Systematic Review / Meta-analysis

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# Efficacy and safety of the FGF19 analog aldafermin for the treatment of nonalcoholic steatohepatitis: a GRADE assessed systematic review and meta-analysis

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**Background:** Nonalcoholic fatty liver disease (NAFLD) is increasingly concerning due to its rising prevalence. It encompasses conditions from simple steatosis to severe nonalcoholic steatohepatitis (NASH), posing risks such as fibrosis, cirrhosis, or hepatocellular carcinoma if untreated. This systematic review and meta-analysis aims to assess aldafermin, an FGF19 analog, for efficacy and safety in NASH patients.

**Methods:** Eligible studies were identified by searching PubMed, Cochrane Library, and Google Scholar, resulting in 1115 studies. Three RCTs were included. The risk of bias was assessed using the Cochrane Risk of Bias tool, and data synthesis utilized Review Manager software. The certainty of evidence was evaluated with the GRADE approach.

**Results:** In the 3 mg dose group, aldafermin significantly improved various parameters. The ELF score decreased notably (pooled MD: −0.46, 95% CI: −0.64 to −0.28; $P < 0.00001$). Additionally, fibrosis improvement without NASH worsening showed a pooled MD of 8.15 (95% CI: −3.62 to 19.93; $P < 0.17$), and fibrosis improvement with NASH resolution displayed a pooled MD of 10.16 (95% CI: 1.68–18.64; $P = 0.02$). Furthermore, significant reductions were noted in absolute AST levels (pooled MD: −13.40, 95% CI: −18.66 to −8.14; $P < 0.00001$) and absolute ALT levels (pooled MD: −19.92, 95% CI: −27.08 to −12.75; $P < 0.00001$), suggesting improved liver function.

**Conclusion:** The meta-analysis indicates that aldafermin, particularly, the 3 mg dose, shows significant efficacy in improving liver histology and biochemical markers in NASH patients compared to placebo, along with a satisfactory safety profile.

**Keywords:** aldafermin, FGF19 analog, nonalcoholic steatohepatitis (NASH)

## Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged as a significant cause of liver-related morbidity and mortality, with its prevalence increasing from 25.5% in 2005 or before to 37.8% in 2016 or after[1]. The condition represents a variety of liver conditions, from the benign accumulation of fat known as simple steatosis to the more severe form called nonalcoholic steatohepatitis (NASH). NASH, characterized by altered metabolism leading to liver inflammation and hepatocyte ballooning, poses a significant health threat, potentially developing into fibrosis, cirrhosis, or hepatocellular carcinoma (HCC) if untreated[2]. Metabolic syndrome, obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia are some of the key risk factors for NAFLD, underscoring the intricate relationship between metabolic health and liver function[3].

Furthermore, NAFLD is not isolated in its impact; it is intricately linked with an elevated prevalence of cardiovascular disease (CVD), irrespective of diabetes status[4]. In a literature review by Dufour *et al.*[5], the prevalence of NAFLD ranged from 11.2 to 37.2% in the general population, with biopsy-confirmed NASH found in 15.9–68.3% of NAFLD cases. Notably, individuals with

### HIGHLIGHTS

- Urgent requirement for novel therapies as NASH lacks approved pharmacotherapy.
- First comprehensive meta-analysis of aldafermin's efficacy in NASH management.
- Aldafermin shows significant potential in improving liver histology and biochemical markers.
- Future directions: calls for larger, diverse clinical trials to confirm aldafermin's role in NASH management.

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T2DM are particularly vulnerable, with a staggering 65.26% prevalence of NASH observed among them. Alarming projec tions anticipate a significant 63% rise in NASH prevalence between 2015 and 2030[6].

Despite the alarming rise in prevalence, only one official pharmacotherapy (resmetirom) has received approval for NASH. Given the link between metabolic health and NASH, lifestyle modification and weight loss have become the mainstay of treatment, demonstrating improvement in liver histology. However, due to variable responses to these modifications, pharmaceutical agents that complement weight loss can be given. Antioxidants and insulin sensitizers are also used in the treatment of NASH[7].

Multiple targeted therapies are under investigation for their use in treating NASH. Various drug classes such as fibroblast growth factor (FGF) analogs, farnesoid X receptor (FXR) agonists, thyroid hormone receptor (THR) agonists, peroxisome proliferator-activated receptors (PPARs), and cytokines are currently under investigation, along with surgical interventions like bariatric surgery[7,8]. Aldafermin, an FGF analog, has shown positive results in various studies[9–11], opening up new avenues for the treatment of this ailment.

Aldafermin is an FGF19 analog that acts on two receptor complexes, termed as FGFR1c-KLB and FGFR4-KLB. The activation of the former leads to improved insulin sensitivity and reduction in liver steatosis[12], while the latter inhibits the de-novo production of bile acids by decreasing the expression of CYP7A1[13]. Elevated bile acids have been shown to be hepato toxic and a risk factor for chronic liver disease[14,15]. Hence, by reducing the bile acid burden coupled with its antisteatotic and anti-inflammatory effects, aldafermin can drastically improve outcomes in patients with NASH.

Understanding the safety and efficacy of aldafermin is crucial to the gap in a novel therapy for this condition. Even though adequate data is available from the clinical trials, there has been no comprehensive meta-analysis conducted to assess the drug's performance in these regards. Thus, our objective was to carry out a systematic review and meta-analysis to determine the safety and efficacy of aldafermin in patients suffering with NASH.

## Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A610) statement, with the help of the Cochrane Handbook for Systematic Reviews of Interventions guidelines[16]. Under the ID CRD42024513038, this review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO). Ethics committee permission was not needed for this study because the analysis was done with already available data. The assessing the methodological quality of systematic reviews (AMSTAR) (Supplemental Digital Content 2, http://links.lww.com/MS9/A611) Guidelines have been followed in the reporting of this work.

### *Eligibility criteria*

The inclusion criteria included: (i) randomized controlled trials (RCTs); (ii) patients with a biopsy-confirmed diagnosis of NASH; (iii) aldafermin as an intervention, and (iv) outcomes of interest such as fibrosis improvement and NASH resolution, enhanced liver fibrosis (ELF) score, fibrosis improvement with no worsening of NASH, absolute neoepitope specific N-terminal propeptide of type III collagen (Pro-C3), absolute aspartate aminotransferase (AST), and absolute alanine aminotransferase (ALT), etc., were reported.

