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Systematic review with network meta-analysis: comparative efficacy of pharmacologic therapies for fibrosis improvement and resolution of NASH

Abdul M. Majzoub[1] | Tarek Nayfeh[2] | Abbey Barnard[3] | Nagambika Munaganuru[3] | Shravan Dave[3] | Siddharth Singh[3] | Mohammad Hassan Murad[2] | Rohit Loomba[3]

[1]Division of Internal Medicine, Conemaugh Memorial Medical Center, Johnstown, Pennsylvania, USA

[2]Evidence-Based Practice Center, Mayo Clinic, Rochester, Minnesota, USA

[3]NAFLD Research Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of California at San Diego, San Diego, California, USA

Correspondence
Rohit Loomba, ACTRI Building, 1W202, 9452 Medical Center Drive La Jolla, CA 92037, USA.
Email: roloomba@ucsd.edu

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Summary

Background: Nonalcoholic steatohepatitis (NASH) is a common cause of chronic liver disease. There is a major need to understand the efficacy of different pharmacological agents for the treatment of NASH.

Aim: To assess the relative rank-order of different pharmacological interventions in fibrosis improvement and NASH resolution.

Methods: A comprehensive search of several databases was conducted by an experienced librarian. We included randomised controlled-trials (RCTs) comparing pharmacological interventions in patients with biopsy-proven NASH. The primary outcome was ≥1 stage improvement in fibrosis. The secondary outcome was NASH resolution.

Results: A total of 26 RCTs with 23 interventions met the eligibility criteria. Lanifibranor and obeticholic acid had the highest probability of being ranked the most effective intervention for achieving ≥1 stage of fibrosis improvement (SUCRA 0.78) and (SUCRA 0.77), respectively. For NASH resolution, semaglutide, liraglutide and vitamin E plus pioglitazone had the highest probability of being ranked the most effective intervention for achieving NASH resolution (SUCRA 0.89), (SUCRA 0.84) and (SUCRA 0.83), respectively. Lanifibranor, obeticholic acid, pioglitazone and vitamin E were significantly better than placebo in achieving ≥1 stage of fibrosis improvement. Conversely, semaglutide, liraglutide, vitamine E plus pioglitazone, pioglitazone, lanifibranor and obeticholic acid were significantly better than placebo in achieving NASH resolution.

Conclusion: These data provide relative rank-order efficacy of various NASH therapies in terms of their improvements in liver fibrosis and NASH resolution. Therapies that have been shown to improve NASH resolution may be combined with therapies that have an antifibrotic effect to further boost treatment response rate in future.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Professor Gideon Hirschfield, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is one of the most common causes of chronic liver disease in the United States (US).[1,2] NASH is a progressive liver disease and can lead to cirrhosis and hepatocellular carcinoma leading to increased liver-related morbidity and mortality.[3] It is the second leading indication of liver transplantation in the US.[1] NASH is commonly associated with obesity, insulin resistance and diabetes.[4] Due to rising rates of obesity and diabetes, the prevalence of NASH and NASH related cirrhosis and HCC is rising worldwide.[5]

Lifestyle interventions are the current main stay of the management of NASH including dietary caloric restriction, Mediterranean diet, and increased physical activity.[4] Several pharmacologic therapies are in various phases of clinical development for the management of NASH and NASH related fibrosis. However, there are no food and drug administration (FDA) approved therapies for the management of NASH.[6]

For therapies to be deemed effective by the FDA in NASH related fibrosis, they have to demonstrate benefit in improving long-term clinical outcomes. However, as part of the subpart H approval pathway, if a pharmacologic therapy is able to demonstrate either ≥1 stage improvement in fibrosis stage without worsening of NASH or NASH resolution without worsening of fibrosis it is eligible to receive conditional approval pending demonstration of long-term clinical benefit.

Emerging data from Phase 2b and 3 trials suggest that treatment effect relative to placebo is small. Furthermore, there is significant heterogeneity in treatment response and certain therapies are more likely to improve fibrosis whereas other agents are more likely to lead to resolution of NASH. There is a major unmet understanding of the relative efficacy of different pharmacological agents for the treatment of NASH.[7] Therefore, we aimed to perform a systematic review and network meta-analysis of studies that assess the effect of different pharmacological interventions on NASH in assessing their relative rank-order in fibrosis improvement as well as NASH resolution. An in-depth understanding of these two outcomes would help better synergise future combination therapeutic approaches in NASH to further improve treatment response rates.

2 | METHODS

We performed a systematic review and network meta-analysis of studies that assess the effect of different pharmacological interventions on NASH. We reported the results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study was based on a pre-established protocol ID CRD42020194405.

