ORIGINAL ARTICLE OPEN ACCESS

Evaluating the Effectiveness of Pegbelfermin in MASH-Associated Hepatic Fibrosis A Meta-Analysis and Systematic Review of Randomized Controlled Trials

Muhammad Shahzil[1] | Fariha Hasan[2] | Syeda Kanza Kazmi[1] | Manesh Kumar Gangwani[3] | UmmeSalma Shabbar[4] | Ammad Javaid Chaudhary[5] | Muhammad Ali Khaqan[6] | Muhammad Saad Faisal[5] | Kathy N. Williams[7] | Babu P. Mohan[8] | Christina Tofani[7]

[1]Department of Internal Medicine, Penn State Health Milton S Hershey Medical Center, Hershey, Pennsylvania, USA | [2]Department of Internal Medicine, Cooper University Hospital, Camden, New Jersey, USA | [3]Department of Internal Medicine, The University of Toledo, Toledo, Ohio, USA | [4]Dow Medical College, Karachi, Pakistan | [5]Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan, USA | [6]Department of Internal Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, Illinois, USA | [7]Department of Gastroenterology, Cooper University Hospital, Camden, New Jersey, USA | [8]Gastroenterology and Hepatology, Orlando Gastroenterology PA, Orlando, Florida, USA

Correspondence: Muhammad Shahzil (mshahzil@pennstatehealth.psu.edu)

Received: 8 July 2024 | **Revised:** 18 February 2025 | **Accepted:** 2 March 2025

Funding: The authors received no specific funding for this work.

Keywords: fatty liver | fibroblast growth factor 21 | liver cirrhosis | non-alcoholic fatty liver disease | pegbelfermin

ABSTRACT

Introduction: Metabolic dysfunction-associated steatohepatitis (MASH), an advanced form of fatty liver disease, is characterized by liver inflammation and fibrosis, with an emerging interest in fibroblast growth factor (FGF)-21 analogs, particularly pegbelfermin (PGBF). This study evaluates the efficacy and safety of PGBF in treating MASH-associated hepatic fibrosis.

Methods: This meta-analysis followed Cochrane guidelines and PRISMA standards. A comprehensive search of databases up to January 2023 focused on randomized controlled trials (RCTs) comparing PGBF to placebo for MASH. Meta-analyses were performed with RevMan 5.4 using a random-effects model.

Results: Data from 452 participants across three RCTs were analyzed. Significant improvements in adiponectin concentration were observed in both the 10 mg [MD = 18.23, 95% CI (6.35, 30.11), $p = 0.003$] and 20 mg [MD = 18.09, 95% CI (5.88, 30.31), $p = 0.004$] PGBF groups compared to placebo. Significant reductions in PRO-C3 concentration were noted in both the 10 mg [MD = −25.50, 95% CI (−43.95, −7.05), $p = 0.007$] and 20 mg [MD = −19.54, 95% CI (−33.33, −5.76), $p = 0.005$] groups. Significant improvement in MASH was seen in the 10 mg group [RR = 2.84, 95% CI (1.18, 6.78), $p = 0.02$] but not in the 20 mg group. No significant improvements in liver stiffness, Modified Ishak scores, collagen proportionate area, ALT and AST levels, or treatment-emergent adverse events (TEAEs) were observed in either dosage group.

Conclusions: Pegbelfermin, a promising therapy for MASH fibrosis, has demonstrated effectiveness at 10 mg, significantly improving MASH and biomarkers including adiponectin and PRO-C3, while maintaining a generally safe profile.

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; CI, Confidence Interval; MASH, Metabolic Dysfunction-Associated Steatohepatitis; MD, Mean Difference; MRE, Magnetic Resonance Elastography; PGBF, Pegbelfermin; PRO-C3, Procollagen Type III N-Terminal Peptide; RCT, Randomized Controlled Trial; RR, Risk Ratio; TEAEs, Treatment-Emergent Adverse Events.

1 | Introduction

Metabolic dysfunction-associated steatohepatitis (MASH), an advanced stage of non-alcoholic fatty liver disease, is identified by steatosis, hepatocyte ballooning, and inflammation evident in liver biopsy [1]. Persistent inflammation, coupled with oxidative stress in individuals with MASH, can lead to hepatic fibrosis. Recent evidence from a multicenter study in Japan highlights that hepatic inflammation and fibrosis are significant factors contributing to mid-term mortality in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), emphasizing the importance of targeting these factors in disease management [2]. MASH has a global prevalence of 1.5%–6.5% in adults [3]. As MASH progresses, there is a risk of developing cirrhosis or hepatocellular carcinoma, often necessitating a liver transplant [4, 5]. While approximately one-third of all adults worldwide are estimated to have non-alcoholic fatty liver disease, a quarter of these are considered to have MASH [4, 6]. With the prevalence of non-alcoholic fatty liver disease expected to increase significantly by 2030 and the rising need for liver transplantation due to MASH cirrhosis, it is imperative to explore better treatment and management strategies [7]. Lifestyle changes, including diet and regular exercise, are the primary treatments for MASH, with weight loss improving liver fibrosis. In some cases, bariatric surgery may also be considered [8, 9]. Additionally, medications such as Pioglitazone and vitamin E can help reduce inflammation, although their impact on fibrosis is limited [8]. Additionally, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been explored for their potential in managing MASLD. Studies suggest that SGLT2 inhibitors may exert hepatoprotective effects by reducing hepatic fibrosis indices, lowering serum ALT levels, and improving metabolic markers in individuals with diabetes and suspected MASLD [10]. A pooled meta-analysis of phase III trials demonstrated that luseogliflozin, an SGLT2 inhibitor, significantly reduced fatty liver index and fibrosis markers in diabetic patients, particularly those with elevated ALT and FIB-4 scores [10]. Furthermore, a large-scale nationwide study in Japan indicated that SGLT2 inhibitors were associated with a decreased incidence of esophageal varices and extrahepatic malignancies in patients with MASLD and type 2 diabetes [11].

Recently, there has been a surge of interest in fibroblast growth factors (FGF) that are recognized as pivotal regulators of energy metabolism. FGF-based medications have exhibited notable effects, including weight loss, improvement of dyslipidemia, and reduction of steatosis in individuals with MASH [12]. The administration of FGF21, a distinguished member of the FGF superfamily, has been associated with pharmacological benefits addressing various metabolic complications [13]. Several FGF21 analogs under investigation via clinical trials have demonstrated substantial improvements in hepatic fat fractions and serum markers of liver fibrosis. These hormones exert their effect on hepatocytes expressing high levels of FGF receptors and hepatic stellate cells. Notably, FGF21 has demonstrated efficacy in attenuating dimethylnitrosamine-induced fibrogenesis and downregulating the expression of transforming growth factor-beta, leading to apoptosis in these cells [13, 14]. Among the FGF21 analogs, pegbelfermin stands out as a PEGylated human FGF21 analog [15]. Numerous clinical trials have delved into the potential of pegbelfermin for addressing MASH-associated hepatic fibrosis. However, a gap exists in the synthesis of evidence comparing the efficacy and safety of pegbelfermin against placebo. Therefore, this systematic review and meta-analysis aim to comprehensively assess the potential of this drug in treating MASH-associated hepatic fibrosis.

2 | Methods

This meta-analysis was meticulously conducted adhering to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16, 17]. Registration was completed with the International Prospective Register of Systematic Reviews (PROSPERO) [CRD42024505461]. Given the nature of this study, which synthesizes data from existing literature, ethical approval was deemed unnecessary.

2.1 | Search Strategy

A comprehensive literature search was performed across several databases including the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE (via Ovid), Embase (Elsevier), and Scopus. The search spanned from each database's inception up to January 2023, aiming to capture the most recent and relevant studies. This review exclusively considered randomized controlled trials (RCTs). A combination of Medical Subject Headings (MeSH) and free-text terms were utilized to identify pertinent studies. These terms included "Pegbelfermin," "non-alcoholic steatohepatitis (NASH)", "BMS-986036," and "NASH." A detailed description of the search strategy, including specific search strings are found in Table S1.