The exclusion criteria included: (i) non-RCTs; (ii) patients not suffering from NASH; (iii) abstracts, correspondence, opinion papers, conference presentations, research-in-progress studies, review articles, nonexperimental and preclinical studies, etc.

### *Information sources*

MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials (via The Cochrane Library), and Google Scholar were the databases and international registers that were searched from the time of their creation until February 2024, without regard to language limitations. A secondary search was conducted for potentially suitable studies by screening the reference lists of the included publications and pertinent systematic reviews. Med Subject Headings (MeSH) terms related to aldafermin and NASH were combined with keywords to create a search strategy. Supplementary Table S1 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612), contains the specific search plan that was used for each collection.

### *Study selection process*

All of the papers that were found through online literature search were screened and deduplicated using Mendeley Desktop 1.19.8 (Mendeley Ltd.). Following the deduplication procedure, the initial screening of titles and abstracts was carried out independently by two writers. The same respective authors then conducted a thorough full-text screening of the remaining chosen publications. A third reviewer arbitrated any disagreements between them.

### *Data collection and data items*

Two reviewers were appointed to extract relevant information items from the included studies and enter them into an Excel sheet following the screening and selection procedure. The relevant data items included study IDs, first author's last names, study design, the countries where the trials were conducted, intervention, duration of intervention, the total number of participants, mean age, sex, body weight, BMI, serum C4 levels, ALT levels, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and AST levels; the number of people with T2DM; lipid parameters such as total cholesterol, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), triglycerides, hepatic fat fraction, use of statins; efficacy outcomes such as fibrosis improvement and NASH resolution, ELF score, fibrosis improvement with no worsening of NASH, Pro-C3, etc., and adverse events such as diarrhea, nausea, constipation, abdominal pain, etc.

### *Risk of bias assessment*

The risk of bias in the included RCTs was evaluated using the Cochrane Risk of Bias tool for randomized trials (RoB 2.0)[17], which assesses bias in five domains: (i) randomization procedure; (ii) deviations from intended interventions; (iii) missing outcome

data; (iv) outcome measurement; and (v) selection of the reported result. Independently, two writers assigned a low, high, or some concern rating to each included study's risk of bias. Any disagreements between them were settled by a third reviewer.

### Data synthesis

The statistical analysis was conducted using Review Manager (RevMan, version 5.4; The Cochrane Collaboration). The mean differences (MDs) and risk ratios (RRs), along with the associated 95% CI, were computed using the random effects model. Because of the estimated variability of the genuine impact sizes, the random-effects model was utilized. The heterogeneity of each synthesis was evaluated using the $I^2$ index and the chi-square test; a value of less than 50% was considered appropriate for the heterogeneity of the included studies. Doi plots were created for outcomes with less than 10 studies, and MetaXL version 5.3 (EpiGear International Pty, Sunrise Beach) was used to assess publication bias using the Luis Furuya-Kanamori (LFK) index. Because the LFK index is more sensitive and powerful than the Egger test, it is appropriate for fewer studies[18]. A *P*-value of less than 0.05 was deemed significant in every case.

### Certainty of evidence assessment

The GRADE Working Group classified the pooled estimates' quality of evidence as high, moderate, low, or very low based on their assessment of the evidence's certainty using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach[19,20].

## Results

### Study selection and characteristics of included studies

The initial screening yielded a total of 1115 results. After deduplication, titles and abstracts were screened, and as a result, three studies were assessed in this systematic review and meta-analysis [9–11]. Abstracts were excluded due to lack of sufficient data present in them. Only studies in English were included. Figure 1 shows the summary of the study selection process in a PRISMA Flow Diagram. These studies administered aldafermin to 278 NASH patients, with 137 patients who received a 1 mg dose of aldafermin and 98 patients who received a 3 mg dose of aldafermin. Among the participants taking aldafermin, 107 were males. The mean age of the patients in the intervention (aldafermin) arm ranged from 49.8 years to 61.3 years. The mean body weight of the patients ranged from 35.3 kg/m$^2$ to 36.2 kg/m$^2$. The mean ELF score of the patients ranged from 9.5 to 10.6. A summary of baseline characteristics of the included studies is included in Table 1.

### Risk of bias assessment

The quality of the assessment is presented in Supplementary Figures 10 and 11 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612). All the included studies were judged to be at low risk of bias in all domains as determined by the RoB2 tool.

### The ELF score

The ELF scores were reported by all the included studies for 1 mg dose of aldafermin while two studies also reported for 3 mg dose of aldafermin. The analysis revealed a pooled MD of −0.13 (95% CI: −0.28 to −0.03; $P = 0.1$; $I^2 = 0\%$; Fig. 2) for the 1 mg dose of aldafermin. The analysis indicated a pooled MD of −0.46 (95% CI: −0.64 to −0.28; $P < 0.00001$; $I^2 = 0\%$; Fig. 2) for the 3 mg dose of aldafermin, favoring the intervention group. There was evidence of publication bias as determined by the shape of the doi plots, which showed minor asymmetry (LFK index = −1.80), as shown in Supplementary Figure 12 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612). The quality of evidence, as determined by GRADE, was ranked to be low (Table 2).

The hyaluronic acid levels were reported by all the included studies for a 1 mg dose of aldafermin, while two studies also reported a 3 mg dose of aldafermin. The analysis yielded a pooled MD of −1.94 (95% CI: −19.94 to 16.06; $P = 0.83$; $I^2 = 0\%$; Supplementary Fig. 3, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 1 mg dose of aldafermin. The analysis showed a pooled MD of −5.77 (95% CI: −28.18 to 16.64; $P = 0.61$; $I^2 = 0\%$; Supplementary Fig. 3, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 3 mg dose of aldafermin.

The N-terminal propeptide of type III collagen (PIIINP) levels were also reported by all the included studies for 1 mg dose of aldafermin while two studies also reported a 3 mg dose of aldafermin. The analysis yielded a pooled MD of −2.24 (95% CI: −3.44 to −1.04; $P = 0.0003$; $I^2 = 0\%$; Supplementary Fig. 4, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 1 mg dose of aldafermin, favoring the experimental arm. The analysis yielded a pooled MD of −4.51 (95% CI: −6.31 to −2.71; $P < 0.00001$; $I^2 = 11\%$; Supplementary Fig. 4, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 3 mg dose of aldafermin, favoring the experimental arm.