2.1 | Eligibility Criteria

Studies included in this meta-analysis were RCTs that met the following inclusion criteria: (a) Patients with biopsy-proven NASH; (b) intervention: established or potentially beneficial therapies for NAFLD including vitamin E, TZDs, pentoxifylline, or OCA or a combination of these for at least 1 year, based on American Association for the Study of Liver Diseases (AASLD) guidelines; (c) comparator: another active agent, or placebo; and (d) primary studies included in this meta-analysis were RCTs that met the following inclusion criteria: (a) Patients with biopsy-proven NASH; (b) intervention: established or potentially beneficial thera- pies for NAFLD including vitamin E, TZDs, pentoxi- fylline, or OCA or a combination of these for at least 1 year, based on AASLD guidelines; (c) comparator: another active agent, or placebo; and (d) primary Studies included in this meta- analysis were RCTs that met the following inclusion criteria: (a) Patients with biopsy-proven NASH; (b) intervention: established or potentially beneficial therapies for NAFLD including vitamin E, TZDs, pentoxifylline, or OCA or a combination of these for at least 1 year, based on AASLD guidelines; (c) comparator: another active agent, or placebo; and (d) primary Studies were included in our systematic review if they met the following criteria : (a) they were randomised controlled trials (RCTs) phase (II, III or, IV); (b) enrolled patients with biopsy-proven NASH; (c) compared one or more of established or potentially beneficial therapies for NASH based on AASLD guidelines[4] to each other or to placebo; (d) had a follow up duration of at least 6 months; and (e) reported the primary outcome (biopsy-proven ≥1 stage improvement in fibrosis) and/or the secondary outcome (biopsy-proven NASH resolution defined as lobular inflammation 0-1 and ballooning 0).

Studies were excluded if they were: (a) observational studies; (b) trials of lifestyle interventions; (c) trials with follow up duration <6 months; (d) trials of futile therapy based on AASLD guidelines (eg, metformin, omega-3 fatty acids, statins, etc.); or (e) enrolling <40 patients.

2.2 | Search strategy

We updated the search of our previous systematic review by Singh et al[8] A comprehensive search of several databases from 2014 to June 23, 2020 was conducted by an experienced medical librarian. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of science and Scopus. (The actual search strategy is available in the Supporting information).

2.3 | Study selection process

Two independent investigators (AMM, TN) reviewed the titles and abstracts of all citations identified by the search. Full-text manuscripts were retrieved for the included abstracts and were subsequently screened for eligibility by two independent investigators (AMM, TN). Disagreements at this level were resolved by consensus and a third reviewer if needed.

2.4 | Data extraction and risk of bias assessment

Data extraction was done individually by (AMM, TN, AB or NM). Extracted data were reviewed again by (AMM). A standardised form was used to extract data about the characteristics of: (a) included studies (first author, year of publication, geographical location and duration of follow up); (b) patients (age, gender, BMI, diabetes); (c) NAFLD (NAFLD activity score (NAS), alanine aminotransferase, aspartate aminotransferase); (d) intervention(s) and comparison(s)(dosing and schedule of the agent and concomitant non-pharmacological interventions); and (e) outcomes (number of patients who achieved at least 1 stage improvement in fibrosis as a primary outcome and number of patients with NASH resolution as a secondary outcome). Patients with no follow up biopsy were deemed to be treatment failure. Risk of bias in the included studies was assessed using the Cochrane risk of bias assessment tool in which studies were deemed to be at low, high, or unclear risk.[9]

2.5 | Data Synthesis and Statistical Analysis

For each comparison, odds ratios (OR) and 95% confidence intervals (95% CI) were meta-analysed using the DerSimonian–Liard random-effects model.[10] We assessed statistical heterogeneity using the I^2 statistic, with values greater than 50% suggesting substantial heterogeneity.[11] Publication bias was assessed by evaluating small study effects suggested by funnel plot asymmetry.[12] Next, we performed a frequentist network meta-analysis based on a random-effects consistency model following a multivariate meta-regression approach as described by Schwarzer et al,[13] and Rücker et al[14,15] using R (R Core Team, 2020) and STATA v.16.0. The frequentist approach provides a point estimate from the network along with 95% CI from the frequency distribution of the estimate. We evaluated coherence in the networks by using the back-calculation method to split direct and indirect evidence.[16] We calculated the relative ranking of the interventions for achieving the primary and the secondary outcome as their surface under the cumulative ranking (SUCRA). SUCRA values range between 0 when a treatment is certainly the worst, and 1 when a treatment is certainly the best,[17] as such, higher scores correspond to higher ranking for achieving ≥1 stage improvement in fibrosis and/or NASH resolution.

2.6 | Certainty of Evidence

We followed the GRADE approach to rate the certainty of evidence of estimates derived from direct meta-analysis.[17-19] In this approach, direct evidence from RCTs starts at high certainty and can be rated down, based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and/or publication bias, to levels of moderate, low and very low.

We followed the Confidence in Network Meta-Analysis (CINeMA) approach to rate the certainty of evidence of estimates derived from network meta-analysis, which is an adaptation of the GRADE approach.[18] CINeMA approach covers six domains: within-study bias (referring to the impact of risk of bias in the included studies), reporting bias (referring to publication and other reporting bias), indirectness, imprecision, heterogeneity and incoherence. The reviewer's input is required at the study level for within-study bias and indirectness. Then, applying user-defined rules, judgments are made as (no concerns, some concerns, or major concerns) to each domain. Judgments across domains can be summarised to obtain four levels of certainty for each relative treatment effect, corresponding to the usual GRADE assessments of very low, low, moderate or high.[20,21]

3 | RESULTS

In total, 4820 titles and abstracts were identified using the search strategy; 26 RCTs met our inclusion criteria (Figure S1 demonstrates the study selection process through a flow chart). Table S1 summarises the characteristics of the included RCTs.

