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SYSTEMATIC REVIEW

Unveiling Resmetirom: A systematic review and meta-analysis on its impact on liver function and safety in non-alcoholic steatohepatitis treatment

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Abstract

Background and Aim: The role of Resmetirom in non-alcoholic steatohepatitis (NASH) represents a promising therapeutic approach in addressing the growing global burden of liver disease. With NASH emerging as a leading cause of liver-related morbidity and mortality worldwide, there is an urgent need for effective treatments. Resmetirom, a selective thyroid hormone receptor-β agonist, offers potential benefits in improving liver histology and metabolic parameters in patients with NASH. This review examines the current evidence surrounding Resmetirom's role in NASH management.

Methods: A systematic review and meta-analysis was done by searching in Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE (including MEDLINE InProcess) (OvidSP), Web of Science, Embase (OvidSP), and Scopus databases. ROB2 Cochrane tool was used for assessing risk of bias in randomized controlled trials (RCTs). In the analysis, we used RevMan Cochrane software.

Results: The study showed that patients who were treated with Resmetirom had significantly lower low-density lipoprotein-cholesterol (LDL-C) levels (mean difference [MD] −10.45; 95% confidence interval [CI] −15.86 to −5.83; $P < 0.001$) and alanine aminotransferase (ALT) levels (MD −7.18; 95% CI −12.67 to −1.68; $P = 0.01$) as compared with those in the placebo group. The risk of adverse events including diarrhea [risk ratio (RR) 1.81; 95% CI 1.40 to 2.35; $P < 0.001$] and nausea (RR 1.72; 95% CI 1.31 to 2.27; $P < 0.001$) was significantly increased for the Resmetirom group as compared with the placebo group.

Conclusion: Resmetirom presents a promising therapeutic option for NASH, offering potential benefits in reducing liver fat content and improving histological outcomes. The encouraging results from clinical trials suggest that Resmetirom may address an unmet need in NASH management, providing hope for patients with this progressive liver disease. Further research and long-term studies are warranted to validate its efficacy and safety profile in larger patient populations.

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to accumulation of liver fat not due to alcohol consumption. The prevalence ranges from 30% in developed countries to 10% in developing countries, making it the most common liver condition affecting the population. Pathogenesis is related to insulin resistance and central obesity, which is usually associated with type 2 diabetes. Also defect in lipid utilization and export is a contributor factor.[1]

NAFLD is commonly asymptomatic, although fatigue has been noted to be associated with it. It is usually detected

incidentally through liver blood tests and imaging conducted for other reasons, with exclusion of other etiologies, especially excessive alcohol use, previous abdominal surgery, and drugs such as amiodarone and tamoxifen.[2]

Non-alcoholic steatohepatitis (NASH) is the major future risk related to NAFLD, about 1–2% of all adults have risk to develop NASH, making them threatened by cirrhosis and carcinoma and future need for liver transplant, which in turn have economic impact that is estimated to be 103$ billion in countries like United States.[3] The European association for the study of the liver (EASL), European association for the study of Diabetes (EASD), and European association for the study of Obesity (EASO) Practice Guidelines for the management of NAFLD recommend lifestyle modification as the strategy of choice to prevent and improve NALFD. However, only few people achieve the target weight loss required for meaningful improvement, which make the demands more urgent to find other solutions.[4]

A promising pharmacological therapy (Resmetirom) is a liver-directed orally active selective thyroid hormone receptor agonist helping NASH by increasing liver fat metabolism and reducing lipotoxicity, so we tried to study it more in this research in the form of laboratory effectiveness and assessing adverse reactions.[5]

Methods

PICOT: Population (P): Studies involved patients diagnosed with NASH by accepted criteria at the time of publication. There are no Resmetirom on patients gender, age, and the region where they live and work.

Intervention (I): The controlled group was composed of 80 mg Resmetirom.

Comparison (C): The experimental group was composed of placebo or conventional therapy.

Outcome (O): Assessing the efficacy, including the levels of liver enzyme (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) gamma-glutamyl transferase (GGT) levels, magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and blood lipids (low-density lipoprotein-cholesterol [LDL-C] levels), and adverse effects of Resmetirom.