The tissue inhibitor of matrix metalloproteinase (TIMP-1) levels were also reported by all the included studies for a 1 mg dose of aldafermin, while two studies also reported a 3 mg dose of aldafermin. The analysis yielded a pooled MD of −15.00 (95% CI: −31.96 to 1.97; $P = 0.08$; $I^2 = 0\%$; Supplementary Fig. 5, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 1 mg dose of aldafermin. While the analysis yielded a pooled MD of −27.24 (95% CI: −52.31 to −2.16; $P = 0.03$; $I^2 = 11\%$; Supplementary Fig. 5, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 3 mg dose of aldafermin, favoring the experimental arm.

### Fibrosis improvement with no NASH worsening

Fibrosis improvement with no worsening of NASH was reported by all the included studies for 1 mg dose of aldafermin while two studies also reported for 3 mg dose of aldafermin. The analysis yielded a pooled MD of 5.53 (95% CI: −7.35 to 18.41; $P = 0.40$; $I^2 = 34\%$; Fig. 3) for the 1 mg dose of aldafermin. The analysis yielded a pooled MD of 8.15 (95% CI: −3.62 to 19.93; $P < 0.17$; $I^2 = 0\%$; Fig. 3) for the 3 mg dose of aldafermin. There was no evidence of publication bias as determined by the shape of the doi plots, which showed no asymmetry (LFK index = 0.67), as shown in Supplementary Figure 13 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612). The quality of evidence, as determined by GRADE, was ranked to be moderate (Table 2).

### Fibrosis improvement and NASH resolution

Fibrosis improvement and NASH resolution were reported by all the included studies for 1 mg dose of aldafermin while two studies

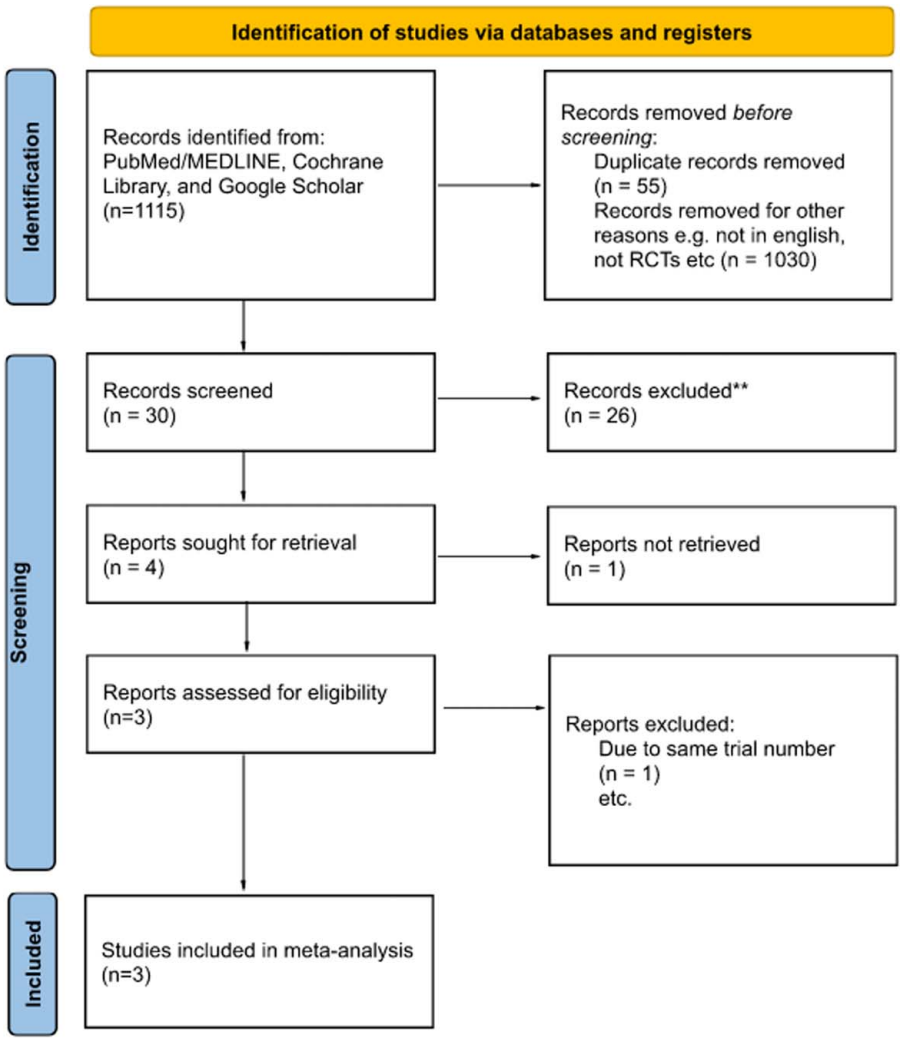


**Figure 1.** PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

also reported for 3 mg dose of aldafermin. The analysis yielded a pooled MD of 11.70 (95% CI: 0.93–22.48; $P = 0.03$; $I^2 = 57\%$; Fig. 4) for the 1 mg dose of aldafermin. The analysis yielded a pooled MD of 10.16 (95% CI: 1.68–18.64; $P = 0.02$; $I^2 = 0\%$; Fig. 4) for the 3 mg dose of aldafermin. There was evidence of publication bias as determined by the shape of the doi plots, which showed minor asymmetry (LFK index = 1.78), as shown in Supplementary Figure 14 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612). The quality of evidence, as determined by GRADE, was ranked to be low (Table 2).

### *Pro-C3*

The Pro-C3 levels were reported by all the included studies for 1 mg dose of aldafermin while two studies also reported for 3 mg dose of aldafermin. The analysis yielded a pooled MD of –4.67 (95% CI: –8.36 to –0.98; $P = 0.01$; $I^2 = 52\%$; Fig. 5) for the 1 mg dose of aldafermin. The analysis yielded a pooled MD of –14.44 (95% CI: –32.77 to 3.90; $P = 0.12$; $I^2 = 79\%$; Fig. 5) for the 3 mg dose of aldafermin. There was evidence of publication bias as determined by the shape of the doi plots, which showed major asymmetry (LFK index = –4.17), as shown in Supplementary Figure 15 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612). The quality of evidence, as determined by GRADE, was ranked to be very low (Table 2).