Overall, these 26 trials had 5129 patients and 23 interventions. Four of the included studies were single center[22-25]; all the others were multicenter. Follow up duration ranged between 24 and 104 weeks. Seventeen of the included studies were two-arm trials comparing active agent with placebo.[22-39] Six studies included multiple arms to compare one active agent in different doses with placebo.[40-45] Two studies had three arms comparing two different interventions and placebo.[46,47] One study compared six distinctive interventions and placebo in a seven-arm trial.[48]

Table S2 describes the baseline characteristics of patients included in the studies. The mean age of the patients ranged from 47 to 63 and from 45 to 59 in the intervention group and placebo group respectively. Two studies included only nondiabetic patients[26,47]; on the other hand, three studies included only diabetic or prediabetics patients.[28,44,46] The mean NAS at baseline ranged from (3 to 5.7).

Overall, studies were judged to be at low risk of bias. Some of the studies were funded by pharmaceutical companies; which we explicitly reported as a study characteristics, but not in the risk of bias assessment, which is based on Cochrane risk of bias assessment tool.[9]

Table S3 summarises the risk of bias assessment for the included studies.

3.1 | Primary outcome: ≥ 1 stage improvement in fibrosis

Twenty-three different interventions were studied for this outcome (Figure 1). Four individual studies showed statistically significant improvement for ≥1 stage fibrosis.[25,34,37,45] Phase 2b NATIVE trial[45] showed that Lanifibranor was superior to placebo (OR 2.38; 95% CI, 1.21-4.67).

Two studies compared Obeticholic acid versus placebo; Neuschwander-Tetri et al[34] showed that Obeticholic acid was superior to placebo (OR 2.30; 95% CI, 1.22-4.35) and Younossi et al[37] also

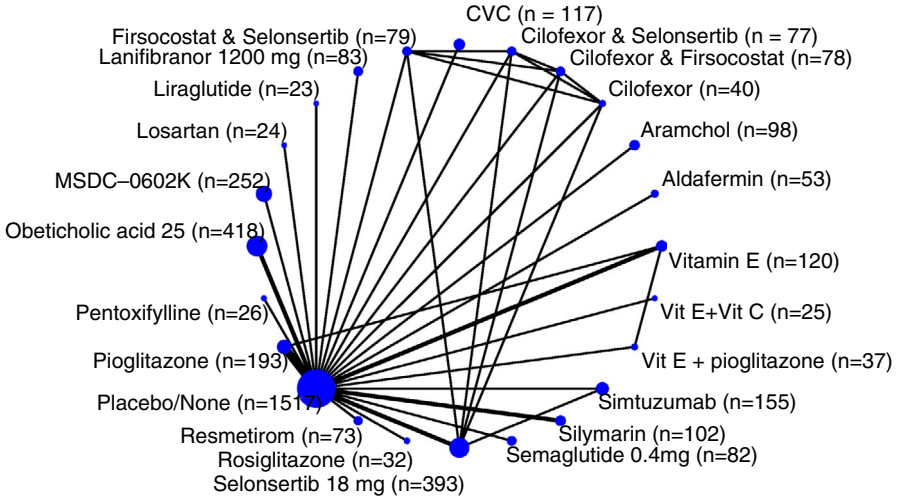

FIGURE 1 Network of the included studies with the available direct comparisons for the primary outcome. The size of the nodes and the thickness of the edges are weighted according to the number of patients and the number of studies evaluating each treatment respectively

showed that Obeticholic acid was superior to placebo (OR 2.22; 95% CI, 1.44-3.42).

Wah Kheong et al[25] showed that Silymarin was superior to placebo (OR 4.54; 95% CI, 1.18-17.43).

There was no statistically significant difference between placebo and the other 20 studied agents in the other trials. (Figure S2 with all direct comparisons for fibrosis improvement is provided in the supplementary figures).

3.1.1 | Direct Meta-analysis

When compared to placebo, the odds of achieving at least 1 stage improvement of fibrosis were statistically significantly higher in patients receiving Obeticholic acid (OR 2.25; 95% CI: 1.57-3.21; I^2 0%; two RCTs[34,37] with 438 patients), Pioglitazone (OR 1.76; 95% CI: 1.14-2.72; I^2 0%; four RCTs[22,26,28,47] with 385 patients), and vitamin E (OR 1.72; 95% CI: 1.01-2.95; I^2 0%; two RCTs[46,47] with 235 patients). In contrast, Silymarin and Selonsertib were not associated with a statistically significant improvement in fibrosis when compared with placebo (OR 1.59; 95% CI: 0.22-11.66; I^2 81%; two RCTs[25,33] with 177 patients) and (OR 0.77; 95% CI: 0.47-1.27; I^2 0%; two RCTs[31,42] with 559 patients) respectively (Figure 2)

3.1.2 | Network Meta-analysis

Compared to placebo, Lanifibranor, Obeticholic acid, Pioglitazone and Vitamin E were statistically significantly better in achieving ≥1 stage of fibrosis improvement (OR 2.38; 95% CI: 1.21-4.67), (OR 2.25; 95% CI 1.57-3.21), (OR 1.83; 95% CI 1.19-2.80) and (OR 1.72; 95% CI 1.04-2.85) respectively; Other interventions did not demonstrate superiority against placebo. (File S1 that describes the direct and indirect comparisons of all the studied agents against each other for fibrosis improvement is available in the supporting information.)