2.2 | Study Selection Process

All identified records were imported into Mendeley (version 1.19.8) for de-duplication. Two reviewers (MS and FH) independently screened titles and abstracts for relevance. Full-text articles were then assessed against the inclusion criteria. Any discrepancies between reviewers were resolved through discussion or consultation with a third, independent reviewer (AJ). A PRISMA flowchart visually depicts the study selection process (Figure 1).

2.3 | Data Collection Process

Data extraction was independently conducted by two reviewers (MS and FH) into a predefined Excel template. Discrepancies were resolved by a consensus or by involving a third reviewer (AJ). Extracted information included patient characteristics, intervention and comparator details, outcome data, and study characteristics based on the PICOS framework.

2.4 | Eligibility Criteria

Inclusion criteria were strictly defined to encompass RCTs comparing Pegbelfermin (PEG) for the treatment of MASH-related fibrosis against a placebo. Studies were selected based on the following criteria: (1) Adults (≥ 18 years) diagnosed with

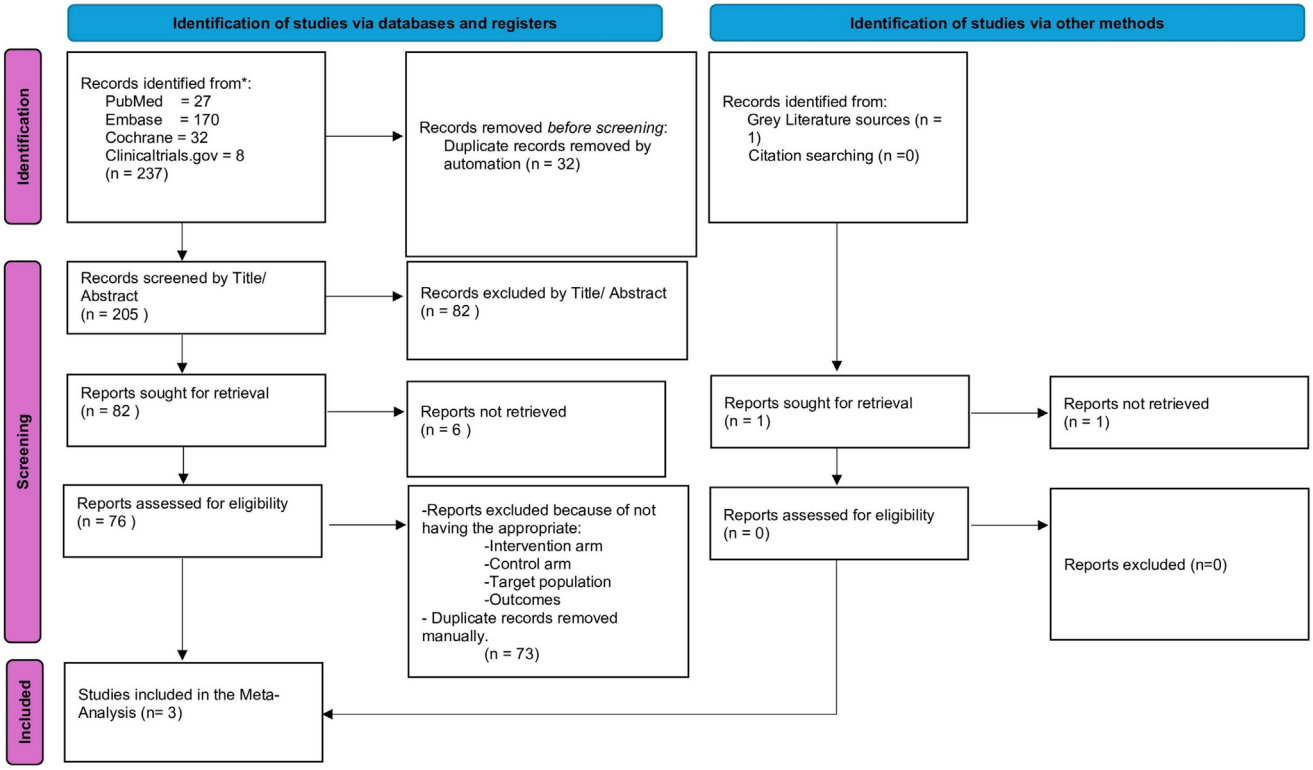


FIGURE 1 | PRISMA flow diagram illustrating the study selection process for the meta-analysis.

MASH-associated hepatic fibrosis (≥1 stage per Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) criteria) (2) Intervention: PEG; (3) Control: Placebo; (4) Outcomes: Adiponectin concentration, liver stiffness (by MRE), PRO-C3 concentration, Alanine aminotransferase, and Aspartate aminotransferase concentrations. Abstracts based on RCTs meeting all these criteria were considered. Exclusions were made for case reports, case series with fewer than 10 patients, guidelines, non-comparative studies (e.g., case–control, cohort studies), and reviews. Observational studies, literature reviews, case reports, duplicates, conference proceedings, animal studies, and unpublished articles were excluded.

2.5 | Outcomes

Primary outcomes focused on Adiponectin concentration, liver stiffness (by MRE), and PRO-C3 concentration. Secondary outcomes encompassed Improvements in Non-alcoholic steatohepatitis (NASH) CRN fibrosis score, changes in Alanine aminotransferase, Aspartate aminotransferase concentrations, Modified Ishak score improvement, and any decrease in collagen proportionate area.

2.6 | Bias Assessment

The quality of included studies was evaluated using the RoB 2.0 tool from the Cochrane Handbook [18]. Each study was independently assessed across several domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Judgments were categorized as low risk, some concerns, or high risk of bias. To determine the certainty of evidence for each outcome, we used the five grades of recommendation, assessment, development, and evaluation (GRADE) considerations [19]. These considerations include evaluating study limitations, consistency of effect, imprecision, indirectness, and publication bias. GRADEPro GDT was utilized to construct the Summary of Findings (SoF) table illustrated in Table S2.

2.7 | Statistical Analysis

Meta-analyses were conducted using RevMan 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) with a random-effects model to account for clinical and methodological heterogeneity among studies. This model was chosen based on the assumption that variations in effect sizes arise not only from sampling error but also from real differences in study populations, interventions, and methodologies. The DerSimonian and Laird method was used to estimate between-study variance (τ^2), providing a more conservative pooled estimate. Dichotomous outcomes were expressed as relative risk ratios (RR), and continuous outcomes as mean differences (MD) with 95% CIs. Statistical significance was set at $p < 0.05$. Heterogeneity was assessed using the Chi-square test and the Higgins I^2 statistic. Funnel plots and DOI plots in MetaXL (using Luis Furuya–Kanamori index) were visually inspected for publication bias in outcomes with >10 studies and <10 studies (But more than three studies) respectively. A sensitivity analysis was conducted on the primary outcome by excluding studies at high risk of bias. Sensitivity analyses were conducted to explore the sources of heterogeneity.

Scatter plots were used in Microsoft Excel to visualize the dose–response relationship between Pegbelfermin dosage (10 and

TABLE 1 | Baseline characteristics of included studies.