### *Absolute and relative AST*

The absolute AST levels were reported by all the included studies for 1 mg dose of aldafermin while two studies also reported for 3 mg dose of aldafermin. The analysis yielded a pooled MD of –9.49 (95% CI: –13.78 to –5.19; $P < 0.0001$; $I^2 = 0\%$; Supplementary Fig. 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 1 mg dose of aldafermin. The analysis yielded a pooled MD of –13.40 (95% CI: –18.66 to –8.14; $P < 0.00001$; $I^2 = 12\%$; Supplementary Fig. 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 3 mg dose of aldafermin. There was no evidence of publication bias as determined by the shape of the doi plots, which showed no asymmetry (LFK index = –0.86), as shown in Supplementary Fig. 16 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612). The quality of evidence, as determined by GRADE, was ranked to be moderate (Table 2).

**Table 1**

**Baseline characteristics of the included studies.**

| | Harrison *et al.* 2021 | | Harrison *et al.* 2022 | | | | Rinella *et al.* 2023[10] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Aldafermin | | | | Aldafermin | | |
| | Aldafermin | Placebo | 0.3 mg dose | 1.0 mg dose | 3.0 mg dose | Placebo | 1.0 mg dose | 3.0 mg dose | Placebo |
| Location | USA | | | USA | | | Australia, Belgium, China [Hong Kong], France, Germany, Poland, United Kingdom, and United States | | |
| Sample size | 53 | 25 | 43 | 42 | 43 | 43 | 42 | 55 | 56 |
| Age [Years][a] | 53.0 (12.1) | 54.1 (9.7) | 54.3 (11.2) | 49.8 (13.2) | 52.7 (11.1) | 53.0 (10.8) | 61.3 (7.6) | 59.6 (8.7) | 58.3 (8.1) |
| Males (*n*) | 27 | 9 | 15 | 13 | 14 | 17 | 19 | 19 | 17 |
| Body weight [kg][a] | 99.8 (20.8) | 102.5 (29.7) | 103·4 (21·7) | 108·0 (26·9) | 109·2 (19·6) | 108·3 (22·3) | 101.5 (22.2) | 95.3 (22.4) | 93.4 (19.9) |
| BMI [kg/m$^2$][a] | 35.8 (6.3) | 36.8 (9.0) | 37·3 (6·9) | 38·2 (6·8) | 38·6 (7·1) | 38·4 (6·6) | 36.0 (6.3) | 34.3 (6.7) | 34.8 (7.1) |
| T2DM [n][a] | 32 | 16 | 20 | 22 | 24 | 18 | 32 | 42 | 42 |
| Serum C4 [ng/ml][a] | 33.2 (27.0) | 42.0 (22.1) | 53·8 (38·9) | 49·7 (34·0) | 43·3 (41·2) | 37·4 (27·8) | 38.7 (25.7) | 43.7 (37.9) | 45.4 (33.5) |
| ALT [U/l][a] | 73.3 (39.6) | 55.1 (29.6) | 64·3 (32·8) | 61·0 (44·3) | 63·7 (50·3) | 58·5 (48·6) | 46.4 (23.2) | 51.2 (29.6) | 45.6 (31.2) |
| AST [U/l][a] | 54.5 (27.4) | 44.3 (23.7) | 46·0 (21·2) | 45·7 (27·3) | 47·3 (30·0) | 48·2 (36·1) | 39.5 (19.4) | 45.0 (25.7) | 36.9 (21.1) |
| ALP [U/l][a] | 84.8 (25.6) | 84.0 (23.0) | 81·2 (25·9) | 80·6 (24·7) | 73·9 (21·2) | 82·9 (46·2) | 74.6 (27.6) | 83.9 (32.3) | 80.9 (25.1) |
| ELF[a] | 9.8 (0.8) | 9.9 (1.0) | 9·6 (0·9) | 9·5 (0·9) | 9·6 (1·0) | 9·8 (1·0) | 10.6 (0.8) | 10.6 (1.1) | 10.6 (1.0) |
| Hyaluronic Acid [ng/ml][a] | 77.2 (82.2) | 91.2 (132.6) | 67·6 (78·7) | 66·9 (88·2) | 61·8 (57·2) | 73·4 (77·3) | 155.6 (104.5) | 188.5 (213.0) | 177.5 (157.2) |
| PIIINP [ng/ml][a] | 11.5 (4.0) | 11.7 (4.9) | 12·3 (5·2) | 12·0 (4·8) | 12·9 (6·8) | 13·6 (6·4) | 14.1 (5.9) | 15.9 (8.4) | 14.0 (6.0) |
| TIMP-1 [ng/ml][a] | 281.4 (75.9) | 278.8 (80.1) | 276·6 (84·0) | 267·5 (81·4) | 278·5 (82·3) | 292·5 (100·2) | 337.9 (114.8) | 326.2 (96.3) | 318.4 (98.7) |
| HOMA-IR[a] | 9.9 (8.6) | 9.9 (10.3) | 9·8 (5·3) | 7·8 (4·6) | 11·1 (9·2) | 15·8 (36·6) | 11.8 (10.0) | 20.0 (32.1) | 11.5 (10.9) |
| Total cholesterol [mg/dl][a] | 173.5 (37.0) | 171.4 (38.0) | 197.2 (46.40) | 177.9 (27.07) | 174.0 (42.54) | 185.6 (42.54) | 158.5 (38.67) | 162.4 (42.54) | 166.3 (38.67) |
| HDL cholesterol [mg/dl][a] | 31.7 (12.5) | 34.5 (16.7) | 42.5 (15.47) | 50.3 (15.47) | 46.4 (11.60) | 46.4 (19.34) | 46.4 (11.60) | 46.4 (11.60) | 46.4 (15.47) |
| LDL cholesterol [mg/dl][a] | 95.1 (31.0) | 95.0 (31.6) | 112.1 (34.80) | 96.7 (27.07) | 96.7 (38.67) | 104.4 (34.80) | 85.1 (34.80) | 88.9 (34.80) | 92.8 (34.80) |
| Triglycerides [mg/dl][a] | 194.2 (164.3) | 167.7 (119.2) | 194.9 (106.28) | 168.3 (106.28) | 159.4 (62.00) | 177.1 (97.43) | 150.6 (62.00) | 141.7 (44.29) | 150.6 (79.71) |
| Prior statin therapy [*n*] | 20 | 5 | 13 | 15 | 18 | 17 | 21 | 38 | 27 |

[a]Reported as Mean (SD).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; HOMA-IR, homeostasis model assessment–estimated insulin resistance; PIIINP, type III procollagen peptide; T2DM, type 2 diabetes mellitus; TIMP-1, tissue inhibitor of metalloproteinase 1.

