-nuo Jiang) independently assessed the risk of bias in included RCTs using the Revised Cochrane risk-of-bias tool (ROB 2). The evaluation covered five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurements, and bias in selection of the reported result. Discrepancies were resolved through consensus discussions within the research team.

Statistical Analyses

Data synthesis was performed using the Cochrane Collaboration's Review Manager (RevMan) software (version 5.4). For dichotomous outcomes, pooled risk ratios (RR) with 95% confidence intervals (CI) were calculated using the Mantel-Haenszel method under a random-effects model. For continuous outcomes, mean differences (MD) with 95% CI were pooled via the inverse variance method, also employing a random-effects model. Statistical significance was set at α=0.05 (two-tailed), with $P < 0.05$ considered significant. To address potential heterogeneity across studies, random-effects models were applied for all meta-analyses, accounting for both within-study and between-study variability. Publication bias is assessed only when the number of included studies exceeds 10, as a small number of studies could compromise the robustness of the tests. Additionally, sensitivity analysis of the primary outcome was performed to assess the robustness and reliability of the findings. Finally, subgroup analysis of resolution of MASH without worsening of fibrosis was conducted based on BMI levels.

Trial Sequential Analysis (TSA)

Conventional meta-analyses may yield false-positive results due to random error, particularly when sample sizes are insufficient or repeated testing is performed. To account for these limitations and estimate the required information size (RIS), we conducted Trial Sequential Analysis (TSA) for primary outcomes using TSA software (version 0.9.5.10 Beta). Type 1 error and power were set at 5% and 80%, respectively.

Certainty of Evidence

The certainty of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach through the official GRADEpro online tool.[18] This systematic assessment examined five critical dimensions: study design, risk of bias, imprecision, indirectness, and inconsistency. Based on these criteria, the certainty of evidence for each outcome was classified into one of four levels: high, moderate, low, or very low.

Results

Literature Retrieval Results and Characteristics

Based on the retrieval strategy, 1244 records were retrieved. After the processes of removing duplicates, screening titles and abstracts, 29 studies were retained for full-text screening. Finally, twenty-five RCTs involving 2481 patients were included.[14,19–42] The sample sizes of the included RCTs ranged from 14 to 800. The basic characteristics of the included trials are presented in Supplementary File 1. Table S3. A flowchart of the screening process and results is shown in Figure 1.

Assessment of Risk of Bias

Based on the risk of bias assessment for the 25 included studies, the overall methodological quality was moderate. The plot of the risk of bias among the 25 RCTs is presented in Supplementary File 1. Figure S1.