Study ID	Study design	Trial setting	Trial duration (weeks)	Dosage, frequency of dosing		Follow up period (weeks)	Sample size (intervention vs. control)
				PGBF	Control		
Abdelmalek et al. [21]	RCT	48 sites in US and 4 in Japan	48 weeks	10 mg, QW 20 mg, QW	PBO QW	4 weeks	PGBF 10 mg $n=37$ PGBF 20 mg $n=37$ PBO = 39
Loomba et al. [20]	RCT	83 sites in US and 6 in Japan	48 weeks	10 mg, QW 20 mg, QW 40 mg QW	PBO QW	4 weeks	PGBF 10 mg $n=49$ PGBF 20 mg $n=50$ PBO = 49
Sanyal et al. [22]	RCT	17 sites in the US	16 weeks	10 mg OD 20 mg QW	PBO OD	26 weeks	PGBF 10 mg $n=25$ PGBF 20 mg $n=24$ PBO = 26

Abbreviations: OD, once daily; PBO, placebo; PGBF, pegbelfermin; QW, per week; RCT, randomized controlled trials.

20 mg) and changes in AST and ALT levels. Due to the limited number of data points, regression analysis could not be performed reliably. Instead, polynomial trendlines were applied to illustrate potential patterns in the data. The trendline equations and R^2 values were displayed to assess the fit, but the interpretation was limited by the small sample size.

3 | Results

Our systematic review and meta-analysis comprised three RCTs, all conducted in the United States and Japan [20–22]. The participants' mean ages ranged from 47 to 61.4 years and were predominantly women. Detailed characteristics of these studies are provided in Table 1. Table 2 summarizes baseline demographics and characteristics of study participants.

3.1 | Quality Assessment and Publication Bias

The risk of bias in the included studies was evaluated using RoB 2.0. Generally, the studies were deemed high quality, with a low risk of bias overall, as shown in Figure 2.

3.2 | Efficacy Outcomes

Evaluable data was provided from RCTs which included a total of 452 participants. One group consisted of 227 participants, with 113 receiving a Pegbelfermin (PGBF) dose of 10 mg and the remaining participants receiving placebo. In the other group, 225 participants were divided, with 111 participants receiving a PGBF dose of 20 mg and the remaining participants receiving placebo.

3.3 | Primary Outcomes

3.3.1 | Changes in Adiponectin Concentration

A statistically significant difference in the adiponectin concentration between the 10 mg PGBF group and the placebo group [MD = 18.23, 95% CI (6.35, 30.11), $p=0.003$] was noted. The 20 mg PGBF group also showed a statistically significant difference between the PGBF group and the placebo group [MD = 18.09, 95% CI (5.88, 30.31), $p=0.004$]. The heterogeneity tests for the 10 and 20 mg dosage groups demonstrated low variability among the included RCTs, yielding p-values of 0.97 and 0.86, respectively, with an I^2 of 0% in both cases, indicating negligible heterogeneity (Figure 3). The GRADE assessment assigned a high level of certainty to the evidence regarding changes in adiponectin concentrations for both dosage groups.

3.3.2 | Changes in PRO-C3 Concentration

For the 10 mg group, the results of the pooled analysis revealed a statistically significant difference between the PGBF group and the placebo group [MD = −25.50, 95% CI (−43.95, −7.05), $p=0.007$]. Similarly, for the 20 mg group, the results indicated a significant difference between the PGBF group and the placebo group [MD = −19.54, 95% CI (−33.33, −5.76), $p=0.005$]. The heterogeneity tests for the 10 mg and 20 mg dosage groups demonstrated low variability among the included RCTs, yielding p-values of 0.30 and 0.78, respectively, with I^2 values of 17% and 0%, respectively, indicating negligible heterogeneity (Figure 4). The GRADE assessment assigned a high level of certainty to the evidence regarding changes in PRO-C3 concentrations for both dosage groups.

TABLE 2 | Baseline patient demographics and disease characteristics.

Study ID	Age, mean (SD)			Female, *n* (%)			Body mass index, mean (SD)			Type 2 diabetes, *n* (%)		
	PGBF 10 mg	PGBF 20 mg	Control	PGBF 10 mg	PGBF 20 mg	Control	PGBF 10 mg	PGBF 20 mg	Control	PGBF 10 mg	PGBF 20 mg	Control
Abdalmalek et al. [21]	60.2 (8.0)	58.9 (9.3)	61.4 (7.5)	28 (71.8)	25 (67.6)	24 (61.5)	34.5 (5.9)	35.5 (6.2)	35.4 (6.4)	27 (77.1)	27 (79.4)	28 (77.8)
Loomba et al. [20]	56.4 (9.6)	56.3 (10.1)	57.5 (8.0)	29 (59.2)	27 (54.0)	29 (59.2)	36.3 (6.7)	35.1 (6.4)	35.2 (8.1)	34 (72.3)	35 (74.5)	34 (73.9)
Sanyal et al. [22]	52 (10)	52 (12)	47 (12)	15 (60)	17 (71)	16 (62)	34 (4)	35 (6)	37 (7)	9 (36)	8 (33)	11 (42)

Abbreviation: PGBF, pegbelfermin.

3.3.3 | Improvement in Liver Stiffness

Pooled analysis showed there was no statistically significant improvement in liver stiffness—measured by Magnetic Resonance Elastography (MRE)—between the 10 mg group and the placebo group [RR = 1.31, 95% CI (0.84, 2.04), $p = 0.23$]. Similarly, the results between the 20 mg group compared to the placebo group did not show any statistically significant difference as well [RR = 1.41, 95% CI (0.98, 2.02), $p = 0.07$]. The heterogeneity tests for the 10 and 20 mg dosage groups demonstrated low variability among the included RCTs, yielding p-values of 0.28 and 0.47, respectively, with an I^2 of 21% and 0%, respectively, indicating negligible heterogeneity (Figure 5). The GRADE assessment assigned a high level of certainty to the evidence regarding improvement in liver stiffness for both dosage groups.

3.4 | Secondary Outcomes

3.4.1 | Improvement in NASH CRN Fibrosis Score

For the 10 mg PEG group, two RCTs contributed evaluable data on ≥1-stage fibrosis improvement in NASH CRN fibrosis score, demonstrating no significant difference compared to placebo [RR = 1.28, 95% CI (0.75, 2.19), $p = 0.36$]. Similarly, when assessing fibrosis improvement without NASH worsening or NASH improvement, no significant difference was observed between PEG and placebo [RR = 1.30, 95% CI (0.74, 2.28), $p = 0.35$]. The heterogeneity across both analyses was low, with $I^2 = 0\%$ ($p = 0.41$ and $p = 0.42$, respectively) (Figure 6).

For the 20 mg PEG group, two RCTs also evaluated ≥1-stage fibrosis improvement in the NASH CRN fibrosis score, showing no significant difference between PEG and placebo [RR = 1.05, 95% CI (0.59, 1.87), $p = 0.87$]. Similarly, when analyzing fibrosis improvement without NASH worsening or NASH improvement, no statistically significant difference was found [RR = 1.39, 95% CI (0.81, 2.40), $p = 0.23$]. Heterogeneity remained low across both analyses ($I^2 = 0\%$, $p = 0.34$ and $p = 0.69$, respectively) (Figure 6).

The GRADE assessment assigned a high level of certainty to the evidence across all NASH CRN fibrosis score-related outcomes.