To be eligible for inclusion in this systematic review, studies were required to meet the following criteria: a population of all age groups who have experienced NASH; provide data that enable the evaluation of the efficacy and adverse effects of Resmeritom; and published in the English language. Study designs eligible for inclusion are randomized controlled trials (RCTs) that have no restrictions to publication time.

Studies meeting any of the following criteria were excluded from the systematic review: involving patients with diagnoses other than NASH; do not provide data on the aforementioned outcomes; languages other than English. Review articles, letters to the editor, Conference abstracts, and gray literature were excluded, and other documents; duplications of the same research, documents inconsistent with the same theme, and animal experiments. Studies for which the complete text was not accessible were also exclusive.

Study screening and selection. Study screening and selection were conducted using the Rayyan software. Two independent reviewers assessed titles and abstracts for eligibility based on the inclusion and exclusion criteria outlined above. Any disagreements between reviewers were resolved through discussion or by involving a third reviewer if necessary (Fig. 1).

Assessment of methodological quality and risk of bias. The methodological quality and risk of bias of the included studies were assessed using the Cochrane Risk of Bias 2 (RoB-2) tool.

Literature search. A comprehensive literature search was conducted. The search strategy combined relevant keywords and Medical Subject Headings (MeSH) where applicable.

Data extraction. A standardized data extraction form was developed and used to extract relevant information from the included studies. Data extraction covered study characteristics, participant details, intervention descriptions, outcome measures, results, and adverse events related to Resmetirom.

Statistical analysis. Data analysis was performed using Revman5.3 software provided on the Cochrane website. To account for discrepancies in the literature, the I^2 and H statistic tests were performed to identify heterogeneity before synthesizing outcomes. For trials with low heterogeneity (P value >0.09, I^2 value <58%), a fixed-effects model was used. For trials with significant heterogeneity (P value ≤0.09, I^2 value ≥58%), a random-effects model was utilized. For continuous variables, mean difference (MD) pooled effect sizes were employed, and differences in outcome indicators were assessed using a 95% confidence interval (CI).

Ethical considerations. This systematic review and meta-analysis adheres to ethical guidelines and standards for conducting research. Data used are from published studies and do not involve human subjects directly. No ethical approval is required for this systematic review and meta-analysis.

Results

For the people writing the initial part of results and discussion, I took the Resmeritom “80 mg” group and placebo group for the analysis. Total number of patients among the studies were 2234 including all the sub-groups. A total of 1415 were included for our head-to-head meta-analysis.

Outcome measures. The study showed that patients who were treated with Resmetirom had significantly lower LDL-C levels (MD −10.45; 95% CI −15.86 to −5.83; $P < 0.001$) and ALT levels (MD −7.18; 95% CI −12.67 to −1.68; $P = 0.01$) as compared with those in the placebo group. However, magnetic resonance imaging-proton density fat fraction (MRI-PDFF) (MD −4.90; 95% CI −9.95 to 0.15; $P = 0.06$) gave nonsignificant results among the groups. Similarly, the AST levels (MD −3.60; 95% CI −7.44 to 0.24; $P = 0.07$) and GGT levels (MD −17.02; 95% CI −35.12 to 1.09; $P = 0.07$) also gave nonsignificant results. Please refer to Figures 2–6 for the forest plots of all outcome measures. (Table 1).