Based on SUCRA score, Lanifibranor and Obeticholic acid had the highest probability of being ranked the most effective intervention for achieving ≥1 stage fibrosis improvement (SUCRA 0.78) and (SUCRA 0.77), respectively. Oppositely, Losartan, Simtuzumab and Selonsertib had the lowest probability of being ranked the most effective intervention (SUCRA 0.05), (SUCRA 0.12) and (SUCRA 0.19) respectively (Figure 3). (File S1 and Figure S3 that describe ranking probabilities for fibrosis improvement are available in the supporting information).

3.2 | Secondary outcome: NASH resolution

Twenty different interventions were studied for this outcome (Figure 4). Five studies had statistically significant difference when comparing placebo versus other agents.[22,27,35,45,46] Newsome et al[35] showed that Semaglutide was superior to placebo (OR 6.66; 95% CI: 3.22-13.74). When comparing Liraglutide to placebo, Armstrong et al[27] showed that Liraglutide was superior to placebo (OR 6.43; 95% CI: 1.20-34.41). Vitamin E plus Pioglitazone was also superior to placebo in Brial, 2019 trial[46] (OR 5.33; 95% CI: 1.55-18.30). Cusi et al[22] compared Pioglitazone versus placebo and showed that Pioglitazone was superior (OR 4.44; 95% CI: 1.83-10.78). Finally, Lanifibranor was superior to placebo in NATIVE, 2020 trial[45] (OR 3.54; 95% CI: 1.74-7.19). There was no statistically significant difference between placebo and the other 15 agents in the remaining studies. (Figure S4 with all direct comparisons for NASH resolution is provided in the supplementary figures.)

3.3 | Direct Meta-analysis

Two studies[34,37] compared Obeticholic acid versus placebo; a total of 838 patients were included in the analysis. Obeticholic acid was superior to placebo (OR 1.62; 95% CI: 1.05-2.50; I^2 0%) (Figure 5). Selonsertib was studied in two different trials[31,42] with 559 patients, and it showed no statistically significant difference when compared to placebo (OR 0.62; 95% CI 0.25-1.53; I^2 6%) (Figure 5).