3.4.2 | Liver Enzymes

For ALT, pooled analysis showed no statistically significant reduction between the 10 mg group and the placebo group [MD = −9.09, 95% CI (−26.21, 8.04), $p = 0.30$] as well as between the 20 mg and the placebo group [MD = −16.87, 95% CI (−34.24, 0.50), $p = 0.06$]. The heterogeneity tests for the 10 mg and 20 mg dosage groups demonstrated low variability among the included RCTs, yielding p-values of 0.83 and 0.93, respectively, with an I^2 of 0% in both cases, indicating negligible heterogeneity (Figures S2.1 and S2.2). The GRADE assessment assigned a high level of certainty to the evidence regarding ALT for both dosage groups. For AST, pooled analysis showed no statistically significant reduction between the 10 mg group and the placebo group [MD = −17.74, 95% CI (−45.69, 10.20), $p = 0.21$] as well as between the 20 mg group and the placebo group [MD = −26.66,

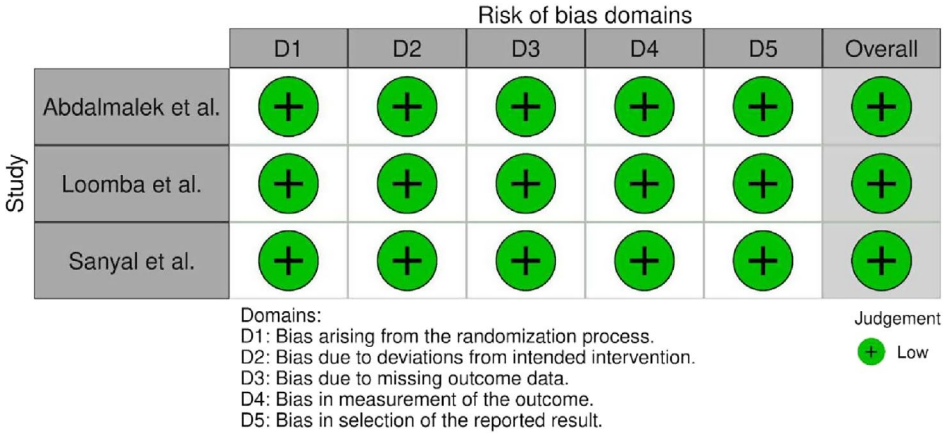


FIGURE 2 | Risk of bias assessment using the RoB 2.0 tool for included studies.

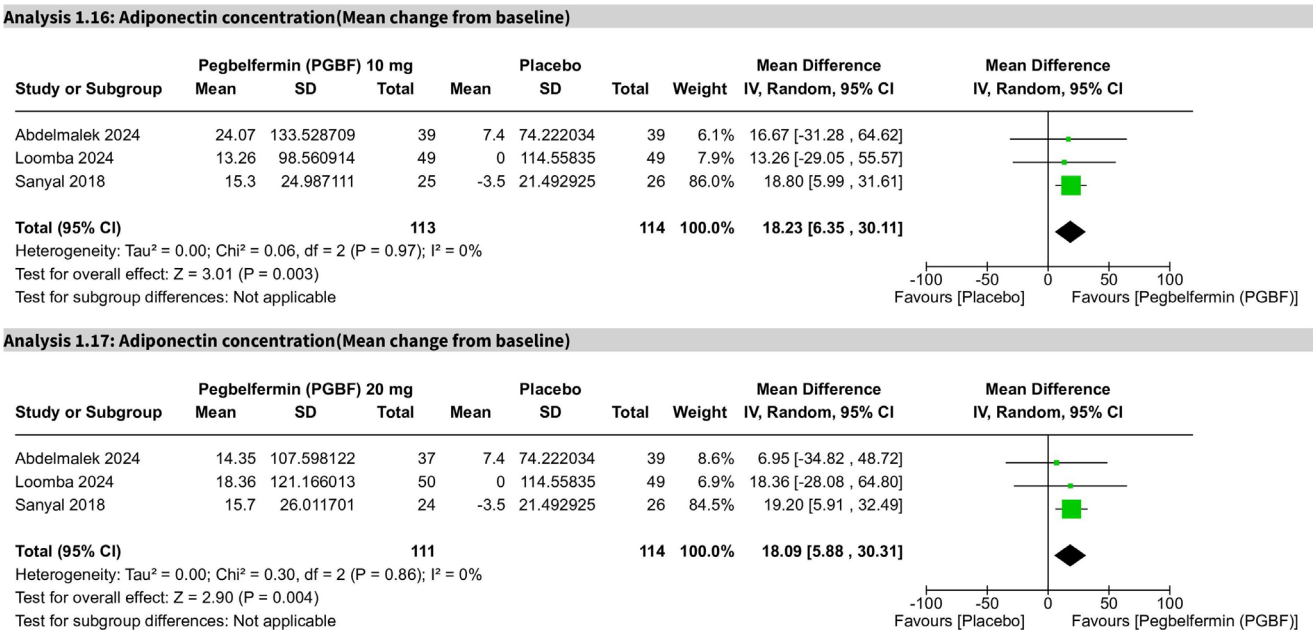


FIGURE 3 | Effect of 10 and 20 mg Pegbelfermin on adiponectin concentration compared to placebo.

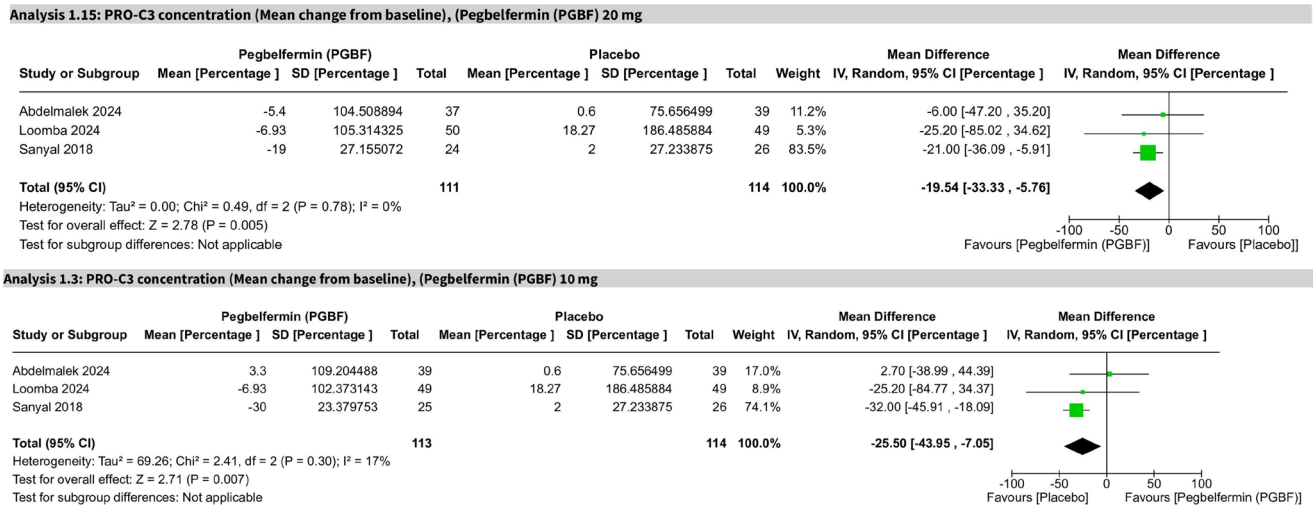


FIGURE 4 | Effect of 10 and 20 mg Pegbelfermin on PRO-C3 concentration compared to placebo.