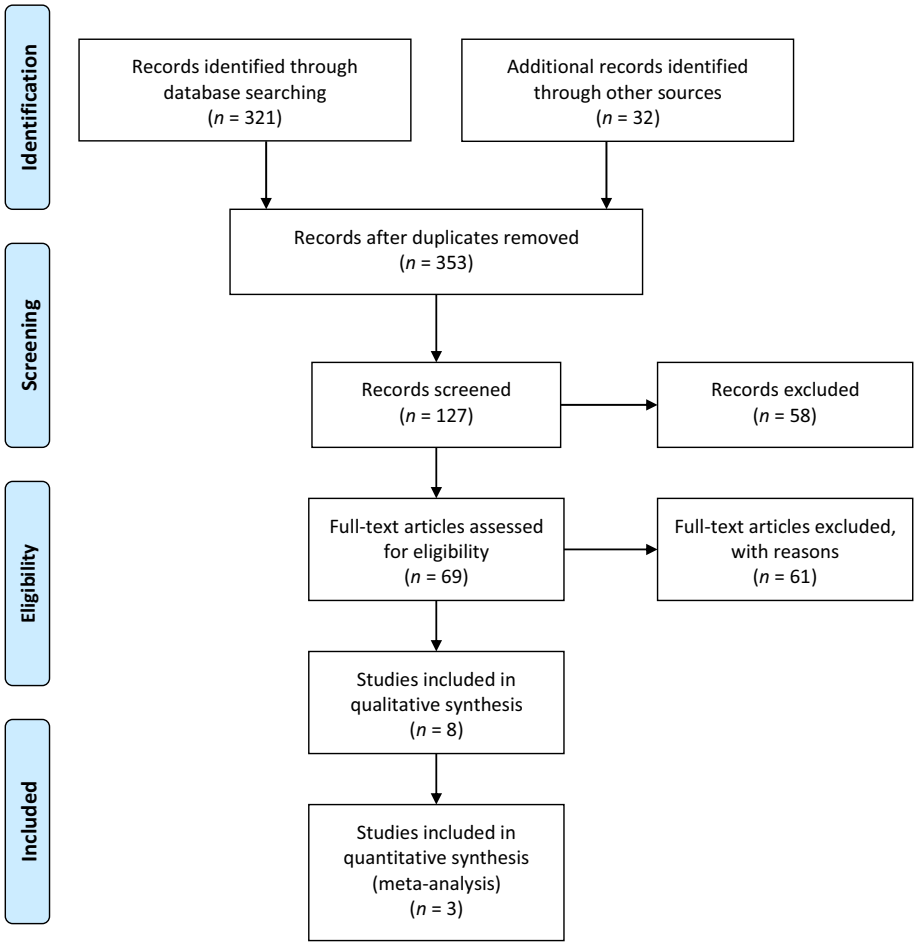

Figure 1 Flowchart of the included studies.

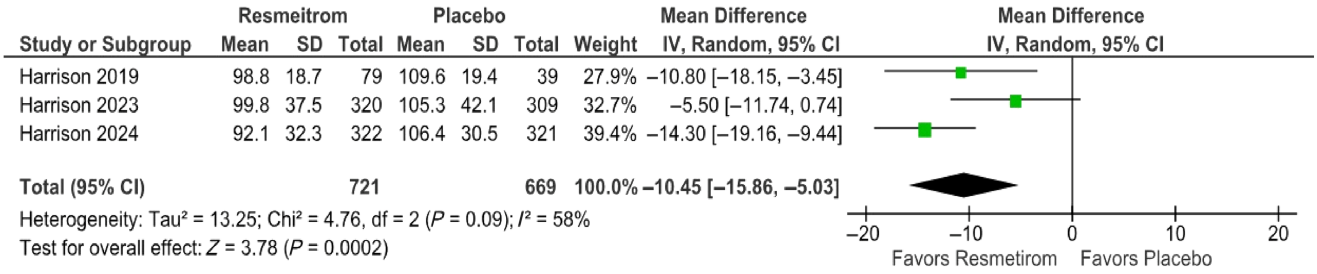

Figure 2 Low-density lipoprotein-cholesterol levels. CI, confidence interval.

Adverse events. The risk of adverse events including diarrhea (RR 1.81; 95% CI 1.40 to 2.35; $P < 0.001$) and nausea (RR 1.72; 95% CI 1.31 to 2.27; $P < 0.001$) was significantly increased for the Resmetirom group as compared with the placebo group. However, the adverse events such as fatigue (RR 1.19; 95% CI 0.77 to 1.83; $P = 0.43$) and the incidence of urinary tract infections (UTIs) (RR 1.07; 95% CI 0.75 to 1.52; $P = 0.07$) gave nonsignificant results among both groups (Figs 7–10).

Quality assessment. According to our assessment using the RoB-2, two trials (cite 2023, 2024) showed low risk of bias. However, one trial (cite 2019) raised some concerns due to missing outcome data. See Figure 11.

