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Clinical Assessment of Common Medications for Nonalcoholic Fatty Liver Disease: A Systematic Review and Bayesian Network Meta-Analysis

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ABSTRACT

Objective: With a steadily rising prevalence, nonalcoholic fatty liver disease (NAFLD) was a leading global cause of liver-related health problems. In the clinical management of NAFLD, various western pharmaceuticals were widely utilized. This network meta-analysis aimed to evaluate the effectiveness of common western medications for NAFLD patients.

Methods: We systematically reviewed and screened articles based on predesigned criterion about western medications for NAFLD, which were from Embase, Cochrane Library, PubMed, CNKI, WanFang, and China Science and Technology Journal Database until August 1, 2024. Eligible studies included randomized controlled trials of patients aged 18 or older with NAFLD, comparing Western medicines to placebos or other Western medicine treatments. The risk of bias assessment tool 2.0 from the Cochrane system was used to assess the quality of the included articles. A Bayesian network meta-analysis was conducted using WinBUGS 1.4.3 with a random-effects model and Markov Chain Monte Carlo methods. Treatment rankings were based on Surface Under the Cumulative Ranking Curve (SUCRA) values, and heterogeneity was assessed with I^2 and Q statistics. The outcomes were analyzed in WinBUGS and visualized using Stata 14.0, generating network plots and cumulative probability rankings to compare treatment effects. The systematic review was registered in PROSPERO (CRD42024509176).

Results: Based on 37 included articles involving 7673 patients, pioglitazone demonstrated the most significant effects in resolving nonalcoholic steatohepatitis without worsening fibrosis, increasing high-density lipoprotein cholesterol levels, and achieving a $\geq$ 2-point reduction in NAFLD activity scores (odds ratio [OR] = 0.09, 95% confidence interval [CI]: 0.01 to 0.81), with a SUCRA probability of 91.4%. Aldafermin showed remarkable effects in improving liver function markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transpeptidase, with cumulative probabilities of 90% for ALT and 69.8% for AST. Cluster analysis revealed that Resmetirom and Aldafermin were superior options for enhancing liver function, while pioglitazone emerged as the best treatment for the comprehensive improvement of NAFLD.

Conclusions: Pioglitazone outperformed other western medicines in terms of overall efficacy when treating NAFLD, but Aldafermin and Resmetirom showed superior improvement in liver function. This study provided a certain level of support for the use of specific clinical medications.

Rui Shi and Keyan Chai contributed equally to this work.

1 | Introduction

Nonalcoholic fatty liver disease (NAFLD) was a metabolic disorder primarily characterized by lipid accumulation in the liver [1]. In its early stages, NAFLD presented as simple fatty liver, marked by steatosis without inflammation. As the disease progresses, it might advance to nonalcoholic steatohepatitis (NASH), which was characterized by hepatocyte swelling and lobular inflammation, along with other signs of liver cell damage. In severe cases, NASH could further progress to cirrhosis or even terminal-stage hepatocellular carcinoma, which could be fatal [2–4]. One study estimated that NAFLD affected approximately 25% of the global population, with China exhibiting a prevalence rate of 25% and an annual growth rate of 0.60%, making it the country with the fastest-growing NAFLD prevalence [5]. The high prevalence of NAFLD was mainly attributed to the rise in metabolic risk factors, such as obesity, type 2 diabetes, and dyslipidemia [6].

Pioglitazone, metformin, liraglutide, and vitamin E were first-line treatments for NAFLD, shown to reduce liver inflammation, mitigate fat accumulation in the liver, and lower transaminase levels [7]. However, there were ongoing debates and concerns about their efficacy. To make optimal pharmaceutical decisions tailored to each patient, clinicians must consider a wide range of research. Bayesian network meta-analysis was a statistical approach that combined direct and indirect evidence to evaluate the relative effectiveness of multiple interventions. This method integrated prior knowledge with observed data, allowing for the ranking of treatments and providing credible intervals to reflect uncertainty in decision-making. Network meta-analysis of existing data could be utilized to determine the relative benefits and comparative effectiveness of these therapies, providing a comprehensive summary of available evidence. This study aimed to conduct a systematic review and network meta-analysis to evaluate the efficacy of commonly used Western medications in improving NAFLD activity score (NAS) and NASH, reducing levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), and low-density lipoprotein cholesterol (LDL-C), and increasing high-density lipoprotein cholesterol (HDL-C) in NAFLD patients. The findings would offer evidence-based support to guide rational drug use in clinical practice.

2 | Methods

The network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the PRISMA statement [8]. The systematic review was registered in PROSPERO (CRD42024509176).

2.1 | Search Strategy

A comprehensive search was conducted across the PubMed, Embase, Cochrane Library, CNKI, WanFang and China Science and Technology Journal Database (VIP) databases from their inception to August 1, 2024. The Population, Intervention, Comparison, Outcomes and Study type (PICOS) principle was applied, using a combination of MeSH terms (e.g., nonalcoholic fatty liver disease) or Emtree terms (e.g., nonalcoholic) and relevant free-text terms (e.g., fatty or liver). Detailed search strategies for each database were provided in Supplementary Material 1.

2.2 | Inclusion Criteria

2.2.1 | Participants

We included articles that enrolled adult patients aged 18 years or older diagnosed with NAFLD.