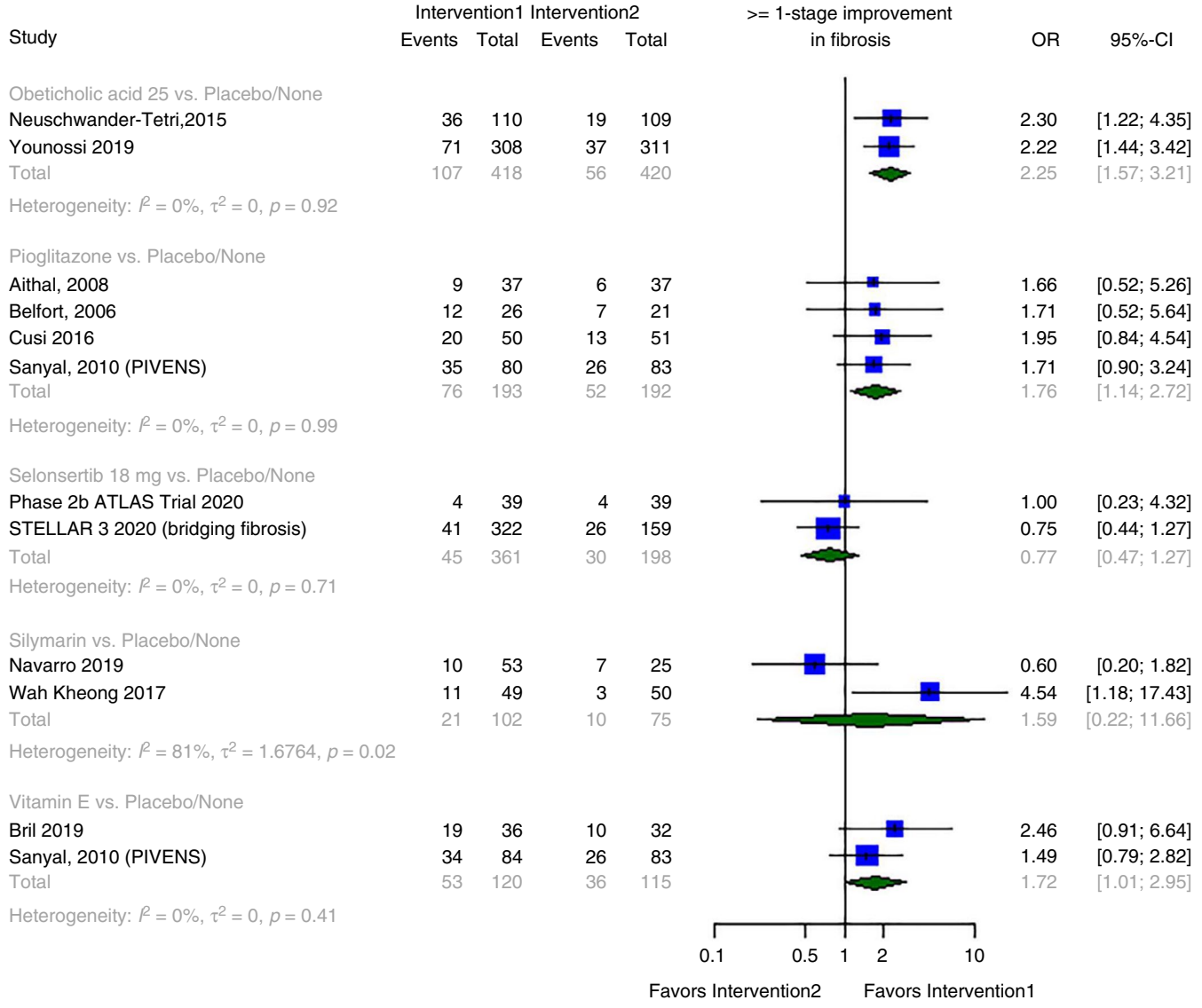

FIGURE 2 Meta-analysis forest plots of different pharmacological interventions compared to placebo for the primary outcome

3.4 | Network Meta-analysis

Compared to placebo, Semaglutide, Liraglutide, Vit E plus Pioglitazone, Pioglitazone, Lanifibranor and Obeticholic acid were statistically significantly better in achieving NASH resolution (OR 6.66; 95% CI 3.22-13.74), (OR 6.43; 95% CI 1.20-34.41), (OR 5.33; 95% CI 1.55-18.30), (OR 4.44; 95% CI 1.83-10.78), (OR 3.54; 95% CI 1.74-7.19) and (OR 1.62; 95% CI 1.05-2.50) respectively. (File S1 that describe the direct and indirect comparisons of all the studied agents against each other for NASH resolution is provided in the supplementary).

Semaglutide, Liraglutide, Vit E plus Pioglitazone had the highest probability of being ranked the most effective intervention for achieving NASH resolution (SUCRA 0.89), (SUCRA 0.84) and (SUCRA 0.83) respectively. On the contrary, Selonsertib, Cilofexor, Firsocostat plus Selonsertib, Cilofexor plus Selonsertib had the lowest probability of ranking the most effective intervention. (SUCRA 0.14), (SUCRA 0.15), (SUCRA 0.17) and (SUCRA 0.17) respectively. Figure 6 (File S1 and Figure S5 that describe ranking probabilities for NASH resolution are available in the supplementary).

3.5 | Publication Bias and Network coherence

We were not able to assess publication bias because of the small number of studies in each comparison. There was no significant difference (incoherence) between direct and indirect estimates when both were available. The two methods had overlapping CIs for all interventions in both primary and secondary outcomes. (two Figures S6 and S7 presenting the direct and indirect comparisons for both outcomes and two files describing the back-calculation method for the coherence test for both outcomes are provided in the supplementary material).

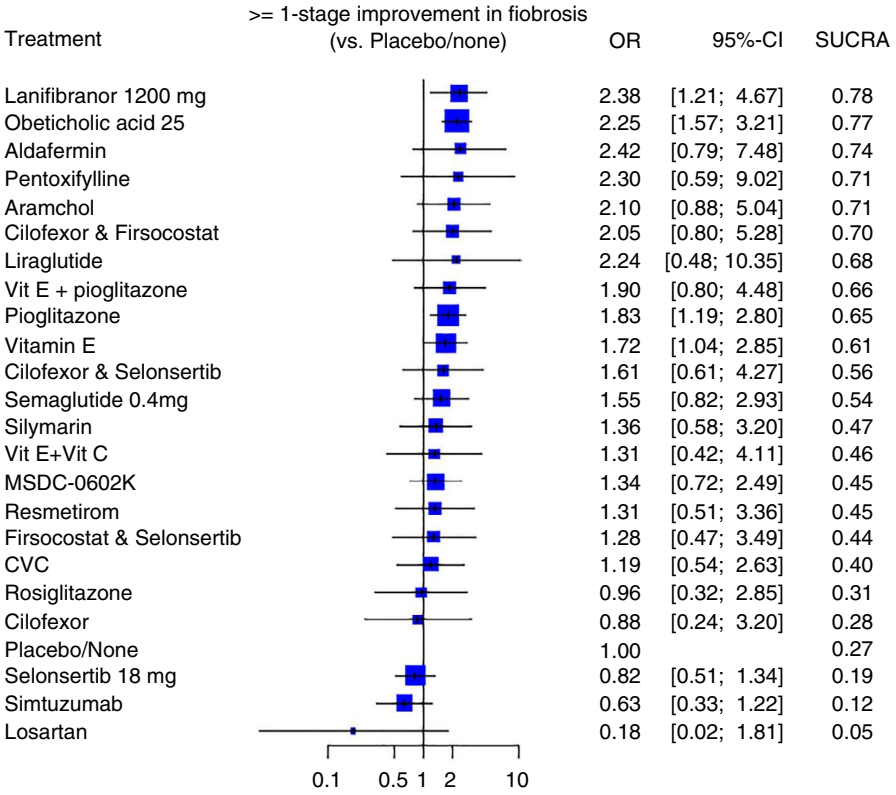

FIGURE 3 Network meta-analysis forest plot of different pharmacological interventions compared to placebo ranking from best to worst based on SUCRA score for the primary outcome