Discussion

The present study evaluates the effects of Resmetirom on levels of liver enzyme (ALT, AST) GGT levels, MRI-PDFF, and blood

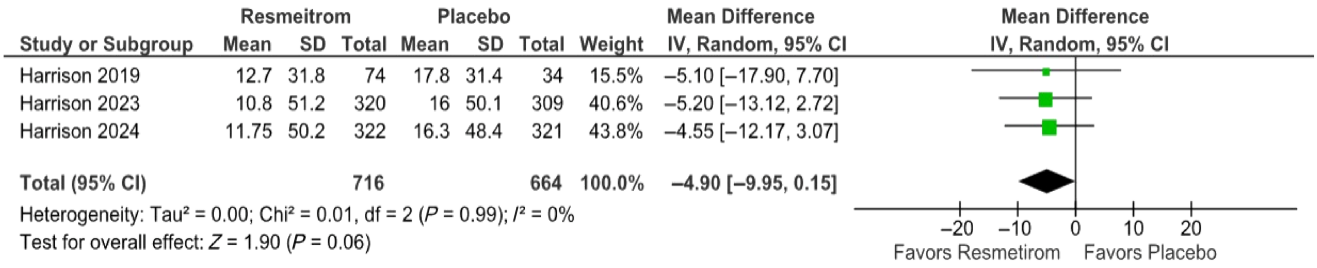

Figure 3 Magnetic resonance imaging-proton density fat fraction. CI, confidence interval.

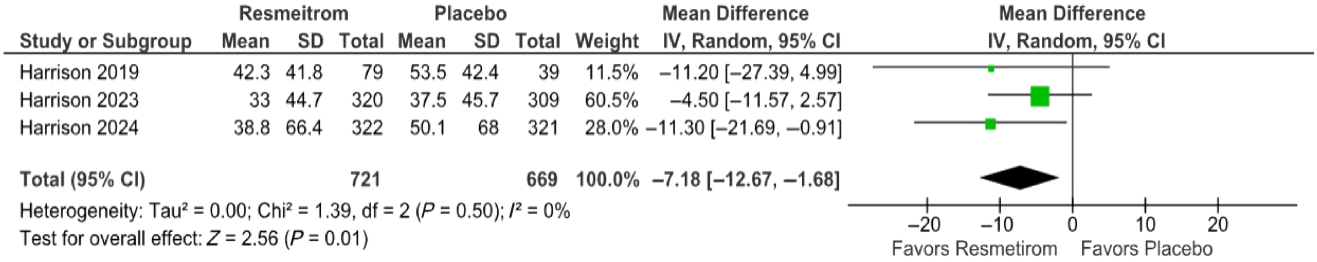

Figure 4 Alanine aminotransferase levels. CI, confidence interval.

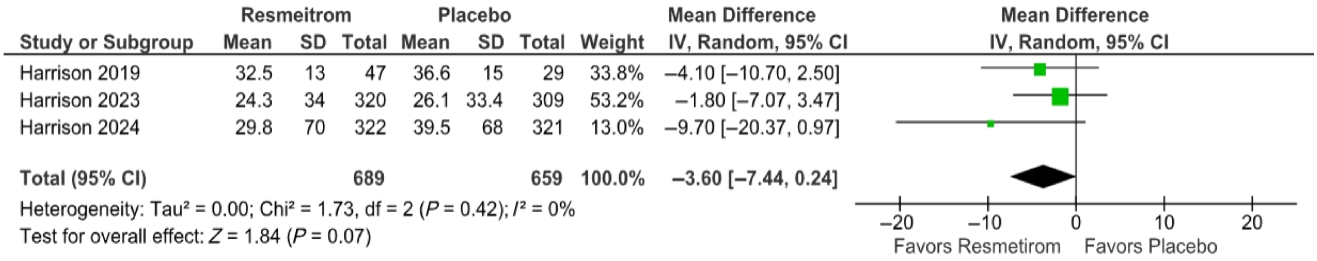

Figure 5 Aspartate aminotransferase levels. CI, confidence interval.