2.2.2 | Interventions and Comparators

We included studies where patients in the trial group were treated with Western medicines, while the control groups received either a placebo or other Western medicine treatments.

2.2.3 | Outcome Assessments

The primary outcome was defined as a $\geq$ 2-point decrease in the NAS and the resolution of NASH without worsening fibrosis. Secondary outcomes included the improvements in ALT, AST, GGT, HDL-C, and LDL-C levels. The NAS, detailed in the NASH Clinical Research Network (CRN) scoring system [9], was assessed on a scale from 0 to 8 points, representing the unweighted sum of individual scores for features such as steatosis, lobular inflammation, and hepatocellular swelling. The primary outcome was established based on current recommendations for clinical trial endpoints in NASH. NASH resolution was defined as the disappearance of hepatocellular swelling (score of 0) and either the disappearance or mild persistence of lobular inflammation (score of 0 or 1). Improvement in fibrosis was defined as a reduction in the lowest stage of fibrosis score [10, 11].

2.2.4 | Type of Studies

The studies included randomized controlled trials (RCTs) employing single-blind or double-blind methods.

2.3 | Exclusion Criteria

The following types of studies were excluded: (1) conference abstracts, editorials, letters, or statements; (2) review articles; (3) animal or in vitro studies; (4) studies where western medicines were used in background treatment plans; (5) studies with incomplete data or data that could not be extracted; (6) studies not employing blinding; (7) studies that compared the combined use of multiple western medicines or employed Chinese medicine.

2.4 | Data Extraction

Literature screening and data extraction were independently performed by two researchers (RS and KYC). The extracted data aligned with the research objectives and encompassed basic information (first author's name, year of publication, sample size, and baseline average age), clinical trial information

with interventions, basic treatment regimen, study duration, and outcome measures. During the data extraction process, the researchers utilized a standardized data extraction form to ensure consistency and accuracy of the information. First, all relevant literature underwent rigorous screening to ensure they met the inclusion criteria. Throughout the extraction process, researchers meticulously recorded the basic characteristics of each study. Additionally, a dual data extraction method was employed to minimize human error: one researcher extracted the data, while another researcher reviewed and verified it. Any disputes that arose during the extraction process were resolved through team discussions to reach a consensus. Furthermore, reference management software EndNote was used for organizing and managing the literature to ensure the completeness and traceability of all information. Ultimately, all extracted data were recorded in tables to facilitate subsequent statistical analyses and comparisons of results.

2.5 | Quality Assessment

The risk of bias in the included literature was also independently evaluated by two reviewers (RS and HJW) using the revised Cochrane Risk of Bias Assessment Tool 2.0 [12]. This tool encompassed five domains, each with three risk assessments: "high risk," "low risk," and "some concerns." Any discrepancies during this process were resolved through discussion or consultation with a third reviewer (JRW).

2.6 | Statistical Analysis

We analyzed the data using WinBUGS 1.4.3 software and Bayesian inference Markov chain Monte Carlo (MCMC) with a random-effect model method. The odds ratio (OR) and mean difference (MD) with the 95% confidence intervals (CIs) were calculated for binary and continuous outcomes respectively. When 95% CIs of OR did not cover 1 or 95% CIs of MD did not contain 0, differences between the groups were considered statistically significant.

Results obtained from WinBUGS 1.4.3 were imported into Stata 14.0 software to rank the interventions outcomes and generate cumulative probability ranking plots. The following steps outline the procedures and configurations used in Stata 14.0: (1) importing data: the output files from WinBUGS, including model estimates and posterior distributions, were imported into Stata using the import delimited command; (2) ranking interventions: we ranked the intervention outcomes based on the Surface Under the Cumulative Ranking Curve (SUCRA) values calculated from the posterior distributions; (3) cumulative probability ranking plots: the command two way (line) was utilized to create cumulative probability ranking plots, visualizing the probabilities of each intervention being the most effective; (4) SUCRA calculation: the SUCRA value was calculated using a custom script that summed the probabilities of each intervention across all comparisons, then expressed as a percentage with 100% indicating absolute effectiveness and 0% indicating ineffectiveness; (5) clustering analysis: we performed clustering analysis based on SUCRA values using the cluster command in Stata, with two clustering indicators—Euclidean distance and ward's method—applied to identify the relatively optimal intervention; (6) visualization: we generated network plots, funnel plots, forest plots, and contribution plots to compare the different interventions related to outcome indicators using commands such as network plots, funnel, and cluster plots. Heterogeneity and inconsistency were assessed using I^2 statistics and Q statistics. A comparison-adjusted funnel plot was generated to detect small sample effects or publication bias, with its symmetry indicating the absence of biases.

3 | Results

3.1 | Literature Search

Following the predefined search strategy, a total of 6329 articles were initially retrieved. After excluding duplicate publications, nonclinical trial articles, and irrelevant articles, a total of 4147 articles were carefully reviewed for further screening and exclusion. Ultimately, 37 literature [13–46], comprising 7673 patients, were selected for inclusion after a thorough review of full texts and the exclusion of studies that did not meet the inclusion criteria. Figure 1 illustrates the systematic search process.