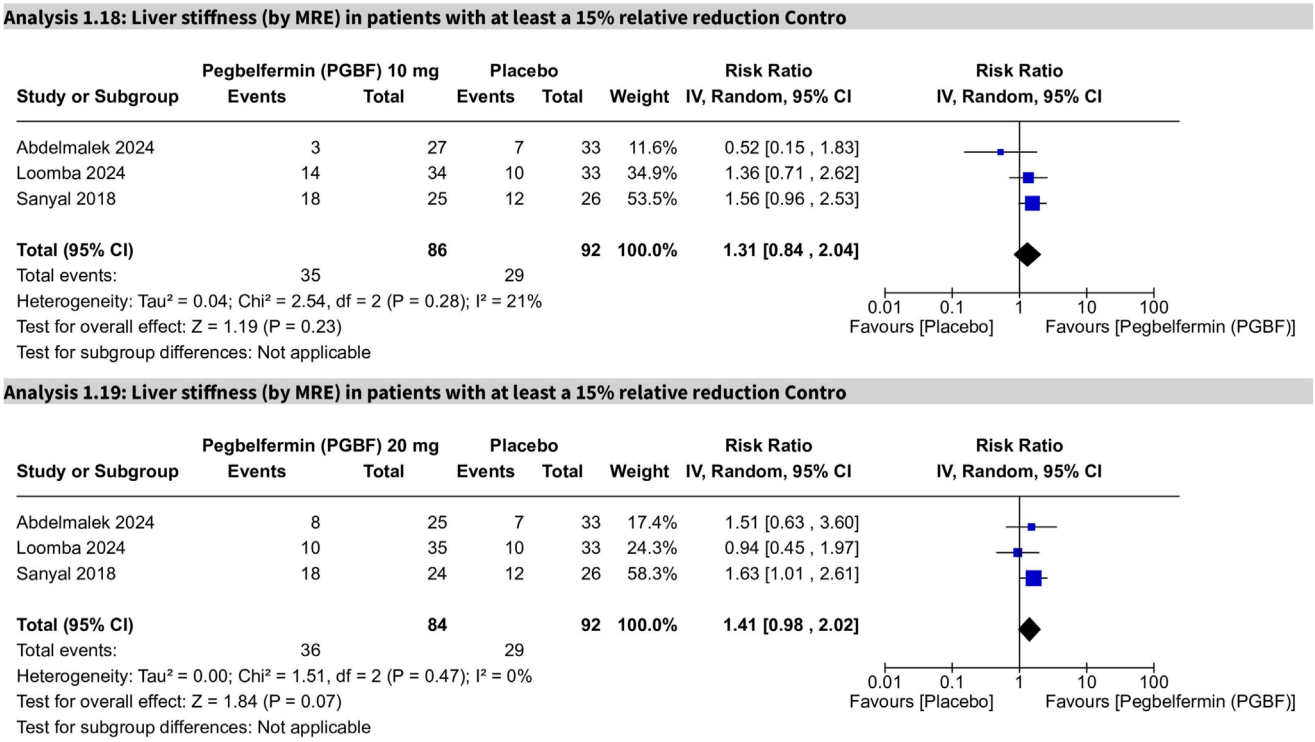


FIGURE 5 | Effect of 10 and 20 mg Pegbelfermin on liver stiffness compared to placebo.

95% CI (−54.46, 1.15), $p = 0.06$]. The heterogeneity tests for the 10 and 20 mg dosage groups demonstrated low variability among the included RCTs, yielding p-values of 0.62 and 0.78, respectively, with an I^2 of 0% in both cases, indicating negligible heterogeneity (Figures S2.1 and S2.3). PEG (10 and 20 mg) showed no significant reduction in AST and ALT levels, with a highly non-linear dose–response relationship and no clear dose-dependent effect (Figure S2.4). The GRADE assessment assigned a high level of certainty to the evidence regarding AST for both dosage groups.

3.4.3 | Changes in Modified Ishak Score

Only two RCTs contributed evaluable data for assessing changes in the Modified Ishak score, comparing doses of 10 and 20 mg to placebo. The results in both the 10 mg group [RR = 1.25, 95% CI (0.77, 2.04), $p = 0.37$] and the 20 mg group [RR = 1.01, 95% CI (0.59, 1.70), $p = 0.98$] showed that there was no significant difference between the PGBF group and the placebo group. The heterogeneity tests for the 10 and 20 mg dosage groups demonstrated low variability among the included RCTs, yielding p-values of 0.33 and 0.53, respectively, with an I^2 of 0% in both cases, indicating negligible heterogeneity (Figures S2.5 and S2.6). The GRADE assessment assigned a high level of certainty to the evidence regarding the modified Ishak score for both dosage groups.

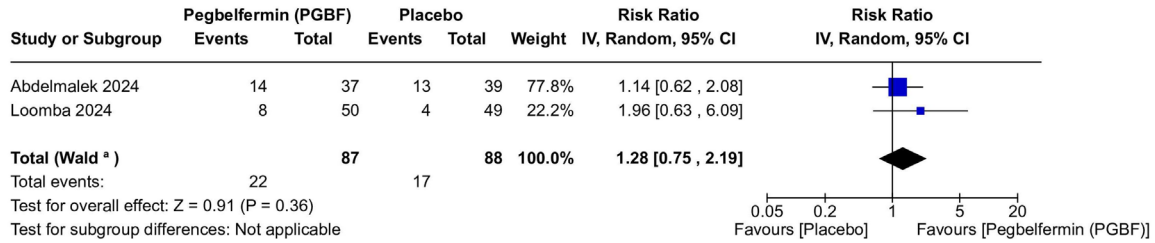
3.4.4 | NASH Improvement[1]

Evaluable data for assessing the improvement in NASH were only provided by two RCTs. These trials compared two doses of PGBF, specifically 10 and 20 mg, to a placebo. A statistically significant improvement in NASH was found when the 10 mg PGBF group and the placebo group were analyzed [RR = 2.84, 95% CI (1.18, 6.78), $p = 0.02$]. However, for the 20 mg group, the results showed no statistically significant difference between the PGBF group and the placebo group [RR = 3.24, 95% CI (0.66, 15.77), $p = 0.15$]. The heterogeneity test for the 10 mg group yielded a result of $p = 0.43$, $I^2 = 0\%$, indicating low heterogeneity among the RCTs. For the 20 mg group, the heterogeneity test result was $p = 0.14$, $I^2 = 53\%$, indicating high heterogeneity among the RCTs (Figures S2.7 and S2.8). The GRADE assessment assigned a high level of certainty to the evidence regarding NASH improvement for both dosage groups.

3.4.5 | Changes in Collagen Proportionate Area

Only two RCTs contributed evaluable data for assessing change in collagen proportionate area, comparing two doses of PGBF, specifically 10 and 20 mg, to placebo. The results showed no statistically significant difference between the PGBF group and the placebo group for both the 10 mg PGBF group [RR = 0.87, 95% CI (0.49, 1.53), $p = 0.63$] as well as the 20 mg PGBF group [RR = 0.88, 95% CI (0.66, 1.17), $p = 0.38$] respectively. The heterogeneity test result in the 10 mg group was $p = 0.05$, $I^2 = 73\%$, suggesting that the heterogeneity among RCTs was high. However, the heterogeneity test result in the 20 mg group was $p = 0.46$, $I^2 = 0\%$, suggesting that the heterogeneity among RCTs was low (Figures S2.9 and S2.10). The GRADE assessment assigned a high level of certainty to the evidence regarding the decrement in collagen proportionate area for both dosage groups.

Analysis 1.4: ≥1-stage improvement in NASH CRN fibrosis score, (Pegbelfermin (PGBF) 10 mg

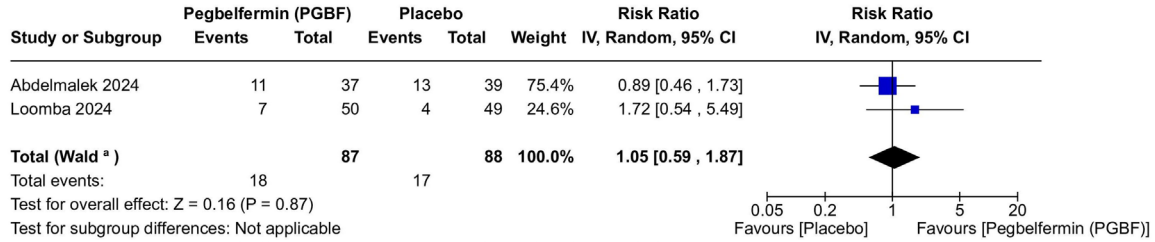


Footnotes

[a] CI calculated by Wald-type method.

[b] Tau² calculated by DerSimonian and Laird method.