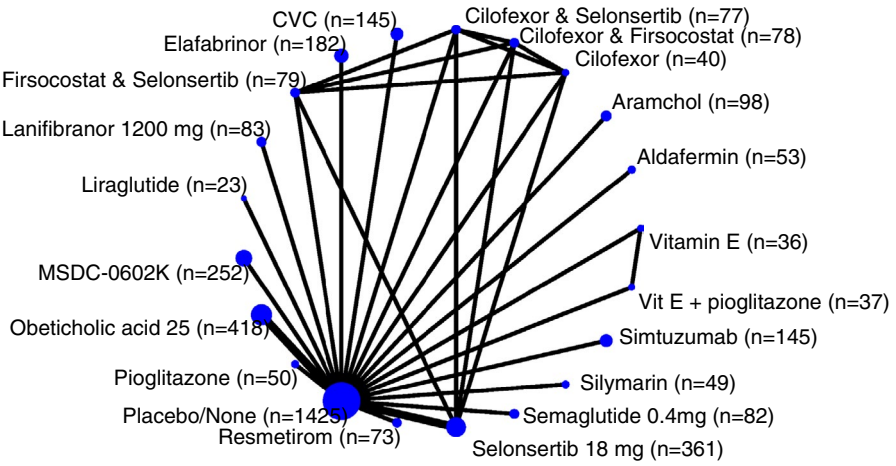

FIGURE 4 Network of the included studies with the available direct comparisons for the secondary outcome. The size of the nodes and the thickness of the edges are weighted according to the number of patients and the number of studies evaluating each treatment respectively

3.6 | Certainty of Evidence

For the outcome of fibrosis Improvement, compared to placebo both Obeticholic acid and Pioglitazone had a better outcome which was supported by high certainty of evidence, whereas Vitamin E had a better outcome which was supported by moderate certainty of evidence.

Both Obeticholic acid and Pioglitazone had a better outcome when compared to Selonsertib and Simtuzumab with a high certainty of evidence. Vitamin E has a better outcome when compared to Selonsertib and Simtuzumab with moderate certainty of evidence. Both Semaglutide and Vit E plus Pioglitazone have a better outcome when compared with Simtuzumab with a moderate certainty of evidence.

Other comparisons were supported by low to very low certainty of evidence because of severe imprecision. For the outcome of Nash resolution, all comparisons were supported by low to very low certainty of evidence because of major concerns for imprecision and heterogeneity (Two files showing the certainty of evidence for the whole comparisons and for the available direct comparisons can be found in the supplementary).

4 | DISCUSSION

In this updated systematic review and network meta-analysis, we combined direct and indirect evidence from 26 RCTs with a total of 5129 patients and 23 interventions to estimate the relative

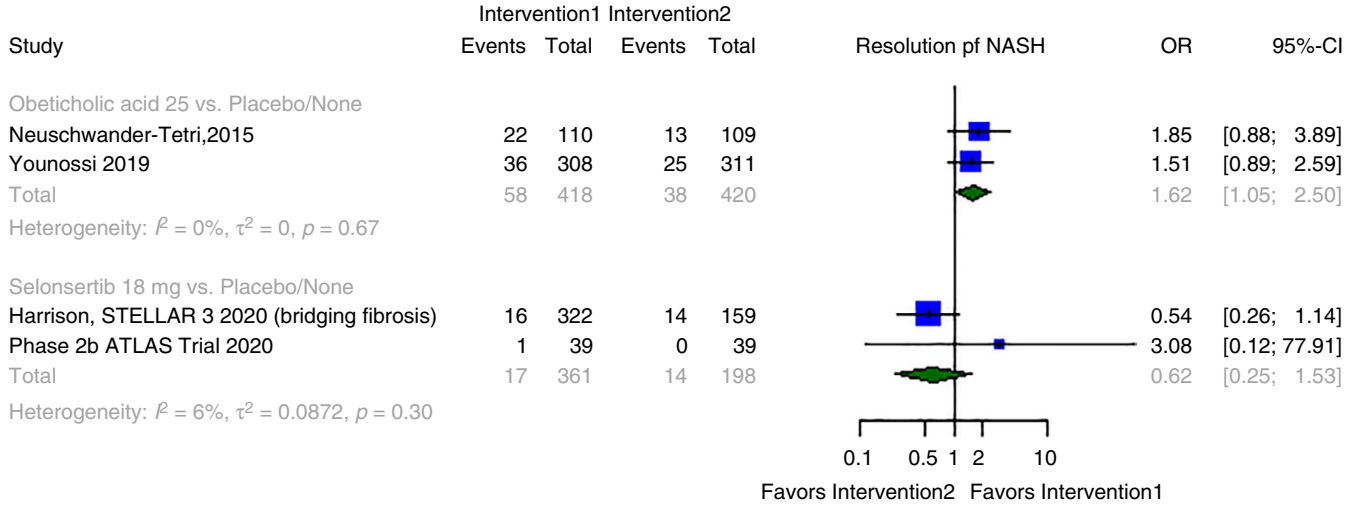

FIGURE 5 Meta-analysis forest plots of different pharmacological interventions compared to placebo for the secondary outcome