3.2 | Study Characteristics

A total of 37 studies, encompassing 28 medications (Table S1) and 7673 patients, were included. The average age of these patients was 50.44 years, with approximately 46.90% being male. Two studies used vitamin E as the control, while the treatment groups received either ursodeoxycholic acid or cetilistat. In other studies, control groups were given a placebo or a different dosage of the medication compared to the treatment groups. All medications were administered orally, and the total treatment duration ranged from 12 to 74 weeks. Among the included studies, 45% reported a $\geq$ 2-point decrease in the NAS, 40% reported NASH resolution without worsening fibrosis, 56.41% reported changes in ALT and AST levels, 30.77% reported changes in GGT levels, and 33.34% reported changes in HDL-C and LDL-C levels. Detailed information about the included studies could be found in Table S2.

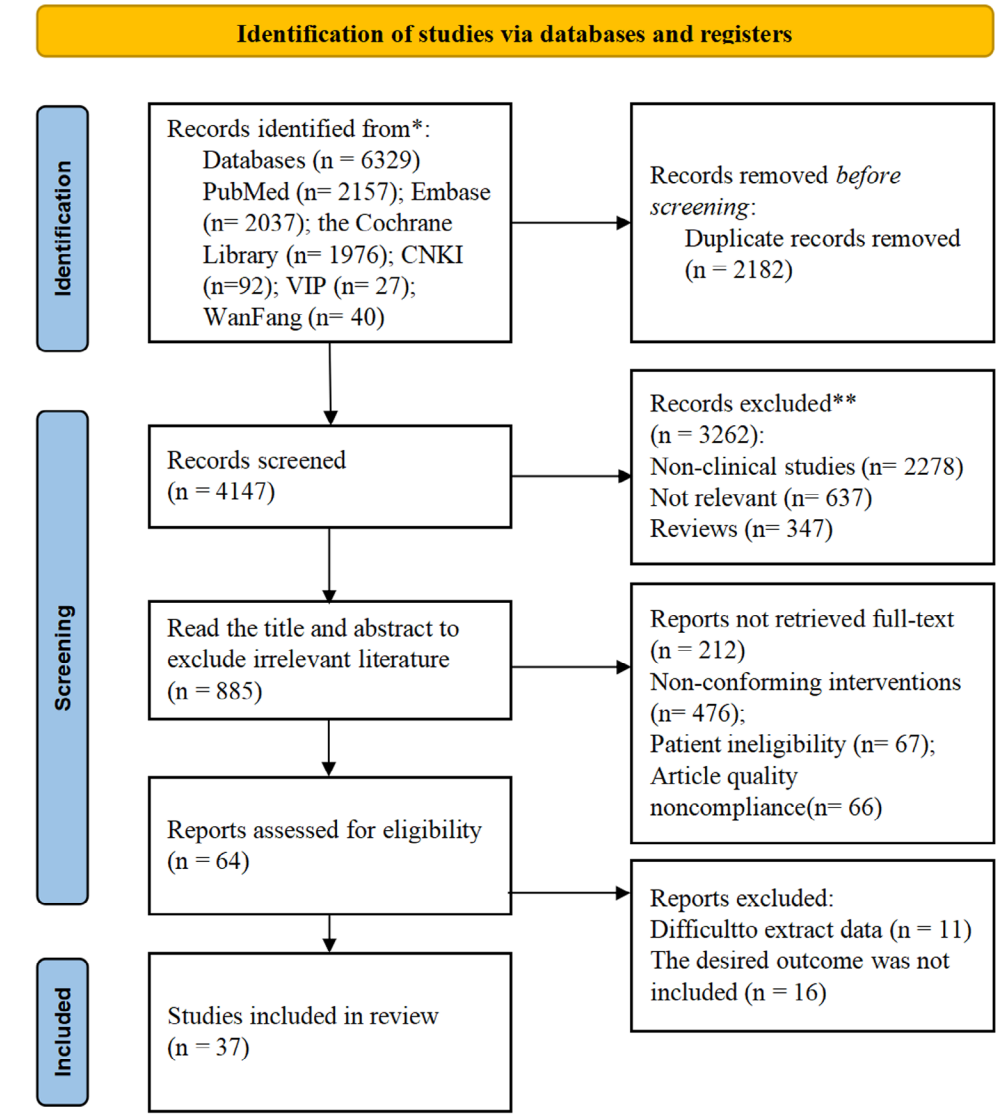
3.3 | Quality Assessment

Among the 37 included studies, 32 employed random sequence generation methods, such as random number tables, demonstrating a "low risk" of bias in the randomization process. Five studies were labeled as "random" without specifying the method, resulting in a "some concerns" rating. No studies allowed for the selection of results from multiple outcomes, contributing to a low reported bias. Despite the absence of some patients, the articles consistently provided evidence indicating that the stability of the outcomes was not affected. Therefore, the assessment of missing outcome data was at a "low risk." Figure S1 illustrates the results of the risk of bias assessment.