Analysis 1.5: ≥1-stage improvement in NASH CRN fibrosis score, (Pegbelfermin (PGBF) 20 mg

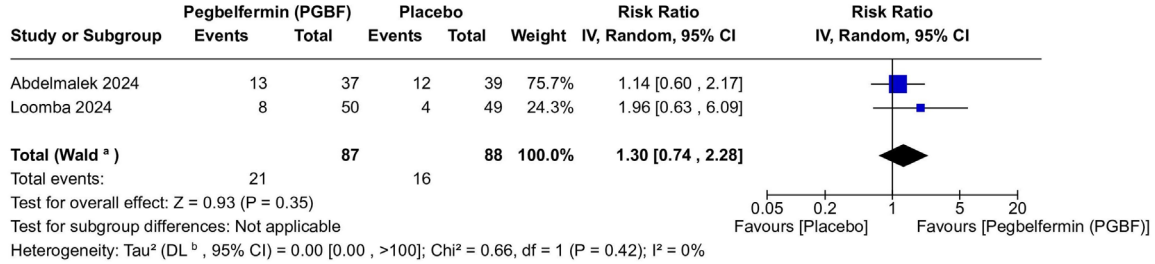


Footnotes

[a] CI calculated by Wald-type method.

[b] Tau² calculated by DerSimonian and Laird method.

Analysis 1.6: ≥1-stage improvement in NASH CRN fibrosis score without NASH worsening or NASH improvement, (Pegbelfermin (PGBF) 10 mg

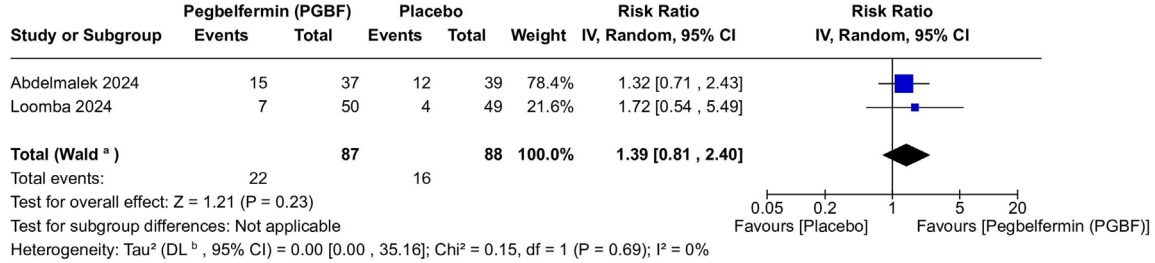


Footnotes

[a] CI calculated by Wald-type method.

[b] Tau² calculated by DerSimonian and Laird method.

Analysis 1.7: ≥1-stage improvement in NASH CRN fibrosis score without NASH worsening or NASH improvement, (Pegbelfermin (PGBF) 20 mg



Footnotes

[a] CI calculated by Wald-type method.

[b] Tau² calculated by DerSimonian and Laird method.

FIGURE 6 | Effect of 10 and 20 mg Pegbelfermin on improvement in NASH CRN fibrosis score compared to placebo.

3.5 | Safety Outcomes

3.5.1 | Drug-Related Treatment-Emergent Adverse Events

Pooled analysis of TEAEs associated with 10 mg PGBF did not show statistically significant risks compared to placebo [RR = 1.05, 95% CI (0.95, 1.16), $p = 0.33$]. The heterogeneity test result in this group was $p = 0.38$, $I^2 = 0\%$, indicating that the heterogeneity among RCTs was low. As per the GRADE assessment, the certainty of evidence was high. Evaluation of specific TEAEs, nausea, and diarrhea (each occurring in > 10% of patients) showed no statistically significant risks. For nausea, the risk was 1.15 [95% CI (0.38, 3.46), $p = 0.8$], and for diarrhea, it was 1.09 [95% CI (0.39, 3.08), $p = 0.87$]. The heterogeneity test result was $p = 0.16$, $I^2 = 45\%$ for nausea and $p = 0.17$, $I^2 = 44\%$ for diarrhea respectively, indicating high heterogeneity among the RCTs. As per the GRADE assessment, the certainty of evidence for both nausea and diarrhea groups, respectively, was high. Pooled analysis of TEAEs associated with 20 mg Pegbelfermin did not show statistically significant risks compared to placebo [RR = 1.06, 95% CI (0.97, 1.17), $p = 0.21$]. The heterogeneity test result in this group was $p = 0.58$, $I^2 = 0\%$, indicating that the heterogeneity among RCTs was low. As per the GRADE assessment, the certainty of evidence was high. Evaluation of specific TEAEs occurring in > 10% of patients showed the following results. For nausea, there was no statistically significant risk [RR = 1.69, 95% CI (0.94, 3.03), $p = 0.7$] however, for diarrhea, the risk was statistically significant [RR = 2.28, 95% CI (1.28, 4.04), $p = 0.005$]. The heterogeneity test result was $p = 0.70$, $I^2 = 0\%$ for nausea and $p = 0.67$, $I^2 = 0\%$ for diarrhea respectively, indicating low heterogeneity among the RCTs. As per the GRADE assessment, the certainty of evidence for both nausea and diarrhea groups, respectively, was high.

4 | Discussion

This systematic review and meta-analysis assessed the efficacy and safety of Pegbelfermin, a PEGylated human FGF21 analog, in treating MASH-associated hepatic fibrosis. Our analysis reveals that MASH patients administered 10 mg of Pegbelfermin experienced a significant MASH improvement compared to those given a placebo. However, when the dose was increased to 20 mg, there was no statistically significant improvement observed compared to a placebo. Additionally, irrespective of dosage, Pegbelfermin treatment led to statistically significant increases in adiponectin concentration, an adipokine associated with hepatic benefits, and statistically significant reductions in PRO-C3 levels, a biomarker of fibrosis, compared to those receiving a placebo. Notably, Pegbelfermin did not improve the NASH CRN Fibrosis Score relative to placebo. Moreover, its use was not associated with a significant increase in treatment-emergent adverse effects. Pegbelfermin did not significantly contribute to any treatment-emergent adverse effects compared to placebo. Various factors such as high-carb diets, fructose, and protein restriction influence circulating FGF21 levels, indicating its potential in regulating carbohydrate intake centrally [23]. Elevated FGF21 levels are associated with obesity-related conditions like type 2 diabetes and hypertension, primarily correlating with BMI [24]. Despite suggesting FGF21 resistance, pharmacological administration improves metabolic health [25].

Pegbelfermin, a polyethylene glycol-modified (PEGylated) recombinant human FGF21 analog with an extended half-life, has been evaluated in clinical trials for treating MASH, with several studies reporting promising results [12, 26]. However, this study represents the first quantitative analysis of Pegbelfermin's efficacy in treating liver fibrosis. Previous research overlooked the assessment of Pegbelfermin's side effects due to its novelty and recent trial status [27]. Thus, this study provides valuable insights for clinical practitioners by synthesizing and quantitatively analyzing both the efficacy and safety of Pegbelfermin. Given that Resmetirom is the only FDA-approved treatment for MASH to date, there is a significant need for novel therapeutic strategies. Pegbelfermin, a systemic therapy that impacts multiple tissues, has shown encouraging results in improving various outcomes associated with MASH [28]. The analysis indicates that individuals with MASH who received a 10 mg dose of Pegbelfermin demonstrated a substantial improvement in MASH compared to those who were administered a placebo. However, individuals with MASH who received a 20 mg dose of Pegbelfermin did not demonstrate any significant improvement in MASH compared to a placebo. This is comparable to the findings of Loomba et al. who reported a lack of dose-related changes in Pegbelfermin response rates in a randomized phase 2b study [20]. The data doesn't clearly show whether the limited efficacy seen was due to the drug's modest activity in this group of advanced patients or if neutralizing antibodies might have had a bigger impact [21].