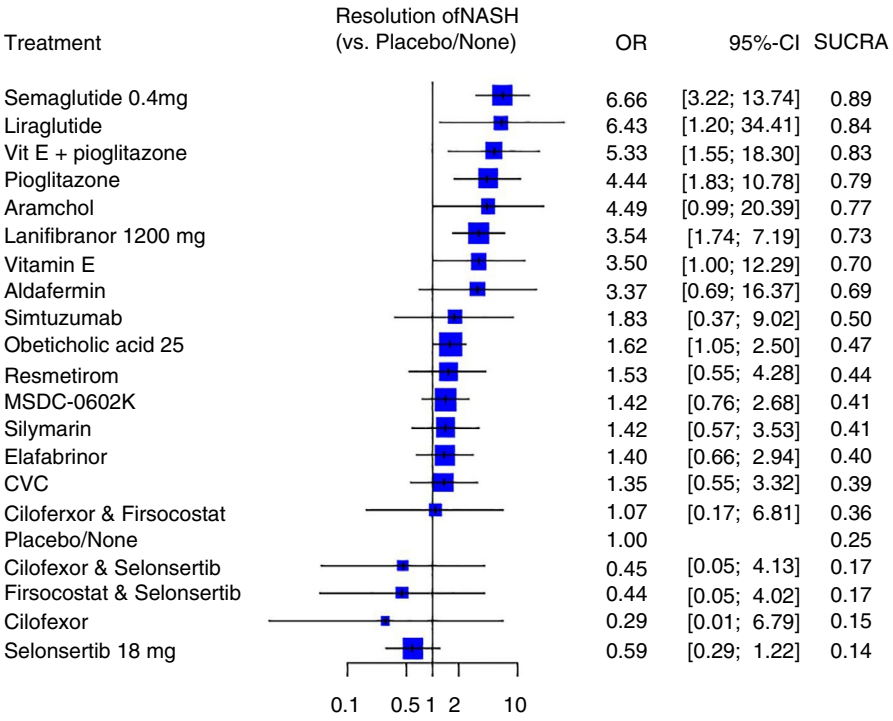

FIGURE 6 Network meta-analysis forest plot of different pharmacological interventions compared to placebo ranking from best to worst based on SUCRA score for the secondary outcome

efficacy of different pharmacological interventions in achieving ≥1 stage improvement in fibrosis and/or NASH resolution. We were able to make some key observations: (a) Lanifibranor, Obeticholic acid, Pioglitazone and Vitamin E were significantly better than placebo in achieving ≥1 stage of fibrosis improvement (b) Lanifibranor and Obeticholic acid had the highest probability of being ranked the most effective intervention for achieving ≥1 stage fibrosis improvement (c) Semaglutide, Liraglutide, Vit E plus Pioglitazone, Pioglitazone, Lanifibranor and Obeticholic acid were significantly better than placebo in achieving NASH resolution. (d) Semaglutide, Liraglutide and Vit E plus Pioglitazone had the highest probability of being ranked the most effective intervention for achieving NASH resolution (Figure 7).

Current AASLD guidelines[4] recommend the use of vitamin E in nondiabetic adults with biopsy-proven NASH and the use of pioglitazone in both diabetic and non-diabetic adults with biopsy-proven NASH. AASLD recommends against using Metformin, UCDA or Omega 3-fatty acids as a specific treatment for NASH. Regarding GLP-1 agonists and OCA, AASLD states that it is premature to consider them to specifically treat NASH.

Our network meta-analysis suggests that several mechanisms may provide therapeutic benefit in NASH. Certain classes of agents (such as Obeticholic acid, an FXR agonist) may have predominantly anti-fibrotic efficacy and others (such as Semaglutide, a GLP-1 analogue) may have greater efficacy in improving NASH resolution. The relative benefits of these therapies in fibrosis regression and NASH