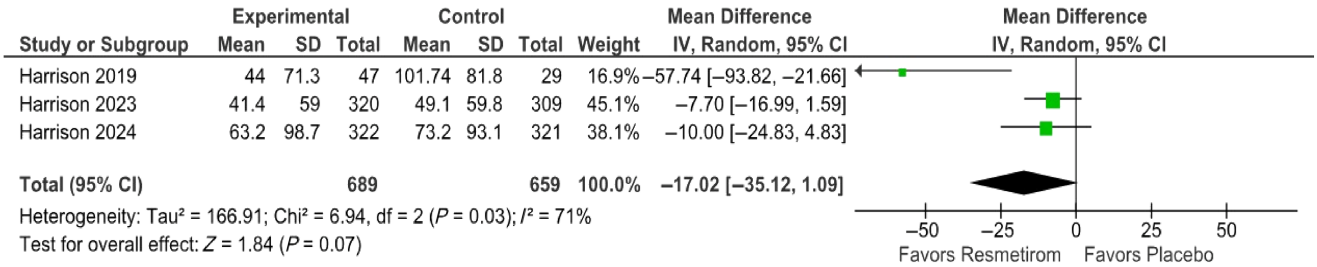

Figure 6 GGT levels. CI, confidence interval.

lipids (LDL-C levels) and adverse effects in Patients with NASH.

NASH is a degenerative liver disease that follows NAFLD, which is characterized by more than 5% liver fat. NAFLD is associated with obesity, type 2 diabetes, and dyslipidemia, which can develop to NASH, then fibrosis, and eventually hepatocellular carcinoma (Fig. 12). This transformation of NAFLD to NASH can be explained by the "two-hit" theory, which posits that damage and oxidative stress occur after steatosis (first strike). Unbalanced energy supply and consumption lead to increased hepatic fat accumulation. Thus, NAFLD is the hepatic expression of dysfunctional adipose tissue brought on by an excess of energy.[6] The global prevalence of NAFLD is estimated to be approximately 25%, has a greater occurrence

Table 1 Baseline characteristics of included studies

Study	Phase of study	Dose of Resmetirom	No. of patients (*n*)		Female, *n* (%)	Age, mean years (SD)		Body mass index, mean kg/m^2 (SD)		LDL-C levels, mean mg/dL (SD)		Fibrosis-4 index score, mean (SD)		Follow-up (weeks)
			Resmetirom	Placebo		Resmetirom	Placebo	Resmetirom	Placebo	Resmetirom	Placebo	Resmetirom	Placebo	
Harrison 2024	Phase 3 RCT	80 mg	322 (80 mg)	32	542 (56.1)	55.9 (11.5)	57.1 (10.5)	35.5 (6.4)	35.3 (6.5)	106.6 (37.4)	106.8 (41.4)	1.4 (0.7)	1.4	52
		100 mg	323 (100 mg)			55.9 (11.5) (80 mg) 57 (10.8) (100 mg)		35.5 (6.4) (80 mg) 36.2 (7.4) (100 mg)		106.6 (37.4) (80 mg) 103 (36.8) (100 mg)		(80 mg) 1.5 (0.7) (100 mg)	(0.7)	
Harrison 2023	Phase 3 RCT	100 mg	327 (80 mg)	318	643 (56.4)	56.2 (11.7)	55.7 (12.1)	35.3 (5.9)	35.3 (5.8)	111.7 (37.6)	106.8 (37.2)	1.0 (0.5)	1.0	24
		80 mg	495 (100 mg)			56.2 (11.7) (80 mg) 55.6 (11.5) (100 mg OL) 55.9 (11.7) (100 mg DB)		35.3 (5.9) (80 mg) 36.1 (6.3) (100 mg OL) 35.4 (6.4) (100 mg DB)		111.7 (37.6) (80 mg) 115.2 (41.0) (100 mg OL) 109.1 (36.4) (100 mg DB)		(80 mg) 1.0 (0.6) (100 mg OL) 1.0 (0.4) (100 mg DB)	(0.5)	
Harrison 2019	Phase 2 RCT	80 mg	84	41	63 (50.4)	51.8 (10.4)	47.3 (11.7)	35.8 (6.2)	33.6 (5.8)	111.3 (30.4)	116.9 (30.0)	N/A	N/A	36

DB, double-blind; LDL-C, low-density lipoprotein-cholesterol; N/A, not available; OL, open-label; RCT, randomized controlled trial.