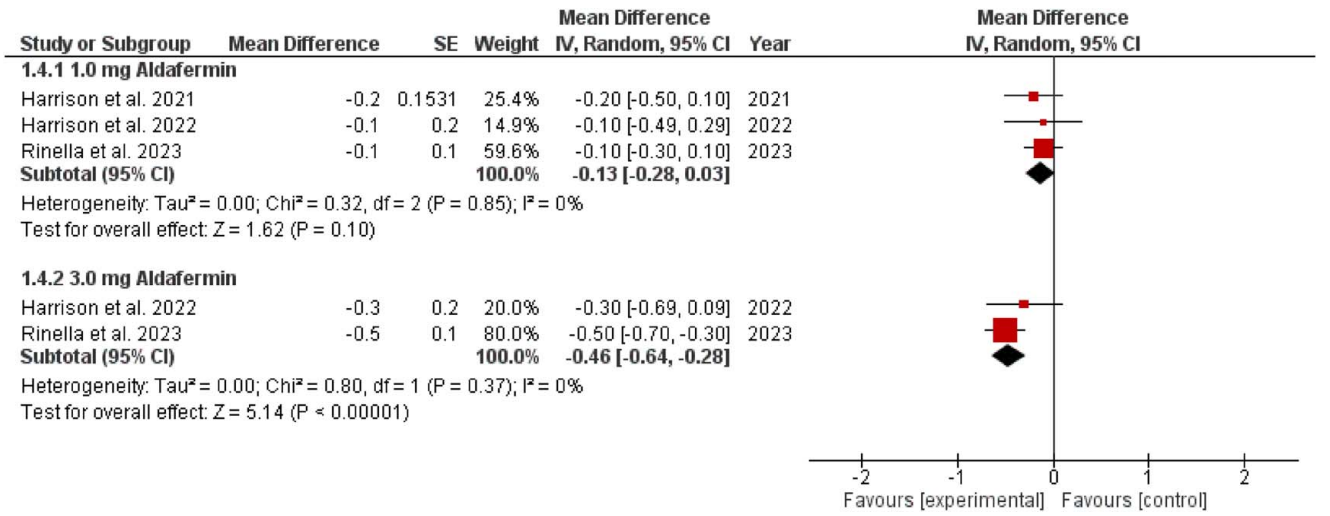


**Figure 2.** Forest plot of pooled ELF scores. ELF, enhanced liver fibrosis.

The relative AST levels were reported by all the included studies for 1 mg dose of aldafermin while two studies also reported for 3 mg dose of aldafermin. The analysis yielded a pooled MD of −22.12 (95% CI: −31.05 to −13.18; $P < 0.00001$; $I^2 = 0\%$; Supplementary Fig. 6, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 1 mg dose of aldafermin. The analysis yielded a pooled MD of −29.34 (95% CI: −39.34 to −19.35; $P < 0.00001$; $I^2 = 0\%$; Supplementary Fig. 6, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 3 mg dose of aldafermin.

### *Absolute and relative ALT*

The absolute ALT levels were reported by all the included studies for 1 mg dose of aldafermin while two studies also reported for 3 mg dose of aldafermin. The analysis yielded a pooled MD of −16.17 (95% CI: −20.70 to −11.64; $P < 0.00001$; $I^2 = 0\%$; Supplementary Fig. 2, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 1 mg dose of aldafermin. The analysis yielded a pooled MD of −19.92 (95% CI: −27.08 to −12.75; $P < 0.00001$; $I^2 = 44\%$; Supplementary Fig. 2, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 3 mg dose of aldafermin. There was no evidence of publication bias as determined by the shape of the doi plots, which showed no asymmetry (LFK index = −0.86), as shown in Supplementary Fig. 17 (Supplemental Digital Content 3, http://links.lww.com/MS9/A612). The quality of evidence, as determined by GRADE, was ranked to be moderate (Table 2).

The relative ALT levels were reported by all the included studies for 1 mg dose of aldafermin while two studies also reported for 3 mg dose of aldafermin. The analysis yielded a pooled MD of −32.33 (95% CI: −40.52 to −24.14; $P < 0.00001$; $I^2 = 0\%$; Supplementary Fig. 7, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 1 mg dose of aldafermin. The analysis yielded a pooled MD of −37.22 (95% CI: −46.65 to −27.79; $P < 0.00001$; $I^2 = 0\%$; Supplementary Fig. 7, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for the 3 mg dose of aldafermin.

### *Absolute and relative liver fat content*

The absolute liver fat content was reported by only two studies for 1 mg dose of aldafermin. The analysis yielded a pooled MD of −4.40 (95% CI: −6.43 to −2.38; $P < 0.0001$; $I^2 = 0\%$; Supplementary Fig. 8, Supplemental Digital Content 3, http://links.lww.com/MS9/A612).

The relative liver fat content was also reported by only two studies for 1 mg dose of aldafermin. The analysis yielded a pooled MD of −24.00 (95% CI: −35.36 to −12.63; $P < 0.0001$; $I^2 = 0\%$; Supplementary Fig. 9, Supplemental Digital Content 3, http://links.lww.com/MS9/A612).