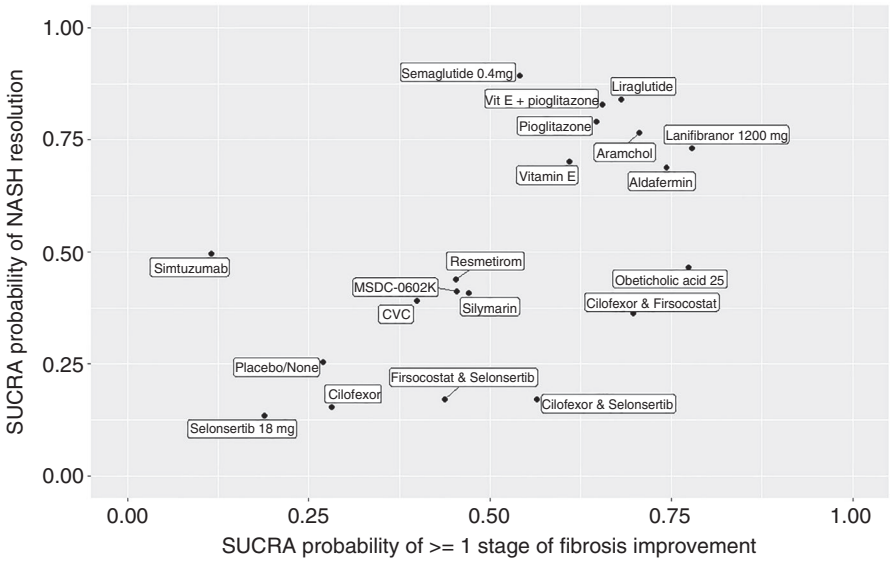

FIGURE 7 SUCRAs for NASH resolution and at least 1 stage fibrosis improvement

resolution will inform future choices for combination therapeutic approaches. Future, larger studies are warranted to validate these results.

The strengths of our analyses include the comprehensive assessment of the relative efficacy of 23 pharmacological agents for both fibrosis improvement and NASH resolution in 5129 patients. The coherent results from direct and indirect comparisons give us more confidence in our observations. We used CINeMA approach to assess the certainty of evidence for this network meta-analysis, and GRADE approach for the direct meta-analysis which benefit in generating guidelines in the future.

The study has limitations. First, there was small number of direct (head-to -head) comparative studies. Second, there is always concern about heterogeneity in any meta-analysis which can take place as differences among trials in study design, patient demographics, interventions and comparisons, outcome assessment; and this may limit the comparability of trials.[19,49] Third, estimates of ranking probabilities can be misleading as they are highly sensitive to both the number of studies per comparisons and the overall network configuration. An unequal number of studies per comparison may result in biased estimates of treatment rank probabilities for every network considered[50]; this can be seen with Aramchol in our study. Aramchol has a SUCRA: 0.77 reflecting high probability of being ranked one of the most effective intervention for achieving NASH resolution. However, it failed to achieve statistically significant better outcome when compared to placebo for NASH resolution. This biased estimate can be relatively solved by not focusing only on the summary estimates and ranking probabilities; rather taking into consideration the certainty of evidence for each comparison.

Finally, our study combined phase II and III trials in the comparison. On one hand this was an advantage as we were able to do comprehensive assessment of all potential pharmacological therapies considered for NASH. On the other hand, some of the early trials results may not be subsequently replicated in a larger sample size. A notable example is Harrison, 2020.[30] The study did not meet primary endpoint of fibrosis improvement by >1 stage with no worsening of NASH versus placebo and the sponsor does not plan to pursue a phase III clinical trial.

4.1 | Implications for Clinical Research

These results provide new supportive evidence on the use of Pioglitazone as suggested by the current AASLD Practice Guidance. Furthermore, there is moderate certainty evidence to support the use of Vitamin E in NASH. Given the data from both the FLINT trial[34] and the REGENERATE trial[37] there is high certainty evidence in support of efficacy of Obeticholic acid in improving NASH related fibrosis. Given only one trial data on Lanifibranor use, the evidence supporting its efficacy is low certainty and would require further validation by a larger Phase 3 trial. These data also support the regulatory requirement to have at least 2 histology-based trial to develop moderate-high certainty evidence of efficacy before widespread clinical use. This network is a major advance compared to our previous meta-analysis conducted by Singh et al[8]; However, in that review a moderate certainty evidence supporting the use of Pentoxifylline for fibrosis improvement was observed. The evidence in our network meta-analysis for Pentoxifylline compared with placebo was downgraded to low in certainty.

In conclusion, we observed that several candidate agents in Phase 2b and a Phase 3 trial have been shown to improve histological features of NASH. In general, monotherapies, even when they improve histologic features of NASH, have been shown to have a small treatment effect delta relative to placebo. Larger comparative RCTs are warranted to further establish the comparative efficacy of different interventions for NASH in demonstrating ≥1 stage improvement in fibrosis and/or NASH resolution. Therapies that have been shown to improve NASH resolution may be combined with therapies that have an anti-fibrotic effect to further boost treatment response rate in future.

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AUTHORSHIP

Guarantor of the article: Rohit Loomba.

Author contributions: Study concept and design: Abdul Majzoub, Rohit Loomba. Acquisition, analysis or interpretation of the data: Abdul Majzoub, Tarek Nayfeh, Abbey Barnard, Nagambika, Shravan Dave, Siddharth Singh, M. Hassan Murad, Rohit Loomba. Drafting of the manuscript: Abdul Majzoub, Rohit Loomba. Critical revision of manuscript for important intellectual content: Abdul Majzoub, Tarek Nayfeh, Abbey Barnard, Nagambika, Shravan Dave, Siddharth Singh, M. Hassan Murad, Rohit Loomba. Statistical analysis: Tarek Nayfeh, Abdul Majzoub. Study supervision: Rohit Loomba. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as online supplemental information. Data details can be provided upon request to credible investigators on verification for patient confidentiality.

ORCID

Shravan Dave https://orcid.org/0000-0002-2875-4926
Rohit Loomba https://orcid.org/0000-0002-4845-9991

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SUPPORTING INFORMATION

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

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