among people with concomitant diseases including obesity and type 2 diabetes.[7] Adults in the United States have a 30–40% prevalence of NAFLD and a 3–12% prevalence of NASH, respectively. There is racial heterogeneity in prevalence; Hispanics have the greatest prevalence, followed by Caucasians rather than African Americans. It can appear at any age, and as people age, so does its frequency.[6] The majority of NASH patients have no symptoms, and the illnesses are typically discovered by chance during normal blood testing. On the other hand, certain NASH patients may exhibit pain or discomfort in the right upper quadrant, possibly as a result of hepatomegaly-induced liver capsular stretching. The results of a nonspecific physical examination can include steatosis-related hepatomegaly, insulin-resistant acanthosis nigricans (increased pigmentation around the neck and joints), and, in the case of liver cirrhosis, stigmata such as palmar erythema, spider telangiectasias, muscle wasting, jaundice, splenomegaly, and ascites.[6] NAFLD/NASH is frequently diagnosed accidentally when routine laboratory testing reveals abnormal liver biochemical tests or imaging studies reveal hepatic steatosis or hepatomegaly. Ultrasonography, computed tomography (CT), and MRI are three imaging modalities. Ultrasonography, on the other hand, is the most extensively utilized modality because of its low cost and availability. NAFLD should only be diagnosed if there is no excessive alcohol consumption (defined as more than 20 g/day for men and more than 10 g/day for women), as well as other causes of liver disease such as viral hepatitis, autoimmune hepatitis, hereditary or drug-induced liver disease, ALT, and AST are normally modestly raised at two to five times the upper limit of normal, with ALT outperforming AST in a 2:1 ratio. This pattern of serum aminotransferase increase distinguishes NAFLD from alcoholic hepatitis, since AST is often larger than ALT in alcoholic hepatitis in more than 2:1 ratio. Please keep in mind that this trend reverses in NASH with severe fibrosis or cirrhosis, with AST often larger than ALT. Serum alkaline phosphatase levels can be moderately increased, reaching up to twice the upper limit of normal. Bilirubin, albumin, and INR are typically within normal ranges, but they will be raised in people who develop cirrhosis. Ferritin levels can be increased in up to 60% of patients, indicating more advanced illness because it is an inflammatory marker. Autoimmune antibodies, such as antinuclear antibody (ANA), can be found in low levels. The gold standard diagnosis for NASH is liver biopsy; steatosis, steatohepatitis, and fibrosis are the three histologic findings on a liver biopsy. The buildup of lipid droplets in hepatocytes is known as steatosis. If more than 5% of the hepatocytes are affected, it is pathogenic. When lipid droplets are enormous and push the nucleus to the cell's periphery, steatosis is referred to as macrovesicular; when the droplets are small and accumulate without moving the nucleus, it is referred to as microvesicular. NAFLD is associated with both mixed and macrovesicular steatosis; however, pure microvesicular patterning is not shown in NAFLD (but is observed in alcoholic hepatitis and other diseases). Steatosis, inflammation (chronic mononuclear cell inflammatory infiltration made up of lymphocytes, rare plasma cells, and monocytes), and hepatocyte ballooning are all associated with NASH.[6]

For NASH, no pharmaceutical treatments are presently licensed. Rather, therapy of comorbidities including obesity, type 2 diabetes, and dyslipidemia is centered on changing one's

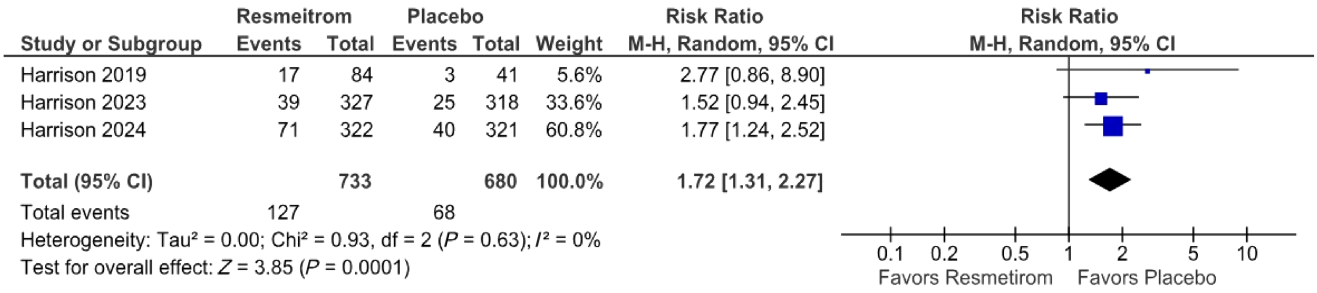

Figure 7 Nausea. CI, confidence interval.