3.4 | Network Plots of Treatment Results

The network plots for each outcome were illustrated in Figure 2. The results clearly revealed the presence of closed-loop structures

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

FIGURE 1 | Flow chart of the eligible studies selection process.

in the networks constructed for key indicators such as ALT, AST, HDL-C, and LDL-C. This indicated that direct pairwise comparisons could be made among various Western medicines, providing a solid basis for accurately evaluating the therapeutic differences between these treatments. In contrast, the remaining outcome measures predominantly reflected a comparison between placebo and various Western medicines, which helped to assess the actual efficacy of these treatments relative to placebo. Notably, the connections corresponding to simtuzumab, n-3 PUFAs (omega-3 polyunsaturated fatty acids), and semaglutide were visibly thicker in the network plots, intuitively indicating a considerable volume of research surrounding these drugs, thereby highlighting their prominence and significant attention within the current research landscape.

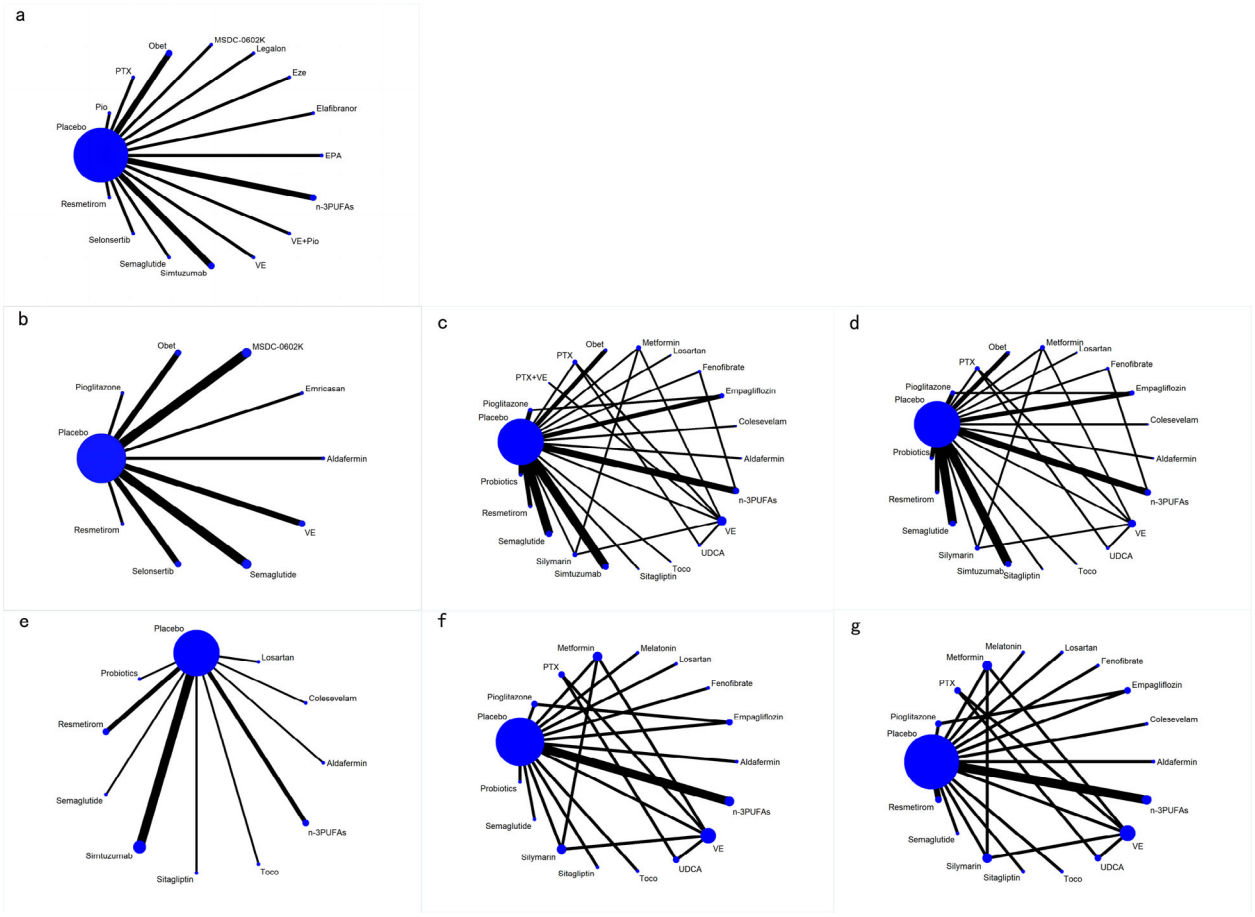


FIGURE 2 | Summary of network plots for outcomes. (a) ≥ 2-point decrease in NAS. (b) NASH resolution without worsening fibrosis. (c) Network plot of ALT level outcome. (d) Network plot of AST outcome. (e) Network plot of GGT level outcome. (f) Network plot of HDL-C level outcome. (g) Network plot of LDL-C level outcome. The size of each node represents the cumulative patient counts for each intervention across all included studies, while the thickness of the lines reflects the number of studies directly comparing the two treatments. NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

3.5 | SUCRA Ranking Plots for Each Outcome

The SUCRA ranking plots were illustrated in Figure 3, with detailed SUCRA ranking values for each outcome presented in Table S3. The cumulative probability indicated that for NAS ≥ 2, Pioglitazone accounted for 91.4%, and for the resolution of NASH without worsening fibrosis, it reached 94.1%, ranking first in both outcomes. In terms of liver function indicators, Aldafermin ranked highest, showing improvements in ALT (90.0%) and AST (69.8%) levels. For HDL-C improvement, Pioglitazone accounted for 83.1%, while Pentoxifylline accounted for 88.5% in LDL-C improvement.