### *Adverse events*

We also pooled the common adverse events that were reported in the included studies. The pooled RRs revealed nonsignificant results for nausea, headache, diarrhea, constipation, and abdominal pain for 1 mg dose of aldafermin in the included studies. The analysis yielded a pooled RR of 1.22 (95% CI: 0.74–2.0; $P = 0.4$; $I^2 = 0\%$; Supplementary Fig. 18, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 1 mg dose of aldafermin and a pooled RR of 2.03 (95% CI: 1.20–3.45; $P = 0.009$; $I^2 = 0\%$; Supplementary Fig. 18, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 3 mg dose of aldafermin for nausea reported as an adverse event. For headache, the analysis yielded pooled RR of 0.52 (95% CI: 0.27–1.0; $P = 0.05$; $I^2 = 0\%$; Supplementary Fig. 19, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 1 mg dose of aldafermin and a pooled RR of 1.35 (95% CI: 0.59–3.07; $P = 0.48$; $I^2 = 0\%$; Supplementary Fig. 19, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 3 mg dose of aldafermin. For diarrhea, the analysis yielded a pooled RR of 1.12 (95% CI: 0.36–3.48; $P = 0.84$; $I^2 = 75\%$; Supplementary Fig. 20, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 1 mg dose of aldafermin and a pooled RR of 1.79 (95% CI: 0.44–7.29; $P = 0.42$; $I^2 = 79\%$; Supplementary Fig. 20, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 3 mg dose of aldafermin. The analysis yielded pooled RR of 0.71 (95% CI: 0.24–2.05; $P = 0.53$; $I^2 = 10\%$;

**Table 2**

**Grading of recommendations, assessment, development, and evaluation (GRADE) summary of findings.**

| Outcome | No. of participants (studies) | Effect estimate (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Quality of Evidence (GRADE) |
|---|---|---|---|---|---|---|---|---|
| ELF Score (3 mg aldafermin) | 197 (2) | MD −0.46 (−0.64 to −0.28) | Not serious | Not serious | Not serious | Serious | Suspected | ⊕⊕⊖⊖ LOW |
| Fibrosis improvement with no worsening of NASH (3 mg aldafermin) | 197 (2) | MD 8.15 (−3.62 to 19.93) | Not serious | Not serious | Not serious | Serious | Not serious | ⊕⊕⊕⊖ MODERATE |
| Fibrosis improvement with NASH resolution (3 mg aldafermin) | 197 (2) | MD 10.16 (1.68–18.64) | Not serious | Not serious | Not serious | Serious | Suspected | ⊕⊕⊖⊖ LOW |
| Absolute Neoepitope (Pro-C3) levels (3 mg aldafermin) | 197 (2) | MD −14.44 (−32.77 to 3.90) | Not serious | Not serious | Not serious | Serious | Suspected | ⊕⊕⊖⊖ LOW |
| Absolute Aspartate Aminotransferase levels (3 mg aldafermin) | 197 (2) | MD −13.40 (−18.66 to −8.14) | Not serious | Not serious | Not serious | Serious | Not serious | ⊕⊕⊕⊖ MODERATE |
| Absolute Alanine Aminotransferase levels (3 mg aldafermin) | 197 (2) | MD −19.92 (−27.08 to −12.75) | Not serious | Not serious | Not serious | Serious | Not serious | ⊕⊕⊕⊖ MODERATE |

ELF, enhanced liver fibrosis; MD, mean difference; NASH, nonalcoholic steatohepatitis.

Supplementary Fig. 21, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 1 mg dose of aldafermin and a pooled RR of 0.94 (95% CI: 0.42–2.14; $P = 0.89$; $I^2 = 0\%$; Supplementary Fig. 21, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 3 mg dose of aldafermin for constipation reported as an adverse event. For abdominal pain, the analysis yielded a pooled RR of 0.53 (95% CI: 0.21–1.35; $P = 0.18$; $I^2 = 0\%$; Supplementary Fig. 22, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 1 mg dose of aldafermin and a pooled RR of 0.66 (95% CI: 0.30–1.44; $P = 0.29$; $I^2 = 0\%$; Supplementary Fig. 22, Supplemental Digital Content 3, http://links.lww.com/MS9/A612) for 3 mg dose of aldafermin.

## Discussion

As far as we are aware, this meta-analysis is the first to examine aldafermin's safety and effectiveness in NASH patients. The pooled results supported the argument that aldafermin has superior efficacy compared to placebo. A dose-dependent response is observed with aldafermin therapy. When compared to a placebo, aldafermin therapy showed a statistically significant improvement in the ELF score for the 3 mg dosage. However, a nonsignificant benefit was observed in terms of ELF score for a 1 mg dose of aldafermin. The individual components of ELF score showed comparable results between aldafermin therapy and placebo, where a statistically significant benefit in terms of reduction in PIIINP and TIMP-1was observed for 3 mg dose of aldafermin and a nonsignificant reduction in hyaluronic acid levels was reported for 1 mg and 3 mg dose of aldafermin. Aldafermin produced a statistically significant benefit in terms of pooled data for fibrosis improvement and NASH resolution for both the 1 mg and 3 mg dosages. On the other hand, aldafermin at doses of 1 mg and 3 mg showed a nonsignificant improvement in fibrosis without aggravating NASH. For the 1 mg dosage, aldafermin therapy produced a statistically significant reduction in the fibrosis marker, Pro-C3. However, a nonsignificant benefit was observed for the 3 mg dose. Regarding hepatic enzymes, aldafermin treatment resulted in a statistically significant decrease in both absolute and relative ALT and AST values for both the 1 mg and 3 mg dosages.

The observed improvement in ELF scores with the 3 mg dose of aldafermin could be attributed to the dose-dependent response of aldafermin. Higher doses may exert a more pronounced effect on liver fibrosis due to enhanced activation of fibroblast growth factor receptors (FGFRs) and downstream signaling pathways involved in fibrosis modulation[21]. Aldafermin likely improves fibrosis through multiple mechanisms, including inhibition of hepatic stellate cell activation, reduction of collagen deposition, and suppression of proinflammatory cytokines, ultimately leading to decreased fibrogenesis and improved tissue remodeling. Moreover, the superior results for improving fibrosis markers (such as Pro-C3) and reduction in liver enzymes (such as ALT and AST) with aldafermin therapy could be attributed to its ability to mitigate hepatocellular injury, inflammation, and oxidative stress, thereby promoting liver function and reducing liver enzyme levels[22]. Additionally, aldafermin's effects on bile acid synthesis and metabolism may contribute to its hepatoprotective properties, further enhancing its efficacy in improving liver func tion parameters and fibrosis outcomes.