No significant improvement in liver stiffness was observed in this study. However, liver stiffness is regulated by various factors, including exercise habits, as highlighted by Nakano et al. [29]. Their study demonstrated that individuals aged ≥ 65 years with MASLD and ALT > 30 U/L had a significantly higher prevalence of hepatic fibrosis, but exercise habits were associated with a lower prevalence of significant fibrosis. This suggests that lifestyle interventions such as regular physical activity may have a modifying effect on liver stiffness even when pharmacological treatments do not yield significant improvements. Given these findings, future studies should explore the combined impact of pharmacological interventions like Pegbelfermin and structured exercise programs to better address fibrosis progression and liver stiffness in MASH patients.

MASLD has been identified as a significant risk factor for hepatocellular carcinoma (HCC) development in elderly patients following HCV eradication, as demonstrated in Sano et al. [30]. Their study showed that elderly patients with MASLD who achieved sustained virologic response (SVR) after direct-acting antiviral (DAA) therapy had a significantly higher risk of HCC than those without MASLD. Notably, the HCC incidence was similar between MASLD patients with low alpha-fetoprotein (AFP < 7 ng/mL) and those with high AFP (≥ 7 ng/mL), suggesting that MASLD serves as a distinct oncogenic factor independent of traditional AFP-based risk stratification. Given that MASLD remains a persistent driver of hepatic inflammation and fibrosis even after viral eradication, this highlights the need for targeted therapies like Pegbelfermin to mitigate fibrosis

progression and potentially reduce HCC incidence in this high-risk population.

Our meta-analysis consistently demonstrates Pegbelfermin's favorable outcomes in improving MASH biomarkers, specifically adiponectin, and PRO-C3, aligning with findings in previous studies [22, 31]. This supports the notion that Pegbelfermin's benefits in MASH may stem from the proposed beneficial role of adiponectin in the disease [27]. Adiponectin is a key adipokine with insulin-sensitizing, anti-inflammatory, and anti-fibrotic properties, whose levels are decreased up to 50% in patients with MASH [32]. In humans, a correlation has been observed between low adiponectin levels and conditions such as obesity and insulin resistance [33]. Notably, a recent meta-analysis of clinical trials involving diabetes therapeutics including pioglitazone and rosiglitazone revealed that elevated adiponectin levels were linked to improvements in both steatosis and fibrosis [34]. Simultaneously, our analysis reveals a significant dose-dependent reduction in PRO-C3 with Pegbelfermin, suggesting the drug's antifibrotic properties. PRO-C3 has been evaluated as a diagnostic marker for significant fibrogenesis by marking the formation of type III collagen and a dynamic biomarker of treatment response [35, 36]. In individuals with chronic hepatitis C virus infection, PRO-C3 levels have been found to correspond with the severity of liver fibrosis, with higher baseline levels associated with more advanced fibrotic disease progression [36, 37]. Similarly, in patients with MASH, PRO-C3 levels have been linked to disease activity and fibrosis stage [38]. Moreover, reductions in PRO-C3 over time have been associated with improvements in hepatic fibrosis, as confirmed by biopsy [39].

The overall safety profile of Pegbelfermin has been positive, as it was generally well tolerated. The most frequent adverse effects observed were gastrointestinal, such as nausea and diarrhea; however, their incidence was not statistically significant. This is reflected in the comparable and generally low rates of discontinuation observed in the Pegbelfermin arm when compared to the placebo group [21]. While the initial trials of Pegbelfermin did not achieve the efficacy thresholds required by Bristol Myers Squibb (BMS) to show significant improvement in liver fibrosis without exacerbating MASH, these findings underscore the importance of continued research [40]. These results contribute valuable insights that can guide future studies and the development of treatments for MASH.

The primary limitations of our meta-analysis stem from the limited number of available studies and their short treatment duration. Although all the studies we included were of high quality, it is important to note that in the study conducted by Sanyal et al. [22], 63% of the 20 mg weekly group and 92% of the 10 mg daily group developed anti-pegbelfermin and anti-FGF21 antibodies, the implications of which have not been studied yet [31]. Additionally, a larger sample size would have increased the statistical power to detect a possible dose–response trend, which is difficult to establish with limited data points. Studying subjects with intermittent dosing and over a variety of doses like 5, 15 mg etc. can help bridge the gap between clinical and statistical efficacy thresholds. Another key limitation is the geographical scope of the included studies, as all were conducted in either the United States or Japan, which may limit the generalizability of our findings to broader, more diverse populations. Our findings highlight the potential of Pegbelfermin in improving MASH-related outcomes and provide valuable insights for future drug development endeavors targeting MASH. As the demand for innovative therapeutic approaches in MASH treatment remains critical, our meta-analysis serves as a foundation for guiding future research and clinical practice in addressing this unmet medical need.

5 | Conclusion

Pegbelfermin, a promising treatment for MASH-related fibrosis, showed significant efficacy at a 10 mg dosage, improving MASH and biomarkers like adiponectin and PRO-C3. While it maintained a favorable safety profile with minimal gastrointestinal side effects, the absence of significant fibrosis improvement highlights the need for further investigation. Future studies should assess its long-term effects, optimal dosing strategies, and potential synergy with agents like Resmetirom to optimize therapeutic outcomes in MASH and fibrosis management.

Conflicts of Interest

The authors declare no conflicts of interest.

Endnotes

[1] NASH is now referred to as MASH. It is written as NASH here to reflect the outcome reported in the studies.

References

1. B. Sharma and S. John, *Nonalcoholic Steatohepatitis (NASH)* (StatPearls, 2023).

2. T. Tsutsumi, T. Kawaguchi, H. Fujii, et al., "Hepatic Inflammation and Fibrosis are Profiles Related to Mid-Term Mortality in Biopsy-Proven MASLD: A Multicenter Study in Japan," *Alimentary Pharmacology & Therapeutics* 59, no. 12 (2024): 1559–1570.

3. Z. M. Younossi, P. Golabi, J. M. Paik, A. Henry, C. Van Dongen, and L. Henry, "The Global Epidemiology of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH): A Systematic Review," *Hepatology* 77, no. 4 (2023): 1335–1347.

4. K. Riazi, H. Azhari, J. H. Charette, et al., "The Prevalence and Incidence of NAFLD Worldwide: A Systematic Review and Meta-Analysis," *Lancet Gastroenterology & Hepatology* 7, no. 9 (2022): 851–861.

5. J. M. Fraile, S. Palliyil, C. Barelle, A. J. Porter, and M. Kovaleva, "Non-Alcoholic Steatohepatitis (NASH) - A Review of a Crowded Clinical Landscape, Driven by a Complex Disease," *Drug Design, Development and Therapy* 15 (2025): 3997–4009.

6. C. Peng, A. G. Stewart, O. L. Woodman, R. H. Ritchie, and C. X. Qin, "Non-Alcoholic Steatohepatitis: A Review of Its Mechanism, Models and Medical Treatments," *Frontiers in Pharmacology* 11 (2020): 1–3.

7. M. L. P. Teng, C. H. Ng, D. Q. Huang, et al., "Global Incidence and Prevalence of Nonalcoholic Fatty Liver Disease," *Clinical and Molecular Hepatology* 29, no. Suppl (2025): 32–42.

8. M. Sharma, M. Premkumar, A. V. Kulkarni, P. Kumar, D. Nageshwar Reddy, and N. P. Rao, "Drugs for Non-Alcoholic Steatohepatitis (NASH): Quest for the Holy Grail," *Journal of Clinical and Translational Hepatology* 9, no. 1 (2021): 40–50.

9. A. C. Sheka, O. Adeyi, J. Thompson, B. Hameed, P. A. Crawford, and S. Ikramuddin, "Nonalcoholic Steatohepatitis: A Review," *Journal of the American Medical Association* 323, no. 12 (2020): 1175–1183.

10. T. Kawaguchi, K. Murotani, H. Kajiyama, et al., "Effects of Luseogliflozin on Suspected MASLD in Patients With Diabetes: A Pooled Meta-Analysis of Phase III Clinical Trials," *Journal of Gastroenterology* 59, no. 9 (2024): 836–848.