3.6 | Network Meta-Analysis Results

The results of the network meta-analysis showed that for the primary outcome of NAS ≥ 2, a total of 18 studies involving 14 drugs were included. The analysis demonstrated that Pioglitazone (OR = 0.09, 95% CI: 0.01 to 0.81) significantly improved NAS scores compared to placebo. Other drugs, such as Vitamin E + Pioglitazone (OR = 0.18, 95% CI: 0.02 to 1.48) and Pentoxifylline (OR = 0.28, 95% CI: 0.02 to 1.97), showed favorable effects but without statistical significance. For the outcome of resolution of NASH without worsening fibrosis, results from nine drugs demonstrated that Pioglitazone (OR = 0.13, 95% CI: 0.03 to 0.44), Vitamin E (OR = 0.21, 95% CI: 0.09 to 0.49), and Semaglutide (OR = 0.26, 95% CI: 0.15 to 0.46) exhibited the best effects, while the remaining drugs showed no statistically significant results. Regarding the secondary outcome, Pentoxifylline (MD = −36.62, 95% CI: −97.97 to −4.41) was identified as the most effective option for LDL-C improvement, whereas other drugs demonstrated neither statistically significant effects nor proved to be optimal therapeutic agents. The OR and MD values for each outcome were summarized in Figures 4 and 5 and Table S4.

3.7 | Cluster Analysis

This study selected data that reported both improvement in NAS score and resolution of NASH, using cluster analysis to evaluate the most effective treatment regimen for NAFLD. The

FIGURE 3 | Summary of SUCRA ranking plots for outcomes. (a) ≥ 2-point decrease in NAS. (b) NASH resolution without worsening fibrosis. (c) SUCRA ranking plots for ALT outcome. (d) SUCRA ranking plots for AST outcome. (e) SUCRA ranking plots for GGT outcome. (f) SUCRA ranking plots for HDL-C outcome. (g) SUCRA ranking plots for LDL-C outcome. NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; SUCRA, surface under the cumulative ranking curve; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

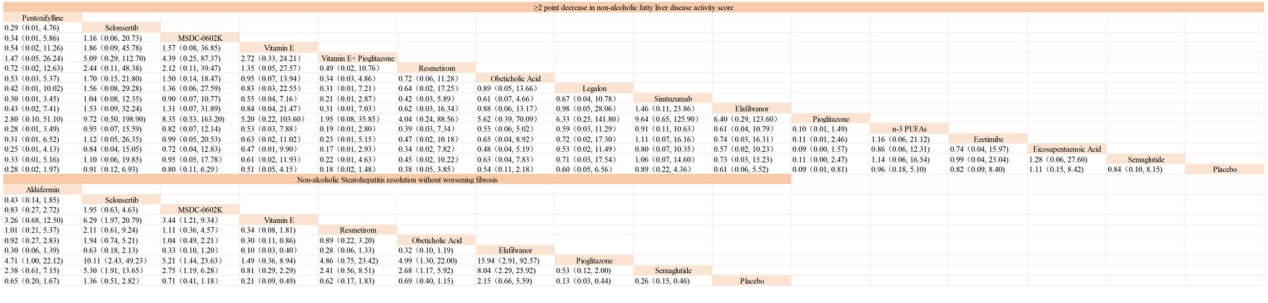


FIGURE 4 | Summary of network meta-analysis results for primary outcomes. n-3PUFAs, omega-3 polyunsaturated fatty acids.

results indicated that the Pioglitazone regimen, being the farthest from the zero point, emerged as the optimal strategy in both dimensions, followed by the Vitamin E and Resmetirom regimens (Figure 6a). For secondary outcomes, this study focused on data reporting improvements in both ALT and AST levels. The results indicated that, in terms of enhancing liver function, the Aldafermin and Resmetirom regimens, which showed equal effectiveness, were the optimal strategies, followed by the Sitagliptin regimen (Figure 6b).

3.8 | Publication Bias

Funnel plots for outcomes were generated using STATA 14.0 software to assess potential publication bias. Visual inspection of asymmetry showed that the effect points in the literature were generally symmetrical, indicating good symmetry in the funnel plots for the primary outcome indicators. This suggested high quality among the included studies, minimal publication bias, and relatively reliable results. Funnel plots for other outcome