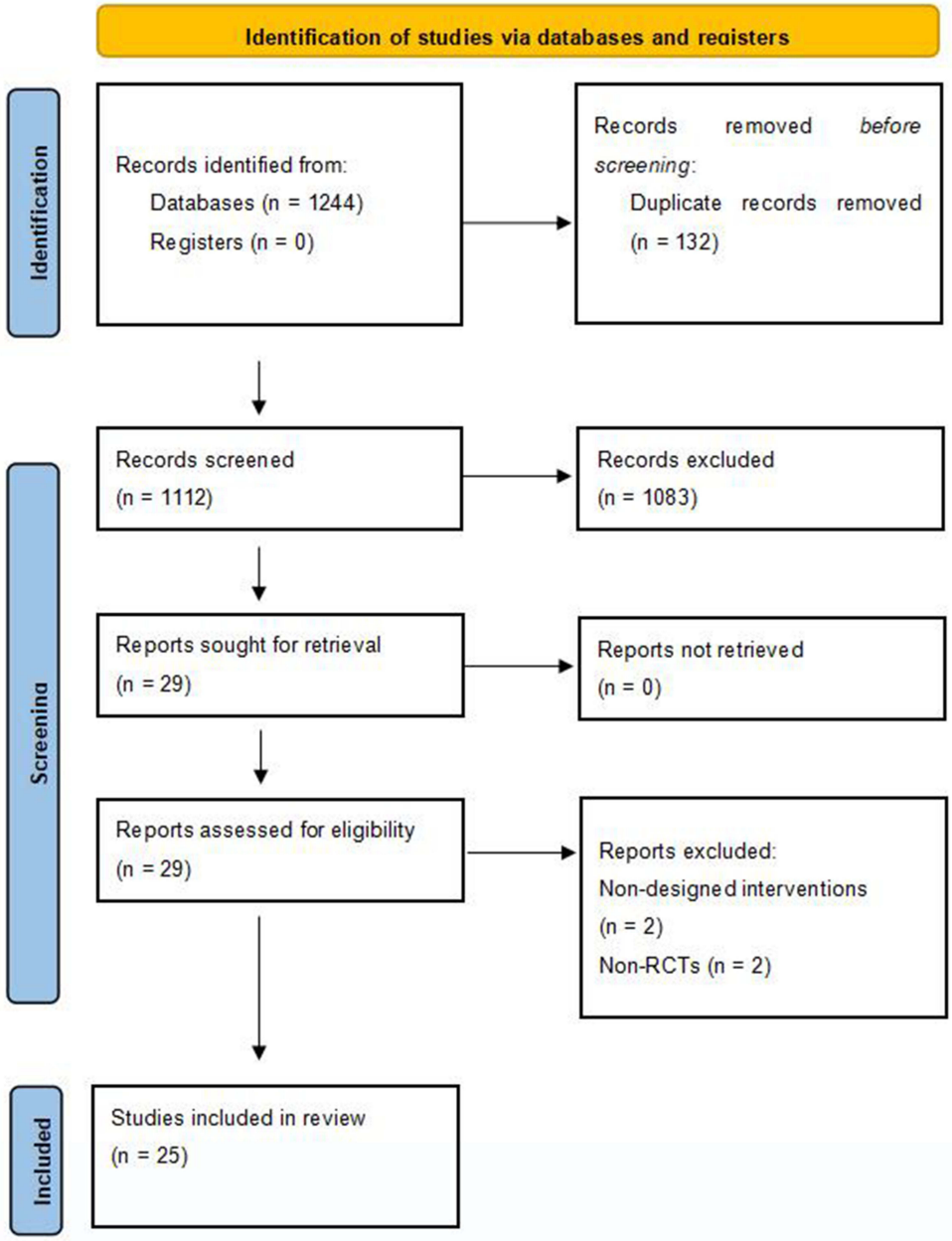

Figure 1 The flowchart of the screening process and results.

Primary Outcomes

Resolution of MASH without Worsening of Fibrosis

Seven RCTs including 1456 patients reported the incidence of resolution of MASH without worsening of fibrosis.[14,21,25,33,34,36,41] Pooled data indicated that GLP-1 RAs in patients with MASH were associated with a higher incidence of resolution of MASH without worsening of fibrosis (OR=4.04; 95% CI, [2.69, 6.05]; P<0.00001; I^2=39%). A forest plot of incidence of resolution of MASH without worsening of fibrosis is shown in Figure 2.

Improvement in Fibrosis without Worsening of Steatohepatitis

Five RCTs including 1277 patients reported improvement in fibrosis without worsening of steatohepatitis.[14,33,34,36,41] Pooled data indicated that there was no statistical significance in improvement in fibrosis without worsening of steatohepatitis between two groups (OR=1.54; 95% CI, [0.95, 2.48]; P=0.08; I^2=58%). The details are shown in Figure 3.

Secondary Outcomes

Physiologic parameters (including change in body weight (kg), change in body mass index (BMI) (kg/m^2), change in waist circumference (WC) (cm)).

Eight RCTs including 523 patients with MASH reported the change in body weight. Eight RCTs including 523 patients with MASH reported the change in BMI. Five RCTs including 215 patients with MASH reported the change in waist circumference. Pooled data indicated that no statistically significant difference in the change of