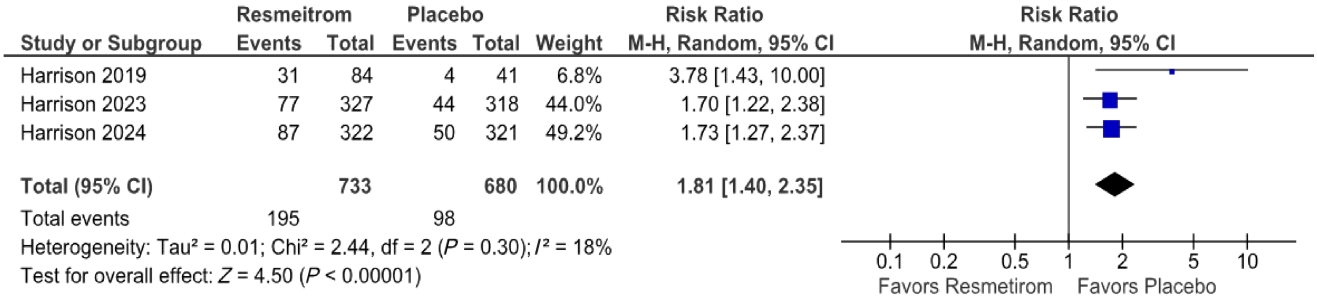

Figure 8 Diarrhea. CI, confidence interval.

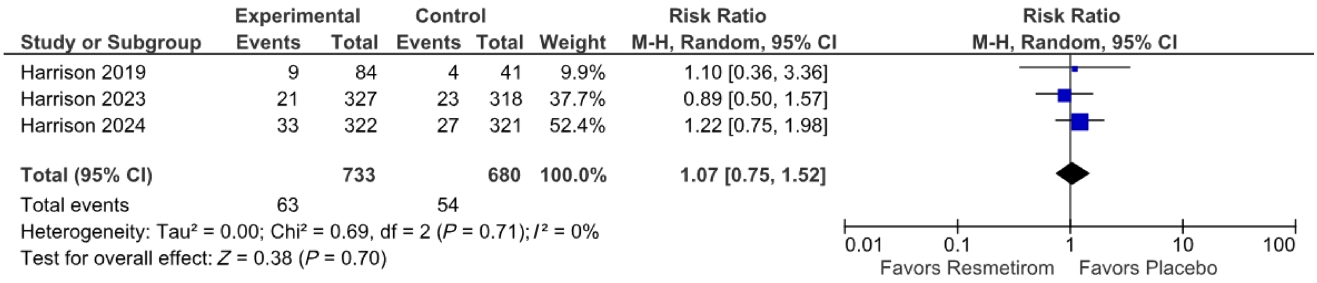

Figure 9 Urinary tract infection. CI, confidence interval.

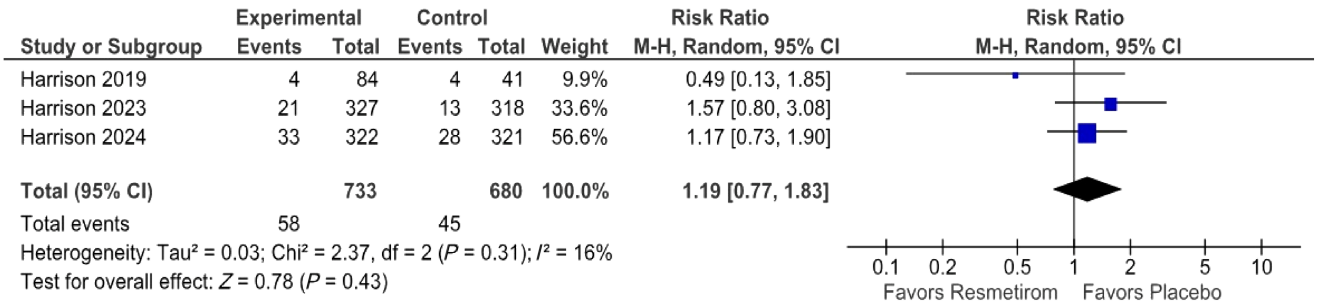

Figure 10 Fatigue. CI, confidence interval.