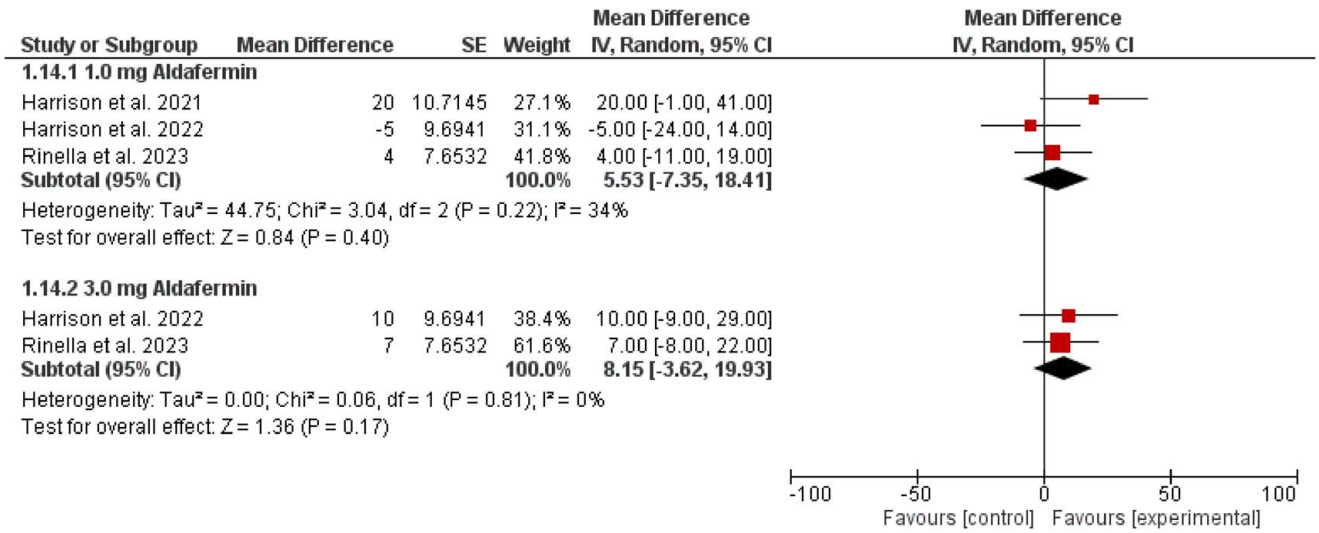


**Figure 3.** Forest plot of fibrosis improvement with no worsening of NASH.

Compared to previous treatment standards for patients with NAFLD, which primarily focused on lifestyle modifications and weight loss[23,24], aldafermin provides a complementary strategy, especially for patients with NASH who are at higher risk of disease progression, such as insulin resistance, inflammation, and bile acid synthesis, potentially halting or reversing disease progression[14,15].

Clinicians can use this information to guide treatment decisions, particularly in patients with advanced NASH or those who do not respond adequately to lifestyle interventions alone. Regular monitoring of liver histology and biochemical markers is essential to assess treatment response and adjust therapy as needed, emphasizing the practical implications of our findings for clinical practice and the evolving landscape of NASH management.

According to the most up-to-date network meta-analysis published by Kovalic AJ[25], aldafermin 1 mg was the most effective medication for achieving a minimum two-point reduction in NAS and overall NASH resolution without aggravating fibrosis. It was also the most well-respected strategy for fibrosis improvement that avoided exacerbating NASH. This was based on a single trial with published results in comparison to other drugs that have ongoing trials; however, with two additional trials now, our meta-analysis reinforces the proposition as an effective treatment for NASH, which, prior to resmetirom, did not have a standard therapeutic medication.

Multiple clinical trials are being done on a number of FGF analogs for NASH[26–31], with aldafermin leading the way along with pegbelfermin and efruxifermin, both FGF21 analogs, demonstrating encouraging outcomes in the resolution of NASH[32]. As mentioned above, aldafermin decreases bile acid synthesis via the FGFR4-KLB receptor, contributing to better out comes in patients, which is not the case with FGF21 analogs since FGF21 primarily modulates fatty acid/glucose metabolism[33]. However, aldafermin's negligible effects on glucose, insulin, and