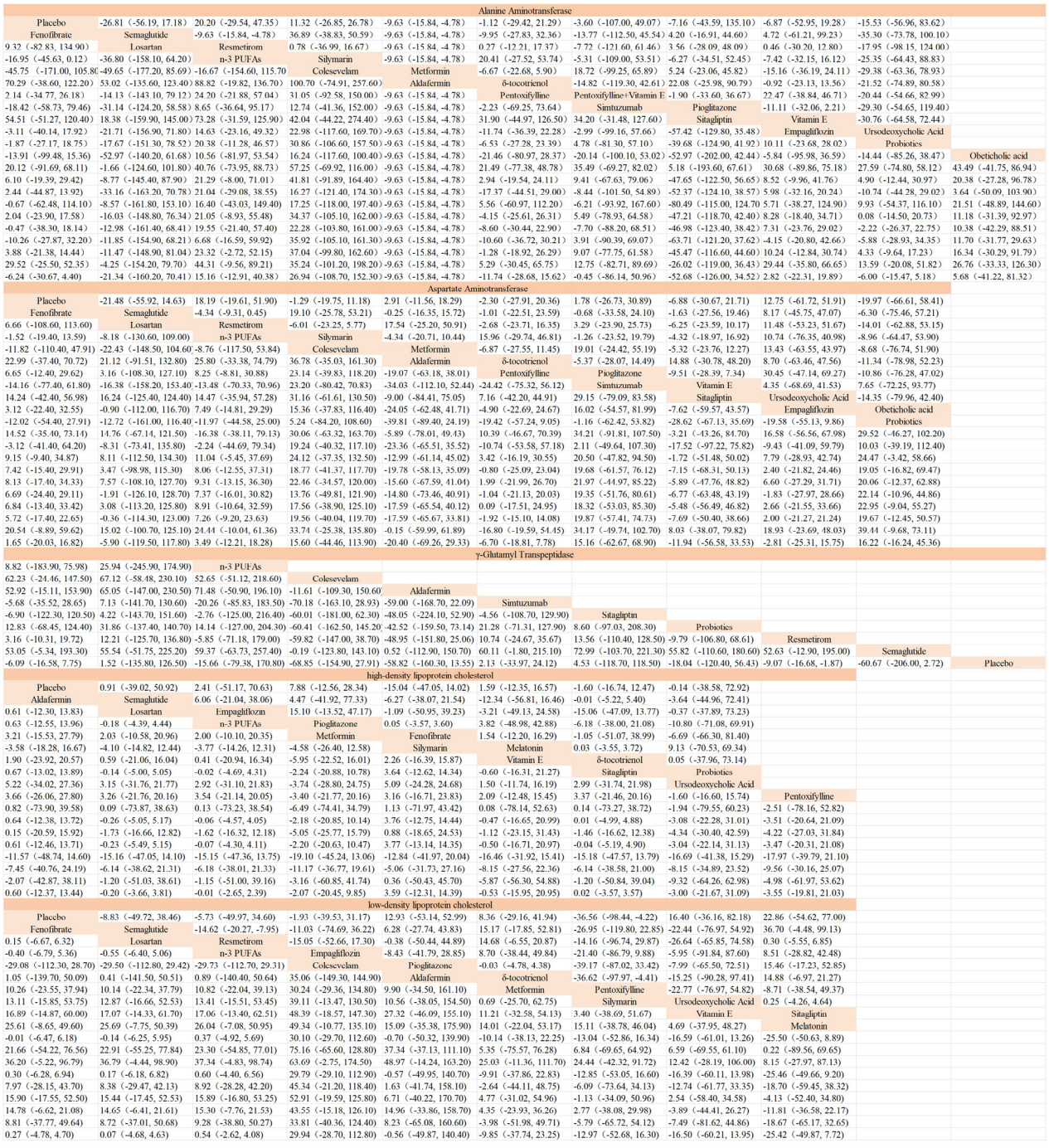


FIGURE 5 | Summary of network meta-analysis results for secondary outcomes. n-3PUFAs, omega-3 polyunsaturated fatty acids.

indicators also demonstrated good symmetry. However, the funnel plots for HDL-C and LDL-C showed some asymmetry, which might be attributed to small sample sizes and a lack of attention to negative study results (Figure S2).

4 | Discussion

As overnutrition and sedentary lifestyles have become prevalent, NAFLD has emerged as the most common chronic liver disease worldwide, placing a significant burden on human health. Closely associated with Type 2 Diabetes Mellitus (T2DM) and Metabolic Syndrome (MetS), NAFLD is a metabolic illness characterized by multi-system involvement. T2DM and MetS increase the risks of cirrhosis, hepatocellular carcinoma, coronary artery disease, chronic kidney disease, and colorectal tumors [47–51]. Recognizing these links, the American Association for the Study of Liver Diseases (AASLD) and other organizations have suggested replacing the term NAFLD with Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) and NASH with Metabolic Associated Steatohepatitis (MASH). Clinically, elevations in ALT and AST are often accompanied by liver function abnormalities and fibrosis changes. Therefore, the primary treatment goal for NAFLD is to resolve the condition