11. T. Kawaguchi, Y. Fujishima, D. Wakasugi, et al., "Effects of SGLT2 Inhibitors on the Onset of Esophageal Varices and Extrahepatic Cancer in Type 2 Diabetic Patients With Suspected MASLD: A Nationwide Database Study in Japan," *Journal of Gastroenterology* 59, no. 12 (2024): 1120–1132.

12. D. Struik, M. B. Dommerholt, and J. W. Jonker, "Fibroblast Growth Factors in Control of Lipid Metabolism: From Biological Function to Clinical Application," *Current Opinion in Lipidology* 30, no. 3 (2019): 235–243.

13. L. Geng, K. S. L. Lam, and A. Xu, "The Therapeutic Potential of FGF21 in Metabolic Diseases: From Bench to Clinic," *Nature Reviews. Endocrinology* 16, no. 11 (2020): 654–667.

14. S. Talukdar and A. Kharitonenkov, "FGF19 and FGF21: In NASH We Trust," *Molecular Metabolism* 46 (2021): 101152.

15. C. Y. Zhang, S. Liu, and M. Yang, "Treatment of Liver Fibrosis: Past, Current, and Future," *World Journal of Hepatology* 15, no. 6 (2023): 755–774.

16. J. P. T. Higgins, J. Thomas, J. Chandler, et al., *Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023)* (Cochrane, 2023).

17. A. Liberati, D. G. Altman, J. Tetzlaff, et al., "The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration," *Journal of Clinical Epidemiology* 62, no. 10 (2009): e1–e34.

18. J. A. C. Sterne, J. Savović, M. J. Page, et al., "RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials," *British Medical Journal* 366 (2019): 2–5.

19. GRADEpro GDT, GRADEpro Guideline Development Tool [Software] McMaster University and Evidence Prime.

20. R. Loomba, A. J. Sanyal, A. Nakajima, et al., "Pegbelfermin in Patients With Nonalcoholic Steatohepatitis and Stage 3 Fibrosis (FALCON 1): A Randomized Phase 2b Study," *Clinical Gastroenterology and Hepatology* 22, no. 1 (2024): 102–112.

21. M. F. Abdelmalek, A. J. Sanyal, A. Nakajima, et al., "Pegbelfermin in Patients With Nonalcoholic Steatohepatitis and Compensated Cirrhosis (FALCON 2): A Randomized Phase 2b Study," *Clinical Gastroenterology and Hepatology* 22, no. 1 (2024): 113–123.

22. A. Sanyal, E. D. Charles, B. A. Neuschwander-Tetri, et al., "Pegbelfermin (BMS-986036), a PEGylated Fibroblast Growth Factor 21 Analogue, in Patients With Non-alcoholic Steatohepatitis: A Randomised, Double-Blind, Placebo-Controlled, Phase 2a Trial," *Lancet* 392, no. 10165 (2018): 2705–2717.

23. S. M. Solon-Biet, V. C. Cogger, T. Pulpitel, et al., "Defining the Nutritional and Metabolic Context of FGF21 Using the Geometric Framework," *Cell Metabolism* 24, no. 4 (2016): 555–565.

24. J. Dushay, P. C. Chui, G. S. Gopalakrishnan, et al., "Increased Fibroblast Growth Factor 21 in Obesity and Nonalcoholic Fatty Liver Disease," *Gastroenterology* 139, no. 2 (2010): 456–463.

25. K. R. Markan, "Defining "FGF21 Resistance" During Obesity: Controversy, Criteria and Unresolved Questions," *F1000Research* 7 (2018): 289.

26. C. R. C. Verzijl, I. P. Van De Peppel, D. Struik, and J. W. Jonker, "Pegbelfermin (BMS-986036): An Investigational PEGylated Fibroblast Growth Factor 21 Analogue for the Treatment of Nonalcoholic Steatohepatitis," *Expert Opinion on Investigational Drugs* 29, no. 2 (2020): 125–133.

27. D. D. Raptis, C. S. Mantzoros, and S. A. Polyzos, "Fibroblast Growth Factor-21 as a Potential Therapeutic Target of Nonalcoholic Fatty Liver Disease," *Therapeutics and Clinical Risk Management* 19 (2025): 77–96.

28. A. S. Brett and M. Resmetirom, "Resmetirom, the First Drug Approved by the U.S. FDA for Treating Patients With Nonalcoholic Steatohepatitis," *NEJM Journal Watch* (2024).

29. M. Nakano, M. Kawaguchi, T. Kawaguchi, and H. Yoshiji, "Profiles Associated With Significant Hepatic Fibrosis Consisting of Alanine Aminotransferase > 30 U/L, Exercise Habits, and Metabolic Dysfunction-Associated Steatotic Liver Disease," *Hepatology Research* 54, no. 7 (2024): 655–666.

30. T. Sano, K. Amano, T. Ide, et al., "Metabolic Management After Sustained Virologic Response in Elderly Patients With Hepatitis C Virus: A Multicenter Study," *Hepatology Research* 54, no. 4 (2024): 326–335.

31. E. D. Charles, B. A. Neuschwander-Tetri, J. Pablo Frias, et al., "Pegbelfermin (BMS-986036), PEGylated FGF21, in Patients With Obesity and Type 2 Diabetes: Results From a Randomized Phase 2 Study," *Obesity (Silver Spring)* 27, no. 1 (2019): 41–49.

32. C. Pagano, G. Soardo, W. Esposito, et al., "Plasma Adiponectin is Decreased in Nonalcoholic Fatty Liver Disease," *European Journal of Endocrinology* 152, no. 1 (2005): 113–118.

33. J. J. Díez and P. Iglesias, "The Role of the Novel Adipocyte-Derived Hormone Adiponectin in Human Disease," *European Journal of Endocrinology* 148, no. 3 (2003): 293–300.

34. S. A. Polyzos and C. S. Mantzoros, "Adiponectin as a Target for the Treatment of Nonalcoholic Steatohepatitis With Thiazolidinediones: A Systematic Review," *Metabolism* 65, no. 9 (2016): 1297–1306.

35. M. A. Karsdal, S. J. Daniels, S. Holm Nielsen, et al., "Collagen Biology and Non-invasive Biomarkers of Liver Fibrosis," *Liver International* 40, no. 4 (2020): 736–750.

36. M. J. Nielsen, K. Kazankov, D. J. Leeming, et al., "Markers of Collagen Remodeling Detect Clinically Significant Fibrosis in Chronic Hepatitis C Patients," *PLoS One* 10, no. 9 (2015): e0137302.

37. M. A. Karsdal, K. Henriksen, M. J. Nielsen, et al., "Fibrogenesis Assessed by Serological Type III Collagen Formation Identifies Patients With Progressive Liver Fibrosis and Responders to a Potential Antifibrotic Therapy," *American Journal of Physiology. Gastrointestinal and Liver Physiology* 311, no. 6 (2016): G1009–G1017.

38. D. J. Leeming, J. I. Grove, P. Kaye, et al., "Estimation of Serum "True Collagen Type III Formation" (Pro-C3) Levels as a Marker of Nonalcoholic Steatohepatitis in a Prospective Cohort," *Journal of Hepatology* 66, no. 1 (2017): S154.

39. A. J. Pellicano, K. Spahn, P. Zhou, I. D. Goldberg, and P. Narayan, "Collagen Characterization in a Model of Nonalcoholic Steatohepatitis With Fibrosis; A Call for Development of Targeted Therapeutics," *Molecules* 26, no. 11 (2021): 5–8.

40. "Bristol Myers Becomes Latest Victim of Unforgiving NASH as Midstage Asset Shelved | Fierce Biotech," (2025), https://www.fiercebiotech.com/biotech/bristol-myers-becomes-latest-victim-unforgiving-nash-as-mid-stage-asset-shelved.

Supporting Information

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