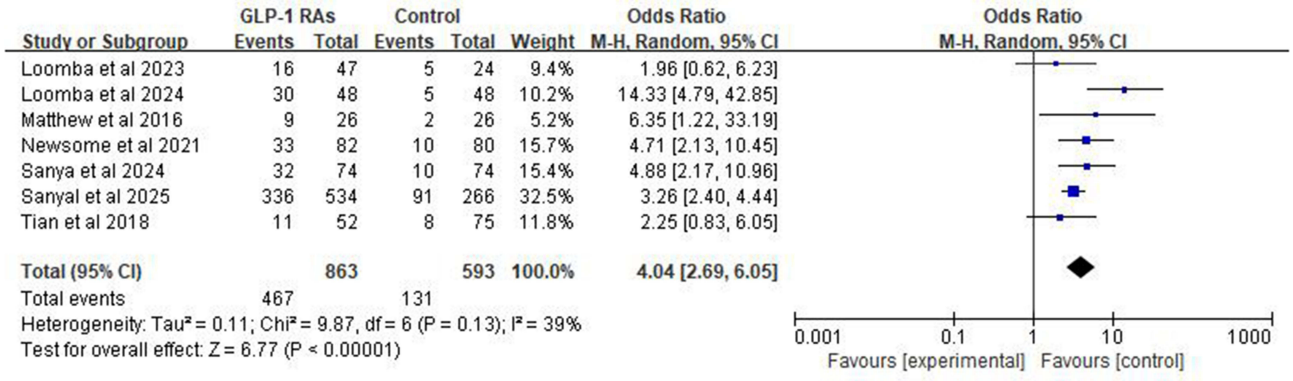

Figure 2 The forest plot of resolution of MASH without worsening of fibrosis. Individual study data are shown as squares (point estimates) with horizontal lines (95% confidence intervals [CIs]). The bolded value (4.04 [2.69, 6.05]) represents the pooled odds ratio using a random-effects model, indicating that GLP-1 receptor agonists significantly increased the odds of MASH resolution without fibrosis worsening compared with control (p < 0.00001). The I^2 value of 39% reflects moderate heterogeneity. The diamond symbol denotes the 95% CI of the pooled estimate.

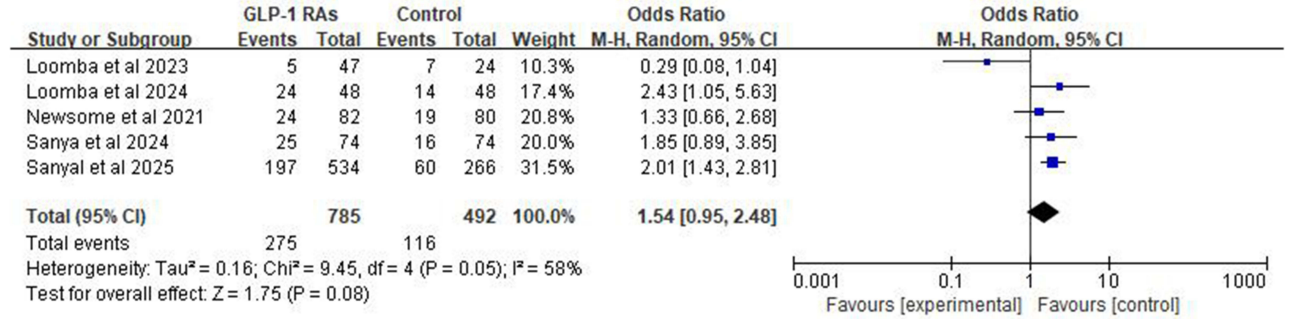

Figure 3 The forest plot of improvement in fibrosis without worsening of steatohepatitis. Individual study data are shown as squares (point estimates) with horizontal lines (95% CIs). The bolded value (1.54 [0.95, 2.48]) represents the pooled odds ratio using a random-effects model, demonstrating a non-significant trend toward fibrosis improvement with GLP-1 receptor agonists versus control (p = 0.08). The I^2 value of 58% indicates substantial heterogeneity. The diamond symbol denotes the 95% CI of the pooled estimate.

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body weight (MD=−1.09 kg; 95% CI, [−2.81, 0.64]; P=0.22; I^2=91%) and waist circumference (MD=−1.95 cm; 95% CI, [−4.26, 0.35]; P=0.10; I^2=74%) between the two groups. GLP-1 RAs in patients with MASH were associated with lower level of BMI (MD=−0.52 kg/m^2; 95% CI, [−1.04, 0.00]; P=0.05; I^2=91%). A forest plot of physiologic parameters is shown in Supplementary File 1. Figure S2.

Biochemical parameters (including ALT (U/L), AST (U/L), triglyceride (mmol/L), total cholesterol (mmol/L), low-density lipoprotein cholesterol (LDL-C) (mmol/L), high-density lipoprotein cholesterol (HDL-C) (mmol/L)).

Eight RCTs including 523 patients with MASH reported changes in ALT and AST. Six RCTs including 469 patients with MASH reported changes in triglyceride. Four RCTs including 288 patients with MASH reported changes in total cholesterol. Six RCTs including 469 patients with MASH reported changes in LDL-C and HDL-C. The pooled data indicated that no statistically significant difference in the changes in ALT (MD=−3.31 U/L; 95% CI, [−11.93, 5.32]; P=0.45; I^2=92%), AST (MD=−1.38 U/L; 95% CI, [−6.39, 3.64]; P=0.59; I^2=90%), triglyceride (MD=−0.12 mmol/L; 95% CI, [−0.47, 0.24]; P=0.51; I^2=67%), total cholesterol (MD=−0.24 mmol/L; 95% CI, [−0.62, 0.14]; P=0.22; I^2=70%), LDL-C (MD=0.04 mmol/L; 95% CI, [−0.1, 0.18]; P=0.6; I^2=10%) and HDL-C (MD=−0.01 mmol/L; 95% CI, [−0.11, 0.09]; P=0.89; I^2=70%) between the two groups. A forest plot of biochemical parameters is shown in Supplementary File 1. Figure S3.