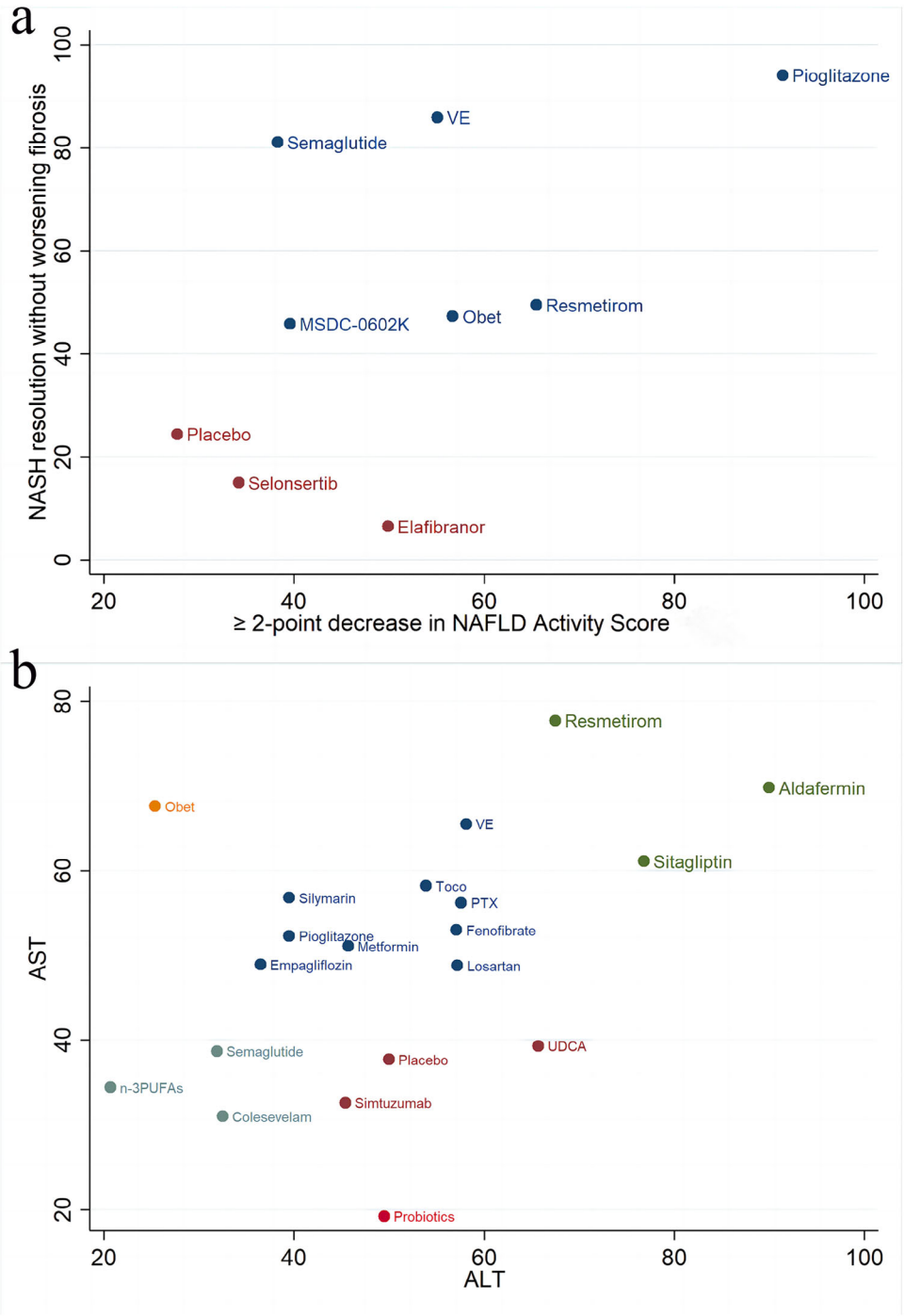


FIGURE 6 | Summary of two-dimensional graphs. (a) Two-dimensional graph about NAS score improvement and NASH resolution. The *x*-axis represented a ≥ 2-point decrease in the nonalcoholic fatty liver disease activity score, while the *y*-axis represented NASH resolution without worsening fibrosis; (b) Two-dimensional graph about AST and ALT levels improvement. The *x*-axis represented ALT levels, while the *y*-axis represented AST levels. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; VE, vitamin E; Obet, obeticholic acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; n-3PUFAs, omega-3 polyunsaturated fatty acids; Toco, δ-tocotrienol; PTX, pentoxifylline; UDCA, ursodeoxycholic acid.

without worsening fibrosis. The American NASH Clinical Research Network recommends using the NAS scoring system, defined as a reduction of ≥ 2 points in NAS and resolution of NASH without fibrosis progression [52, 53]. To evaluate the benefits of various interventions and support clinical decision-making, this study compared the effects of different drugs on these parameters.

Currently, no medications are specifically licensed for the treatment of NAFLD, as noted in the 2023 AASLD practice guideline on the clinical assessment and management of NAFLD. Instead, medications targeting related comorbidities—such as those promoting weight loss, lowering blood sugar, and reducing cholesterol levels—are commonly used in clinical practice. To provide evidence-based recommendations for clinical treatment,

this article conducted a network meta-analysis on commonly used medications for NAFLD. The findings revealed that Pioglitazone outperformed other pharmacological options in terms of overall therapeutic outcomes, particularly in improving NAS scores and resolving NASH without worsening fibrosis. Based on SUCRA rankings, OR/MD values, and cluster analysis results, Pioglitazone demonstrated outstanding performance across the primary outcomes, showing the best therapeutic effects. Vitamin E also exhibited notable efficacy in resolving NASH without worsening fibrosis. For liver function markers, Aldafermin showed favorable results in both cluster analysis and SUCRA rankings. The high heterogeneity in some indicators, combined with funnel plots, article characteristics, and methodological considerations, suggested that variability might have been due to clinical diversity among studies, differences in treatment duration, sample sizes, study designs, or a greater likelihood of positive results being published. This study was also limited by significant heterogeneity among the included studies.