lifestyle, which includes nutrition and exercise. Because NASH is a chronic illness, treatment may be needed for the rest of one's life to stop or delay the disease's progression. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta-selective agonist; in some articles, the lowering of thyroid hormone levels associated with NASH,[4] THR-β agonist should aim to achieve

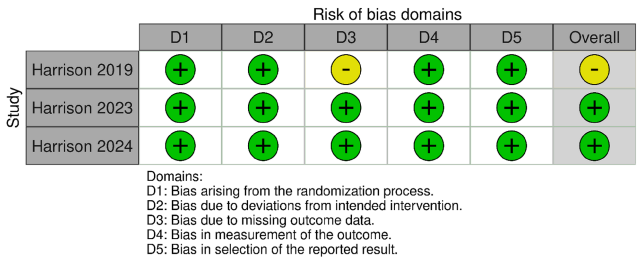

Figure 11 Risk of bias assessment. Judgement: (-), Some concerns; (+), low.

three goals: (i) reduced hepatic steatosis, inflammation, and fibrosis; (ii) liver specificity with no effect on the hypothalamus–pituitary–thyroid axis, which governs serum thyroid levels; (iii) and high THR-β selectivity to prevent off-target effects on bone/cartilage and heart, Resmetirom (MGL-3196), VK2809 (MB07811), ASC-41, and TERN 501. VK2809 is a prodrug activated by cytochrome P4503A (CYP3A) in the liver and is being investigated for the treatment of NASH with F2/F3 fibrosis in a phase IIb clinical trial;[8] TERN-501 is being investigated for the treatment of NASH in a phase IIa.[9] ASC-45, also a prodrug metabolized by CYP3A, is being investigated in a phase II trial and is limited to China.[10] Resmetirom is being developed in dose 80 mg daily for the treatment of NASH with liver fibrosis.[11] Our results show that Resmetirom play a significant role in LDL-C and AST levels compared with placebo, which is also noticed in other articles[5–7,11–14] while nonsignificant role in its effect on MRI-PDFF, GGT. While another study shows Resmetirom causes significant decrease in MRI-PDFF, LDL-C apolipoprotein, and triglycerides.[8] According to our result, Diarrhea and nausea are significantly increased as adverse effect of Resmetirom, which also mentioned in another article as adverse effect to Resmetirom more than placebo,[11] mentioned only diarrhea as adverse effect;[15] in another clinical trial it shows that nausea and vomiting are more with placebo group than Resmetirom group, which is reversed to what we found in our result,[7] while fatigue and UTI show nonsignificant results among both groups.

Our study integrated all available direct and indirect evidence to assess therapies in NASH patients concurrently, which is our study's major benefit. Furthermore, our work is relevant because medication interventions for NASH are complicated and diverse, and there are no proven therapies for the illness, and this is the first meta-analysis about using Resmetirom to treat NASH patients. However, we have one article with low quality assessment that did not talk about its effect on liver fibrosis and other side effects like dizziness and itchiness.

In conclusion, Resmetirom provides a promising therapeutic option to treat NASH, offering potential benefits in reducing liver fat content and improving histological outcomes. Usage of Resmetirom to treat NASH patients is not approved yet by FDA, so further randomized clinical trial is recommended to investigate more about effects and long-term adverse effects for this medication.

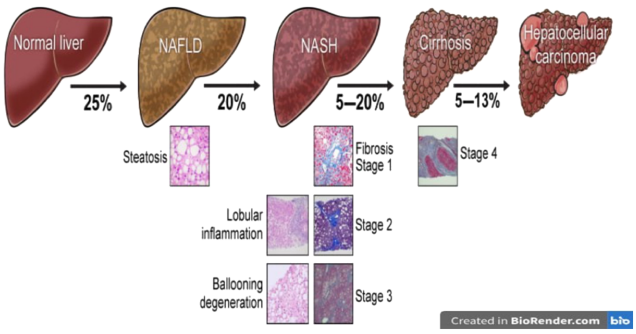

Figure 12 Diagram depicting the evolution of non-alcoholic fatty liver disease (NAFLD) to cirrhosis and hepatocellular cancer. NASH, non-alcoholic steatohepatitis.

Informed consent

All the authors gave their consents.

Data availability statement. Data can be requested from the authors.

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