Sensitivity Analysis

Sensitivity analysis was conducted to assess the stability of the primary outcomes. Regarding primary outcomes, the exclusion of individual studies did not influence the overall pooled results. The details are shown in Supplementary File 1. Figures S4 and S5.

Subgroup Analysis

Subgroup analysis was conducted based on different BMI (≥35; <35). Results indicated GLP-1 RAs in patients with MASH was associated with a higher incidence of resolution of MASH without worsening of fibrosis regardless of whether patients had a ≥ 35 (OR=3.27; 95% CI, [2.23, 4.79]; P<0.00001; I^2=13%) or <35 (OR=1.85; 95% CI, [1.55, 2.20]; P<0.00001; I^2=0%). The details are shown in Supplementary File 1. Figure S6.

Trial Sequential Analysis

The RIS of incidence of resolution of MASH without worsening of fibrosis was estimated to be 197 through TSA, and the RIS of improvement in fibrosis without worsening of steatohepatitis was estimated to be 1693, which meant the result of resolution of MASH without worsening of fibrosis was reliable. The details are shown in Figures 4 and 5.

GRADE Summary of Evidence Table for Key Outcomes

We used GRADEpro to evaluate the certainty of the outcomes. Overall, the overall certainty of evidence for this systematic review and meta-analysis was high. The details are summarized in Supplementary File 1. Table S4.

Discussion

This systematic review and meta-analysis integrated 25 randomized controlled trials involving 2481 patients with metabolic dysfunction-associated steatohepatitis, and for the first time confirmed through trial sequential analysis that glucagon-like peptide-1 receptor agonists can significantly improve the probability of patients achieving the histological endpoint of " no fibrosis progression in MASH remission" (OR = 4.04, 95% CI [2.69–6.05]), with high certainty of evidence (GRADE rating). This finding has important clinical implications, as MASH, an advanced form of metabolic-associated fatty liver disease, has become the leading cause of chronic liver disease globally, and the efficacy of traditional lifestyle interventions is often limited by patient adherence. The multi-targeted mechanism of action of GLP-1 RAs—including activation of the hypothalamic appetite centre to reduce body weight, improvement of insulin sensitivity, regulation of lipid metabolism profiles, and inhibition of hepatic inflammatory pathways—directly addresses the core pathophysiological mechanisms of MASH.[43–45] Notably, this histological benefit exhibits a "decoupling phenomenon" from fibrosis improvement: in five studies involving 1277 patients, GLP-1 RAs failed to significantly increase the rate of "fibrosis improvement without worsening of non-alcoholic steatohepatitis" (OR = 1.54, P = 0.08), and