Pioglitazone, classified as a thiazolidinedione, primarily exerts its therapeutic effects by activating peroxisome proliferator-activated receptor gamma. While its efficacy in managing type 2 diabetes mellitus is well established, its application has expanded to the treatment of NAFLD and the more severe NASH. Compared to other pharmaceutical interventions, pioglitazone offers several distinct advantages in NAFLD treatment: (1) Reduction of insulin resistance: pioglitazone enhances insulin sensitivity in peripheral tissues, which significantly reduces insulin resistance—a fundamental pathological mechanism underlying NAFLD. As insulin resistance is prevalent among NAFLD patients, pioglitazone effectively addresses this core issue [54]. (2) Reduction in hepatic fat accumulation: pioglitazone improves lipid metabolism and reduces hepatic fat content. Studies have demonstrated its efficacy in mitigating hepatic steatosis by activating PPAR-γ, promoting adipocyte differentiation, increasing the number of smaller adipocytes, enhancing insulin responsiveness, and facilitating glucose uptake. Consequently, this process limits excess energy storage in adipose tissue, thereby reducing hepatic fat accumulation and inflammation [55]. (3) Mitigation of liver inflammation and fibrosis: pioglitazone has demonstrated efficacy in reducing hepatic inflammation and decelerating the progression of fibrosis in NAFLD patients, particularly those with NASH. Compared to other therapeutic options, pioglitazone is more effective in improving liver histology and delaying the development of fibrosis [56]. (4) Efficacy in nondiabetic NAFLD patients: although primarily prescribed for diabetic individuals, evidence suggests that pioglitazone also confers benefits to nondiabetic NAFLD patients, particularly in improving hepatic function. Studies indicate similar histopathological improvements in both diabetic and nondiabetic NAFLD patients [55].

A study had investigated the mechanisms by which silymarin's main component, silybin, exhibits protective effects against NAFLD [57]. These studies demonstrated that silybin reduced liver enzyme levels (ALT, AST) and lipid levels (TC, TG, HDL-C, LDL-C), and lowers the expression of pro-inflammatory and pro-apoptotic proteins such as IL-6, MAPK1, Caspase 3, p53, and VEGFA, while increasing the expression of the protective protein AKT1. These findings highlighted the hepatoprotective role of silybin, which aligned closely with the outcome indicators considered in this study, such as ALT, AST, and lipid markers. The consistency between silybin's demonstrated mechanisms and our chosen endpoints strengthened the conclusions drawn from this study, underscoring the clinical relevance of our findings. Furthermore, the alignment with previous mechanistic insights added robustness to our conclusions, suggesting that silybin's effects could translate effectively into therapeutic outcomes for patients with NAFLD [57].

In the pharmacological treatment and drug development for NAFLD, as clinical research progressed, an increasing number of clinical trials began to emphasize drug safety, which could become a key factor for the future approval of these drugs for NASH treatment. Particularly in this study, pioglitazone showed significant improvements in NAS scores and resolution of NASH without worsening fibrosis, demonstrating its effectiveness and safety in treating NAFLD. This provides important reference for future drug safety assessments in NAFLD drug development [58]. Previous studies have highlighted several key aspects in the development of NAFLD drugs: first, patient stratification is crucial for selecting the most effective treatment drugs. Given the varying effects of different drugs on clinical outcomes, especially in secondary outcomes such as liver function improvement (e.g., Aldafermin's significant impact on liver function markers), rational stratification based on patients' pathological characteristics is essential for improving treatment precision. Second, determining the optimal intervention timing is key to treatment success. Because the progression of NAFLD and patients' clinical characteristics vary significantly, early intervention may yield better results in inhibiting liver fibrosis, which aligns with the improvements seen in primary outcomes in this study. Additionally, the development of clinical biomarkers to predict treatment response can help personalize treatment. For example, the network meta-analysis conducted in this study provided clinical decision-making support, particularly when recommending pioglitazone as the first-line therapy, with clinical biomarkers like NAS and prominent indicators guiding treatment choices. Finally, evaluating the long-term benefits of drugs is especially important, particularly considering that some drugs, despite being ineffective in significantly improving liver fibrosis, may still exert important effects on long-term patient prognosis by improving secondary outcomes such as liver function. Aldafermin better performance in improving liver function highlights that, in treatment, we should not only focus on improving fibrosis but also give importance to the overall improvement of liver function [50].

The field of direct treatment comparisons in NAFLD was notably scarce, with most available evidence primarily derived from comparisons between pharmacological interventions and placebos, which relied heavily on the indirect evidence from network meta-analysis. In this study, some outcome indicators showed high heterogeneity and potential publication bias, suggesting the need for caution in interpreting the results. Although changes in HDL-C and LDL-C were observed, further high-quality clinical trial data were required to ensure more robust and reliable conclusions. Despite these limitations, this study provided the most comprehensive evidence base to date, offering important guidance for clinicians in selecting pharmacological treatments for adults with NAFLD, with pioglitazone recommended as the preferred drug due to its outstanding efficacy in primary outcome measures. It is worth noting that while this study provided valuable insights for clinical decision-making, ongoing

research and further validation remain critical to strengthening the evidence base for clinical decisions and refining treatment strategies for NAFLD.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.