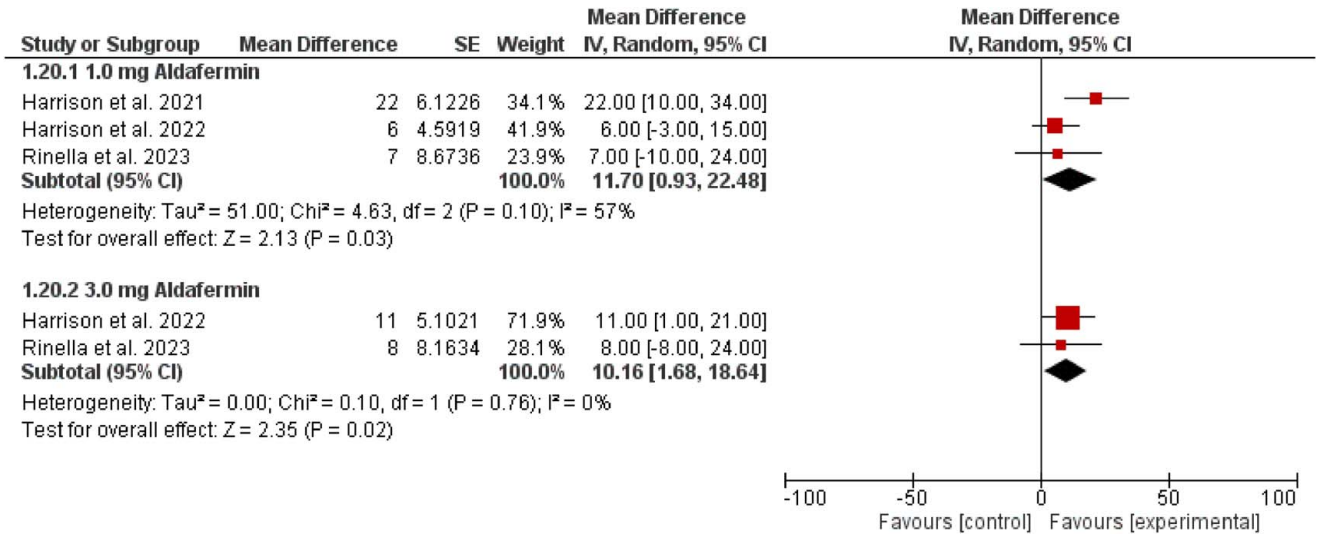


**Figure 4.** Forest plot of fibrosis improvement with NASH resolution. NASH, nonalcoholic steatohepatitis.

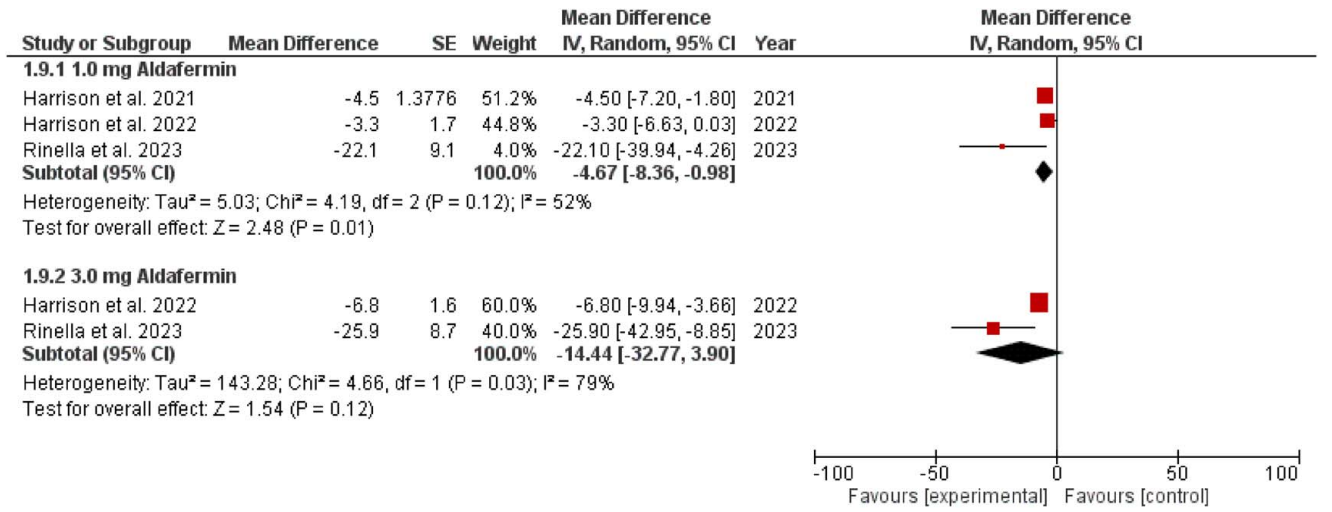


**Figure 5.** Forest plot of pooled absolute neoepitope (Pro-C3) levels.

HbA1c concentrations, as seen in trials, suggest a lack of corrective action on metabolic dysfunction, contrasting with the observed responses elicited by FGF21 analogs[28].

In addition, another network meta-analysis comparing the effectiveness of the respective interventions on liver histology highlighted that the drugs with the best probability of reducing fibrosis by at least one stage without making NASH worse were aldafermin, lanifibranor, and obeticholic acid, respectively[34]. This again indicates Aldafermin's potential, with the highest probability of reducing fibrosis by one stage among current drugs being tested for NASH. Additionally, obeticholic acid has been observed to cause severe liver injury risk in patients with advanced cirrhosis and primary biliary cholangitis. Therefore, the FDA has restricted its use in the concerned population[35].

It is critical to recognize any potential limitations that our study may have while being conducted. Our meta-analysis included only three RCTs, indicating a need for further trials to provide more concrete evidence. A significant concern was the variation in the primary endpoints selected in each study. In addition, the sample sizes for most of the experimental studies were comparatively small. Moreover, doi plots suggested moderate asymmetry, indicating possible bias in our respective studies. Meanwhile, there was a lack of diversity in these trials since the proportion of white participants was noticeably higher. This may reduce the result's global applicability and lead to different reactions from participants who are not of the same race. Thus, additional research is required to gain a deeper comprehension of Aldafermin's effectiveness in NASH. Longer follow-up periods and a larger sample size should be included in future research. The inclusion of more diverse individuals should be preferred. Primary endpoints ought to be consistent in subsequent future research as well.

In conclusion, our meta-analysis suggests that aldafermin demonstrates promising efficacy in improving liver histology and biochemical markers in patients with NASH. The findings support its potential as a therapeutic option for NASH, particularly in combination with lifestyle modifications. However, further large-scale, diverse clinical trials are warranted to confirm these findings and comprehensively establish Aldafermin's role in the management of NASH.

## Impact and Implications

1. Our meta-analysis addresses the pressing need for effective treatments for nonalcoholic steatohepatitis (NASH), a condition associated with increasing prevalence and severe health outcomes.
2. The findings reveal that aldafermin shows promise in improving liver histology and biochemical markers in NASH patients, offering a potential therapeutic avenue where current options are limited.
3. These results hold significant implications for clinicians, researchers, and policymakers grappling with the lack of approved pharmacotherapy for NASH and the growing burden it poses on public health systems.
4. However, methodological limitations, such as small sample sizes and potential publication bias, emphasize the importance of cautious interpretation and the necessity for further robust clinical trials to confirm these findings and guide future treatment strategies.

## Ethical approval

Ethics approval was not required for this systematic review.

## Consent

Informed consent was not required for this systematic review.

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None.

## Author contribution

M.H.A. and M.T.: writing – original draft, conceptualization, methodology, and data curation; O.U.R. and E.F.: writing – original draft, data curation, and software; L.F.: writing – original draft, review and editing; A.Z. and M.A.H.: writing – reviewing and editing.

## Conflicts of interest disclosure

The authors declare no conflict of interest.

## Research registration unique identifying number (UIN)

PROSPERO UIN: CRD42024513038. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=513038.

## Guarantor

Mohammad Haris Ali.

## Data availability statement

Data sharing is not applicable to this review.

## Provenance and peer review

Not commissioned; externally peer-reviewed.

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