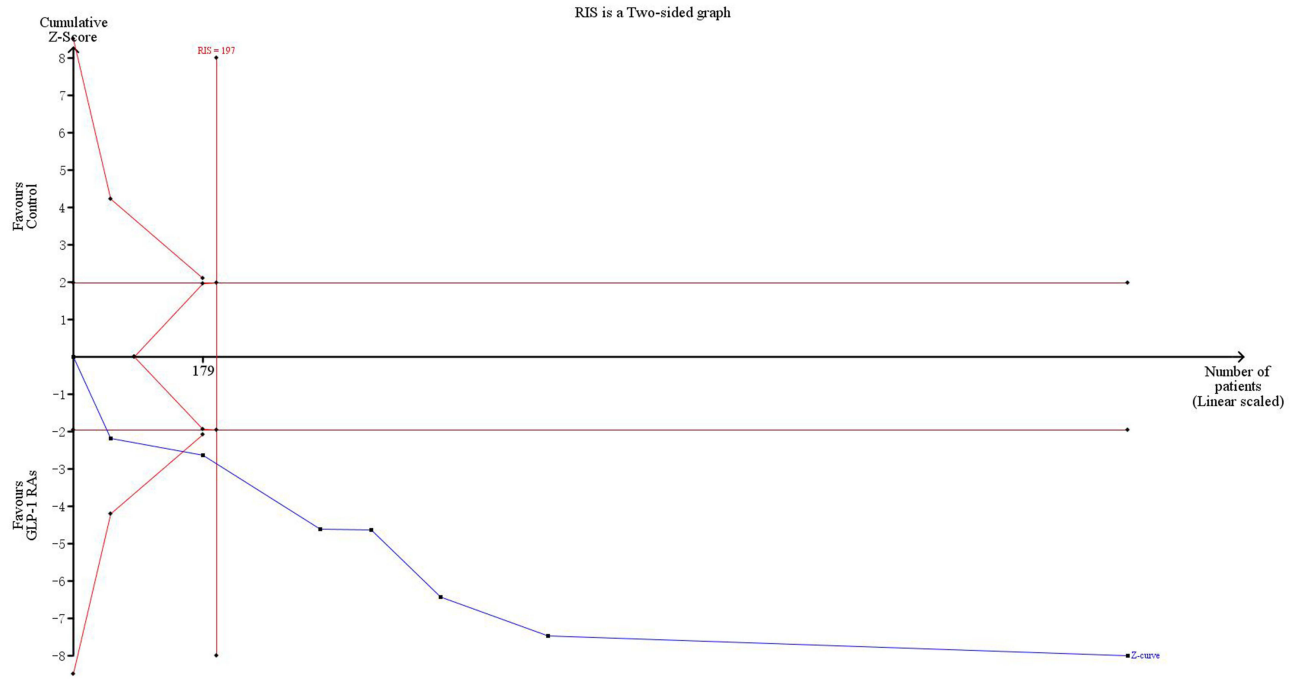

Figure 4 TSA of incidence of resolution of MASH without worsening of fibrosis.

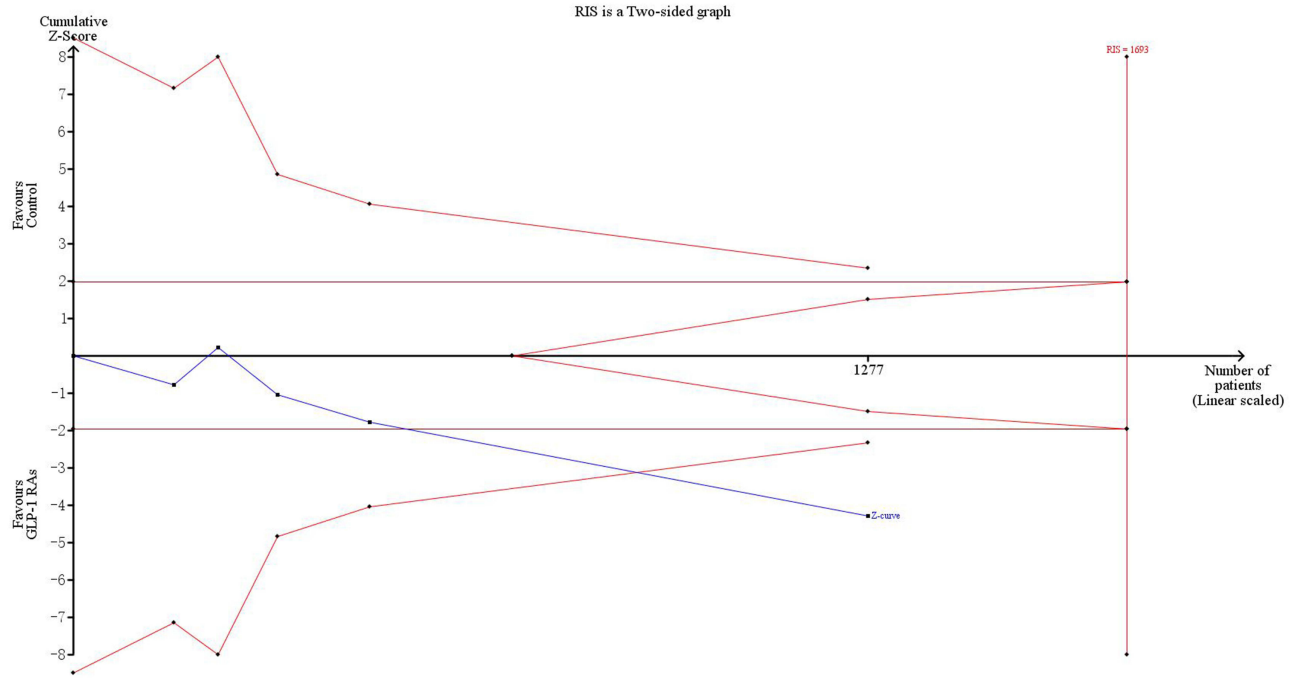

Figure 5 TSA of improvement in fibrosis without worsening of steatohepatitis.

secondary endpoints including liver enzymes (ALT/AST) and lipid parameters also showed no statistically significant changes. This contradictory result suggests that the therapeutic effect of GLP-1 RAs on MASH may primarily be achieved through metabolic regulation rather than direct targeting of hepatic stellate cell activation; it may also reflect that fibrosis reversal requires a longer intervention period, and the treatment duration in the included trials may have been insufficient to capture dynamic changes in fibrosis. Additional factors contributing to this lack of significant fibrosis

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improvement include: GLP-1 RAs act indirectly on fibrosis (by resolving steatohepatitis) rather than directly inhibiting hepatic stellate cell activation— the key driver of fibrosis; most included trials had short follow-up periods, which is insufficient for detecting fibrosis reversal; and liver biopsy sampling error or inconsistent staging systems across studies may have obscured subtle fibrosis changes. These factors, rather than true ineffectiveness, likely explain the null finding for fibrosis.

In terms of clinical application and translation, the results of this study provide important evidence for individualized treatment strategies. For early-stage MASH patients with comorbid obesity (BMI $\geq$ 30 kg/m^2) or type 2 diabetes, GLP-1 receptor agonists (GLP-1 RAs) can be considered as first-line medications to achieve synergistic benefits for both metabolic and hepatic outcomes. The public health implications of this study are particularly noteworthy. The global prevalence of MASH has reached 6.5%, and it is expected to become the leading cause of liver transplantation by 2030. GLP-1 RAs, as drugs already approved for diabetes and obesity, can significantly shorten the research and development cycle.

Although this study provides high-quality evidence through rigorous methodological design, it is important to recognize its limitations. The primary issue is the clinical heterogeneity of the included studies: the patient population included both pure MASH and MASH co-occurring with type 2 diabetes mellitus, which have distinct pathophysiological mechanisms; the intervention drugs encompassed various GLP-1 receptor agonists (from short-acting exenatide to long-acting semaglutide), whose pharmacokinetic properties and tissue distribution differences may influence hepatic exposure concentrations; and the treatment dose range was highly variable. Second, there is significant methodological heterogeneity: liver histological assessments used different scoring systems, and biopsy sampling errors are inevitable More importantly, the trial sequential analysis revealed severe insufficient information regarding the fibrosis improvement endpoint: the actual sample size (n=1277) was far below the required information size (RIS=1693), meaning that the current negative results may be due to insufficient statistical power, leading to Type II errors. Additionally, there is high heterogeneity in the secondary endpoints, suggesting the presence of unmeasured confounding factors, such as dietary compliance and differences in basal metabolic rate, which have not been adequately documented.

In addition, there is a significant lack of race-specific data: the proportion of Asian populations in the included studies is low, and populations from different regions may respond differently to GLP-1 RAs, necessitating the conduct of registration studies targeting this population. Furthermore, a long-term safety monitoring system has not yet been established: while gastrointestinal adverse reactions associated with GLP-1 RAs are well-recognized, data on their potential risks of thyroid C-cell hyperplasia, drug accumulation toxicity in patients with chronic kidney disease, and muscle loss risk (sarcopenia) remain scarce in follow-up periods of $\geq$5 years. This necessitates the development of biomarker-based risk stratification models in future studies.

Conclusions

GLP-1 RAs promote MASH resolution but do not significantly improve fibrosis. Their benefits appear to be driven by metabolic mechanisms rather than direct antifibrotic effects. Larger RCTs targeting fibrosis endpoints are warranted.

Abbreviations

MASH, metabolic dysfunction-associated steatohepatitis; MAFLD, metabolic-associated fatty liver disease; TSA, trial sequential analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs, randomized controlled trials; ROB2, Revised Cochrane risk-of-bias tool; RevMan, Review Manager; RR, risk ratios; CI, confidence intervals; MD, mean difference; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RIS, required information size; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; T2DM, type 2 diabetes mellitus.

Data Sharing Statement

All data and materials related to this systematic review and meta-analysis are available from the corresponding author.

Author Contributions

Mei-jun Wang – Conceptualization, Data curation, Writing – Original draft, Supervision; Yuan-jie Wu – Conceptualization, Writing – Review & Editing; Yu-nuo Jiang – Data curation, Writing – Review & Editing; Pei-pei Li – Visualization,

Writing – Review & Editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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